CLINICAL TRIAL PROTOCOL

A phase 2, 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)

Trial Code: 000434

ABLE-22
(Adstiladrin in BLadder cancEr, phase 2, clinical trial no. 2)

EU Clinical Trial Number:	2024-512177-27-00
IND Number:	012,547
UTN Number:	U1111-1299-0176
Investigational Medicinal Product:	Nadofaragene firadenovec, suspension for instillation Gemcitabine, solution for instillation Docetaxel, solution for instillation Pembrolizumab, solution for injection, for intravenous use
Indication:	Treatment of adult patients with high-risk Bacillus Calmette-Guerin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours
Phase:	2
Name and Address of Sponsor:	Ferring Pharmaceuticals A/S Amager Strandvej 405 2770 Kastrup Denmark Telephone number: +45 88 33 88 34
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A phase 2, 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)

SIGNATORY INVESTIGATOR

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TRIAL SITE(S)

Sites: Approximately 40-75

Countries/regions: United States (US), Canada and Europe. Additionally, sites in Asia and Australia may be included.

PLANNED TRIAL PERIOD

The estimated timelines are:

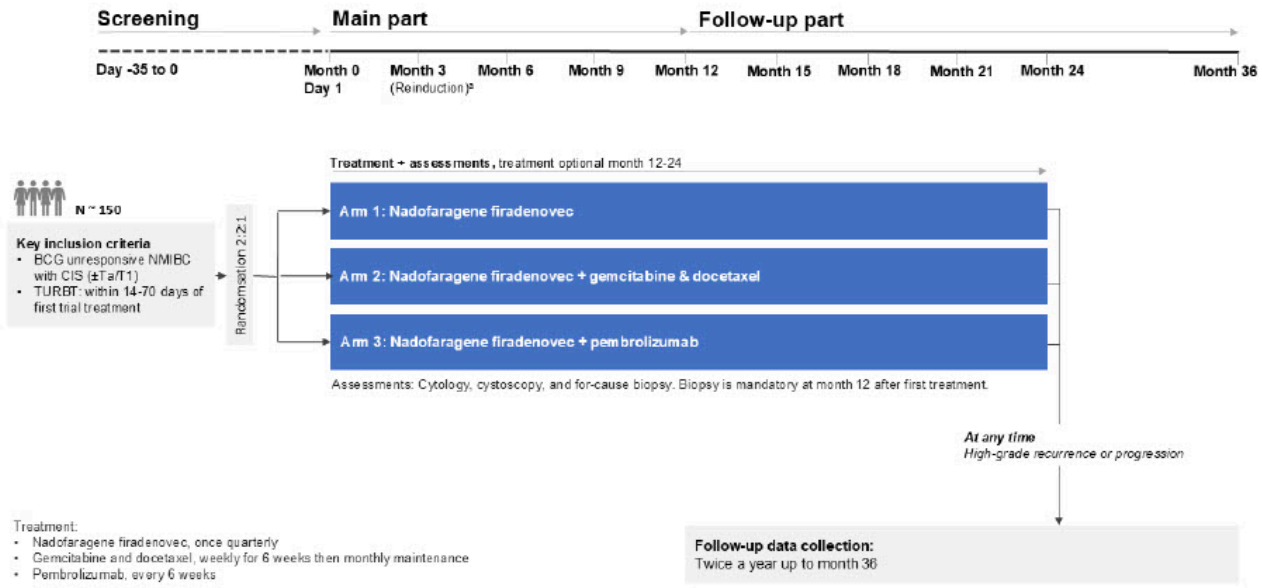
- First Subject First Visit (FSFV): Q4 2024-Q1 2025
- Last Subject Last Visit (LSLV) for main part: Q1-2 2027
- LSLV for the trial: Q1-2- 2029

CLINICAL PHASE

2

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

This trial will evaluate the safety and efficacy, including reinduction, of intravesical instillation of nadofaragene firadenovec in subjects with high-grade Bacillus Calmette-Guerin (BCG) unresponsive non-muscle-invasive bladder cancer (NMIBC) with carcinoma in situ ([CIS] (with or without papillary tumours). This will be evaluated in 3 treatment arms:



Abbreviations: BCG, Bacillus Calmette-Guerin; CIS, carcinoma in situ; NMIBC, non-muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumour.
Note: Months indicate time-point of each nadofaragene firadenovec instillation. Assessments are done quarterly up to 14 days prior to each nadofaragene firadenovec instillation.
a) Reinduction is offered at month 3 to subjects with presence of CIS, and/or high-grade Ta, and absence of any T1 or progression to T2 or higher, following a TURBT/biopsy.

Figure 3-1 Trial Design Overview

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

The trial population consists of adult male and female subjects with BCG-unresponsive NMIBC with CIS ± high-grade Ta/T1 disease.

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for participation in the trial.

4.1.1 Inclusion Criteria

1. Signed informed consent obtained before beginning any trial-related procedures
2. Diagnosed, as documented, with carcinoma in situ (CIS) ±Ta/T1 high-grade disease
   - For T1 disease biopsies should contain muscle fibres
3. Unresponsive to ≥2 courses of Bacillus Calmette-Guerin (BCG) therapy within the last 12 months. BCG-unresponsive refers to subjects with high-grade non-muscle-invasive bladder cancer (NMIBC) who are unlikely to benefit from and who will not be receiving further intravesical BCG. The term "BCG-unresponsive" includes subjects who did not respond to BCG treatment and have a persistent high-grade recurrence within 12 months after BCG was initiated, and those who despite an initial complete response (CR) to BCG, relapse with CIS within 12 months of their last intravesical treatment with BCG or relapse with high-grade Ta/T1 NMIBC within 6 months of their last intravesical treatment with BCG. The following criteria define the subjects who may be included in the trial:
   - Have received at least 2 courses of BCG within a 12-month period – defined as at least 5 of 6 induction BCG instillations and at least 2 of 3 instillations of maintenance BCG, or at least 2 of 6 instillations of a second induction course, where maintenance BCG is not given.
     - Exception: those who have T1 high-grade disease at 1st evaluation after induction BCG alone (at least 5 of 6 doses) may qualify in the absence of disease progression
   - At the time of tumour recurrence, subjects with CIS alone or high-grade Ta/T1 with CIS should be within 12 months of last exposure to BCG
   - No maximum limit to the amount of BCG administered
   - All visible papillary tumours must be resected and those with persistent T1 disease on transurethral resection of bladder tumour (TURBT) should undergo an additional re-TURBT within 14 to 70 days prior to beginning trial treatment. Obvious areas of CIS should also be fulgurated
4. Eastern Cooperative Oncology Group (ECOG) status ≤2
5. Aged ≥18 years at the time of consent
6. Available for the whole duration of the trial
7. Life expectancy >2 years, in the opinion of the investigator

8. Absence of concomitant upper tract urothelial carcinoma or urothelial carcinoma within the prostatic urethra. Freedom from upper tract disease (if clinically indicated) as indicated by no evidence of upper tract tumour by either intravenous pyelogram, retrograde pyelogram, computed tomography (CT) scan with or without urogram, or magnetic resonance imaging (MRI) with or without urogram performed within 6 months of enrolment. Absence of locally advanced disease as assessed by CT scan or MRI
9. Subjects who elect not to undergo cystectomy
10. Subjects with prostate cancer on active surveillance at low risk for progression are permitted to be included into the trial at the discretion of the investigator (see exclusion criterion 16)
11. Female subjects of reproductive potential must be willing to use effective contraception during treatment with investigational medicinal product(s) (IMP([s]) and for 6 months following the last dose and must have a negative urine or serum pregnancy test upon entry into this trial. Otherwise, female subjects must be postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile. Effective contraception means that the subject, if sexually active, should be using a combination of 2 methods of birth control that are approved and recognised to be effective by regulatory agencies
12. Male subjects with female partners of reproductive potential must be surgically sterile or willing to use effective contraception during treatment with IMP(s) and for 3 months following the last dose. Effective contraception is specified in inclusion criterion 11
13. Adequate laboratory values:
    - Haemoglobin ≥10 g/dL
    - White blood cells (WBC) ≥3800/µL
    - Absolute neutrophil count (ANC) ≥2000/µL
    - Platelet count ≥100,000/µL
    - International normalised ratio (INR)[a] below institutional upper limit of normal (ULN)
    - Activated partial thromboplastin time (aPTT)[a] below institutional ULN
    - Aspartate aminotransferase (AST) ≤1.5 x ULN
    - Alanine aminotransferase (ALT) ≤1.5 x ULN
    - Total bilirubin ≤1.5 x ULN
    - Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2

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

4.1.2 Exclusion Criteria

1. Current or previous evidence of muscle-invasive (muscularis propria) or metastatic disease presented at the screening visit. Examples of increased risk of muscle-invasive disease include but are not limited to:
   - Presence of lymphovascular invasion and / or micropapillary, sarcomatoid, plasmacytoid and / or neuroendocrine disease as shown in the histology of the biopsy sample
   - Subjects with CIS+T1 disease accompanied by the presence of hydronephrosis secondary to the primary tumour
2. Current systemic therapy for bladder cancer other than IMP used in randomisation arm
3. Current or prior investigational treatment for BCG-unresponsive NMIBC or any other investigational drug (drug used in a clinical trial, i.e drug used in a Ferring sponsored non-interventional study does not apply) within 1 month prior to screening
4. Current or prior pelvic external beam radiotherapy within 5 years of screening
5. Prior treatment with nadofaragene firadenovec at any time
6. Prior systemic therapy for bladder cancer at any time
7. Prior intravesical chemotherapy for the treatment of BCG-unresponsive NMIBC (see exclusion criterion 19)
8. Use of other adenovirus vector-based drugs, e.g. COVID-19 vaccines, within 14 days before and after nadofaragene firadenovec instillation
9. Suspected hypersensitivity or immune-mediated reactions to any of the IMPs
10. Current or prior autoimmune disease
11. Immunocompromised, or immunodeficient, or undergoing any form of treatment known to cause immunosuppression
12. Symptomatic urinary tract infection or bacterial cystitis (once satisfactorily treated, subjects can enter the trial)
13. Clinically significant and unexplained elevated liver or renal function tests
14. Female subjects who are pregnant or lactating or refuse to commit to use contraception during the trial
15. Any other significant disease or other clinical findings which in the opinion of the investigator would prevent trial entry
16. History of malignancy of other organ system within past 5 years, except treated basal cell carcinoma or squamous cell carcinoma of the skin and ≤pT2 upper tract urothelial carcinoma at least 24 months after nephroureterectomy. Also subjects with genitourinary cancers other than urothelial cancer or prostate cancer, and subjects with renal mass ≤3 cm that are under active surveillance are excluded (see inclusion criterion 10)

17. Subjects who cannot hold instillation for 1 hour

18. Subjects who cannot tolerate intravesical dosing or intravesical surgical manipulation

19. Intravesical therapy within 8 weeks prior to beginning IMP with the exception of:

- Cytotoxic agents (e.g., Mitomycin C, doxorubicin, epirubicin and gemcitabine) when administered as a single instillation immediately following a TURBT procedure, which is permitted within 70 days prior to beginning trial treatment
- Previous intravesical BCG therapy, which can be given ≥5 weeks prior to the biopsy that is required for trial entry

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

The participating subjects will be recruited among the patients attending the clinics included in the trial. Advertisements may be used if approved by the local ethics committee and regulatory authorities, as applicable according to local regulations.

4.2.2 Screening

A screening number is automatically assigned by the electronic data capture system (EDC) to each subject who has signed the informed consent form. A subject must always be assigned to the lowest available screening number at each site. Once a screening number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the trial. If a screening number is allocated incorrectly, the trial monitor must be notified as soon as the error is discovered. The investigator must maintain a subject screening log for all screened subjects including screening failures.

Assessments that do not meet the inclusion and exclusion criteria may be repeated once if this can be medically justified, at the discretion of the investigator.

4.2.3 Randomisation

Randomisation should occur no more than 14 days before the first IMP dose and allow 10 days for shipment. Randomisation may be scheduled closer to the subject's first dose if the site has IMP(s) supply to administer the first dose (of each IMP). It may be done in absentia, if a negative pregnancy test and subject eligibility has been confirmed. Subjects will be informed of randomisation allocation on M0D1.

Subjects will be randomised according to all of the below:

- In strata defined by region (US vs non-US) and type of disease (CIS alone or CIS with Ta/T1) at trial enrolment
- In a 2:2:1 ratio to 1 of 3 treatment arms (Section 3.1.2)
- Using a computer-generated randomisation list prepared by Ferring Global Biometrics Department