Nadofaragene firadenovec (Adstiladrin®) for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours

General information

Drug description [1]	Indication [2]
Nadofaragene firadenovec (Adstiladrin®, rAd-IFNa/Syn3, Instiladrin™, FE 999326) is a replication-deficient recombinant adenovirus that delivers human interferon alfa-2b cDNA into the bladder epithelium.	Adstiladrin® (nadofaragene firadenovec-vncg) is indicated for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours.

Incidence

In **Austria** in 2020**,** for bladder cancer, the age standardised incidence rate[1] was **15.2 per 100,000** persons per year (25.8/100,000 in men and 7.0/100,000 in women). In 2020, 1,381 persons were newly diagnosed with bladder cancer [3].
The worldwide age-standardised incidence rate (in 2020, per 100,000 person/year) is 9.5 in men and 2.4 in women. In the European Union the age-standardised incidence rate is 20/100,000 for men and 4.6/100,000 for women (in 2020) [4].
75% of bladder cancers are NMIBCs [5, 6].

Current treatment

For patients with high-grade NMIBC after one or two transurethral resections of a bladder tumour (TURBT) operations, NICE recommends to [7]:

- Offer the choice of intravesical BCG or radical cystectomy.
- Offer induction and maintenance intravesical BCG to people having treatment with intravesical BCG.
- If induction BCG fails (because it is not tolerated, or bladder cancer persists or recurs after treatment with BCG), NICE recommend to refer the person's care to a specialist urology multidisciplinary team.
- For people in whom induction BCG has failed, the specialist urology multidisciplinary team should assess the suitability of radical cystectomy, or further intravesical therapy if radical cystectomy is unsuitable or declined by the person, or if the bladder cancer that recurs is intermediate- or low-risk.

For the treatment of NMIBC, the DGHO recommends the following [5]:

- TURBT is indicated:
  - In patients with an incomplete TUR.
  - In patients without histopathological evidence of muscular tissue (except for pTa, low risk).
  - In pT1 tumours
  - In patients with high risk tumours (other than pTis, CIS).
- Bladder instillation therapy
  - Early bladder chemotherapy instillation can be offered after complication-free TURBT.
  - Alternatively, and only in patients with intermediate or high risk, a subsequent intravesical instillation of chemotherapy (mitomycin C or BCG) can be useful.
  - In patients with high-risk NMIBC cystectomy provides an option; if unsuitable or declined by the patient, a bladder-preserving therapy (consisting of TURBT and radiotherapy) can be offered.

Regulatory status

EMA	FDA [2, 8]
Approval status for this indication: not approved **Other indications**: none	**Approval status for this indication**: On 16 December 2022, the FDA approved Adstiladrin® (nadofaragene firadenovec-vncg), for the treatment of adult patients with high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumours. ✓ Priority review ✓ Breakthrough therapy designation ✓ Fast track designation

[1] For the European Standard Population 2013.

	✓ Orphan drug designation **Other indications**: none

Manufacturer [9]

Adstiladrin® is manufactured by Ferring Pharmaceuticals A/S.

Costs

Currently, there is no cost information available for the European Market.
According to ICER, the annual drug cost will be $164,337.00 (the estimated annual price for nadofaragene firadenovec was assumed to be the annual price of pembrolizumab) [10].

Posology [2]

- Adstiladrin® is administered once every three months into the bladder via a urinary catheter.

Warnings and precautions [11]

- **Delaying cystectomy** could lead to the development of metastatic bladder cancer, which can be lethal.
- **Risk of disseminated adenovirus infection:**
  - Persons who are immunocompromised or immunodeficient may be at risk for disseminated infection from Adstiladrin® due to low levels of replication-competent adenovirus.
  - Avoid Adstiladrin® exposure to immunocompromised or immunodeficient individuals.

Study characteristics [1, 12, 13]

Trial name/identifier	n	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
NCT02773849	157 (2 cohorts by diagnosis at enrolment)[2]	75 mL nadofaragene firadenovec (3×10^{11} viral particles per mL) by intravesical administration through a urinary catheter[3]. Repeat dosing at months 3, 6, and 9 was done in the	-	Complete response (CR: defined as negative urine cytology and cystoscopy as assessed by the treating physician) at any time in patients with CIS (with or without a high-grade Ta or T1 tumour)	**CIS cohort:** 19.7 months (IQR: 16.0-24.8) **High-grade Ta or T1 cohort:** 20.2 months (IQR: 17.2-25.5)	**Ongoing[4],** multicentre, single-arm, open-label, repeat-dose, clinical phase 3[5] study	-	FKD Therapies Oy[6]	NCT02773849 [1]

[2] **CIS cohort** (n=107): patients with CIS with or without concomitant high-grade Ta or T1 NMIBC; **High-grade Ta or T1 cohort** (n=50): patients with high-grade Ta or T1 tumours without concomitant CIS.
[3] At enrolment, all visible tumours were required to be resected, and patients with T1 disease on transurethral resection of bladder tumour had an additional transurethral resection 14–60 days before study treatment. Obvious areas of CIS were also fulgurated before beginning study treatment, which was standard practice before BCG administration at all centres. After administration, the medication was left in the bladder for 1 h, while patients were asked to rotate positions to maximise bladder surface exposure. Patients received appropriate supportive care as needed, including pre-treatment anticholinergic therapeutic agents on each instillation dosing day to minimise irritative voiding symptoms. Dosing of anticholinergics was not standardised and was at the discretion of the treating physician (or could be omitted if contraindicated).
[4] NCT02773849 is currently **ongoing**; estimated study completion date is 06/2023.
[5] The single-arm study design was based on the 2018 Food and Drug Administration (FDA) guidance that single-arm trials are appropriate for assessment of therapies for patients with BCG-unresponsive non-muscle-invasive bladder cancer because of the paucity of effective available medical therapies, the only alternative being radical cystectomy.
[6] The funders had no role in study design, data collection, analysis, interpretation, or writing of the report.

		absence of high-grade recurrence.							

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (all enrolled patients)
❖ Age: ≥18 years ❖ Persistent CIS, high-grade Ta tumours or high-grade T1 tumours at 6 months despite receiving adequate BCG therapy ❖ Recurrences of high-grade Ta or T1 NMIBC within 6 months, CIS within 12 months of disease-free state after BCG ❖ Persistent high-grade Ta or CIS or progression to T1 disease after BCG ❖ ECOG performance status of ≤2 ❖ Life expectancy of ≥2 years	❖ Upper urinary tract disease ❖ Urothelial carcinoma within the prostatic urethra ❖ Lympho-vascular invasion ❖ Micropapillary disease ❖ Hydronephrosis	❖ **Median age, years (IQR)**: 71 (66-77) ❖ **Male sex, %**: 82 ❖ **Time from initial diagnosis of bladder cancer, months (IQR)**: 18 (13-29) ❖ **Patients were heavily pre-treated**: 50% of patients had previously received at least 3 courses of BCG ❖ **Stage at baseline, %**: CIS only (52), Ta (22), Ta + CIS (13), T1 (10), T1 + CIS (3) ❖ **ECOG Status, %**: 0 (89), 1 (8), 2 (3)

Efficacy (n=151[7])	Safety (I vs. C)
Data analysis cut-off (July 8, 2019) **CIS cohort (n=103):** **CR:** 53.4% (95% CI, 43.3-63.3); all complete responses noted at month 3 **Median duration of CR**: 9.69 months (95% CI, 9.17-NE); with 24.3% (95% CI, 16.4-33.7) remaining high-grade recurrence-free at 12 months **45.5%** of patients with an initial CR remained free from high-grade recurrence at **12 months** **71%** developed recurrent high-grade NMIBC and 5% progressed to detrusor muscle invasion (grade pT2 or higher)[8]. **High-grade Ta or T1 cohort (n=48):** **High-grade recurrence-free at month 3**: 72.9% (95% CI, 58.2-84.7) **Recurrence-free at month 12:** 43.8% (95% CI,29.5-58.8); 60% of patients **maintained** that status at 12 months **Median duration of high-grade recurrence-free survival**: 12.35 months (95% CI, 6.67-NE) 48% had a biopsy-proven recurrence of high-grade NMIBC during follow-up, 2% died of a non-bladder cancer-related cause (with no evidence of recurrence), and 6%[9] progressed to MIBC. **Overall population (n=151):** **Recurrences of any stage**: 69% **High-grade recurrence-free survival at 1 year:** 30.5% (95% CI, 23.2–38.5)	**AEs, n (%)**: 146/157 (93%) **Study drug-related AEs, n (%)**: 110/157 (70%) **Grade 3 or 4 AEs, n (%)**: 29/157 (18%); of whom 6 (4%) had events that were study drug-related[10] A **grade 4 event** of sepsis was considered study drug-unrelated but was procedure-related. **Grade 5 AEs, n**: 0 **Serious AEs, n (%)**: 14/157 (9%); of which 3 (2%) were designated related to drug or procedure[11] **AE-related discontinuation of study drug, n**: 3[12] **Deaths during long-term follow-up when the patients were off treatment, n (%):** 5/157 (3%)[13]

[7] 6 patients did not meet the definition of BCG-unresponsive NMIBC and were therefore excluded from efficacy analyses; the remaining 151 patients were included in the per-protocol efficacy analyses.
[8] 3/5 patients who progressed to MIBC had a history of T1 NMIBC at trial entry, 2% had recurrence with CIS (one at month 3 and one at month 9; these 2 patients had occult pT2 tumour identified at radical cystectomy).
[9] Of these 3 patients (6%), 2 were identified with occult MIBC at radical cystectomy (one of whom had recurrence at month 9 with CIS and was found to have pT2bNo MIBC at time of cystectomy, and the other was found to have pT2aNo MIBC after cT1 NMIBC recurrence at month 12.
[10] Micturition urgency (n=2), bladder spasms (n=1), urinary incontinence (n=1), syncope (n=1), and hypertension (n=1).
11 The aforementioned events of syncope and sepsis and one case of haematuria.
[12] Bladder spasms (n=1), discharge around the catheter during instillation (n=1), identification of a urothelial hyperplasia that was believed by the investigators to be related to the study drug (n=1).
13 Secondary to a cardiac event (n=3), pneumonia (n=1), cause of death unknown (n=1); All 5 deaths occurred at least 4 months after the last administration of the study drug.

Cystectomy by the month 12 data cut-off: 26% (29% in the CIS cohort, median time to cystectomy of 8.87 months and 21% in the high-grade Ta or T1 cohort, median time to cystectomy of 8.31 months)
24-month cystectomy-free survival: 64.5% (95% CI, 53.6–73.4)
Post-hoc explanatory analysis:
CIS cohort: Patients who achieved a CR had a **significantly longer median time to cystectomy**: 11.35 months (IQR 7.67–14.93), compared with those who did not (6.36 months, IQR 4.17–10.64, p=0.043).
High-grade Ta or T1 cohort: Patients who were free of high-grade recurrence at month 3 had **significantly longer median time to cystectomy**: 12.42 months (IQR 9.79–14.32) than did those with high-grade recurrence at month 3 (5.31 months, 4.37–6.06; p=0.0095).

Pathological data (n=149):
12.5% of patients were **upstaged** to muscle-invasive or extravesical disease at cystectomy.
Among 30 patients in the CIS cohort who **underwent cystectomy**, 3.3% (n=1) was **downstaged** to pTo and 10% (n=3) were **upstaged** to pT2 or greater, including 1 patient with pT2N1 disease who had recurrence with CIS after nadofaragene firadenovec and progressed after subsequent treatment with pembrolizumab. 2/3 patients also had history of cT1 NMIBC before entering the trial with CIS.
Of 10 patients in the high-grade Ta or T1 cohort who underwent cystectomy, 40% (n=4) had occult CIS present in the cystectomy specimen, and 20% (n=2) were identified with occult MIBC.
24-month OS rate: 91.9% (95% CI, 80.9–96.7) in all patients who received at least one dose, 91.2% (95% CI, 74.7–97.1) in the CIS cohort, and 93.5% (95% CI, 75.0–98.5) in the high-grade Ta or T1 cohort.
6 deaths overall: 4 in the CIS cohort and 2 in the high-grade Ta or T1 cohort

Patient-reported outcomes

Evaluation of patient-reported outcomes (PROs) is not provided in this trial.

ESMO-MCBS version 1.1 [14]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Not applicable due to the primary outcome of the study (CR).											

Risk of bias - study level (case series) [15]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	yes[14]	yes	yes	yes	no[15]
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	no	yes	yes	unclear[16]	yes

[14] The patients entered the study at different stages of disease at baseline but were enrolled into two cohorts by diagnosis.
[15] The cytopathologist was not masked to the study and no centralised pathology review was done for enrolment or cytology assessment.
[16] NCT02773849 is currently ongoing.

Overall risk of bias: moderate

Ongoing trials[16]

NCT number/ trial name	Description	Estimated study completion date	Link
NCT02773849	Please see above.	06/2023	[13]
NCT05704244	A phase 3, open label trial to evaluate the safety and efficacy of FE 999326 administered intravesically to Japanese subjects with high-grade, BCG unresponsive, **NMIBC.**	12/2028	[17]
NCT03710876/ INFINITE	A phase 3, open-label, randomised, parallel group study to evaluate the efficacy and safety of intrapleural administration of adenovirus-delivered interferon alpha-2b (rAd-IFN) in combination with celecoxib and gemcitabine in patients with **malignant pleural mesothelioma**.	11/2024	[18]

Available assessments

- 2 assessments, evaluating the (cost-)effectiveness of nadofaragene firadenovec were identified via ICER [10]:
  - The effectiveness and value of nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab for BCG-unresponsive non-muscle-invasive bladder cancer. A summary from the Institute for Clinical and Economic Review's Midwest Comparative Effectiveness Public Advisory Council [19].
  - Cost-Effectiveness of Nadofaragene Firadenovec and Pembrolizumab in Bacillus Calmette-Guérin Immunotherapy Unresponsive Non–Muscle Invasive Bladder Cancer [20].
- Currently, there are no assessments available from NICE, CADTH and G-BA.

Other aspects and conclusions

- In NCT02773849, patients aged ≥18 years, with BCG-unresponsive NMIBC and an ECOG status of ≤2 were included. Adstiladrin® is **not** approved for this indication by the **EMA**, but by the FDA since December 2022.
- Patients with upper urinary tract disease, urothelial carcinoma within the prostatic urethra, lympho-vascular invasion, micropapillary disease, or hydronephrosis were excluded from the study [1].
- Due to the fact that NCT02773849 is currently ongoing [13], there is **no final analysis data** available. According to the study protocol, long term survival data and information regarding invasive disease and cystectomy will be collected from all patients that received at least one dose of Adstiladrin® for up to 4 years from first dose.
- There is **no quality of life (QoL)/PROs data** provided in NCT02773849.
- Due to the given **primary endpoint (CR)**, the ESMO-MCBS form 3 for single-arm studies is currently not applicable.
- The open-label-design, the ongoing status (no final analysis data) and the partially different stages of disease when patients entered the study **increase the risk of bias of the study**.
- Of note, NCT02773849 is a single-arm trial focussing on the evaluation of surrogate parameters. Even though OS is a secondary endpoint of NCT02773849, robust OS and PFS data from further trials are required.
- There is an ongoing phase 3 trial to evaluate the safety and efficacy of Adstiladrin® administered intravesically to Japanese subjects with high-grade, BCG unresponsive NMIBC. The study is currently recruiting patients and is estimated to be completed in 2028 [17].
- Besides, there is an ongoing trial to evaluate intrapleural administration of rAd-IFN in combination with Celecoxib and Gemcitabine in patients with histologically confirmed **malignant pleural mesothelioma** who have failed a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen. The estimated study completion date of NCT03710876 is 11/2024 [18]. Adstiladrin® is **not** approved for this indication by the EMA and the FDA.

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Abbreviations: AE=adverse event, AJ=adjustment, BGC=Bacillus Calmette-Guérin, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CIS=carcinoma in situ, CR=complete response, DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie, =ECOG=Eastern Co-operative Oncology Group, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MIBC=muscle-invasive bladder cancer, MG=median gain, n=number of patients, NICE=National Institute for Health and Care Excellence, NMIBC=non-muscle- invasive bladder cancer, OS=overall survival,

PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PROs=patient-reported outcomes, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TUR=transurethral resection, TURB=trans urethral resection of bladder tumour

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