CLINICAL TRIAL PROTOCOL

A Phase 3b, Randomised, Controlled Trial of Nadofaragene Firadenovec vs. Observation in Subjects with Intermediate Risk (IR) Non-Muscle Invasive Bladder Cancer (NMIBC)

Trial Code: 000423

ABLE-32

Adstiladrin in **BL**adder canc**E**r, phase **3**b, clinical trial no. **2**

IND Number:	12,547
EU Clinical Trial Number:	2024-512029-10-00
UTN Number:	U1111-1284-0685
Investigational Medicinal Product:	Nadofaragene firadenovec, suspension for intravesical instillation
Indication:	Intermediate risk, non-muscle invasive bladder cancer
Phase:	3b
Name and Address of Sponsor:	Ferring Pharmaceuticals A/S Amager Strandvej 405 DK 2770 Kastrup Denmark
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A phase 3b, Randomised, Controlled Trial of Nadofaragene Firadenovec vs. Observation in Subjects with Intermediate Risk (IR) Non-Muscle Invasive Bladder Cancer (NMIBC)

ABLE-32 (**A**dstiladrin in **BL**adder canc**E**r, phase **3**b, clinical trial no. **2**)

SIGNATORY INVESTIGATOR

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TRIAL SITES

Approximately 100 sites in the United States (US). Additional countries/regions may also be included, such as Canada, Australia, Europe, and Asia.

PLANNED TRIAL PERIOD

- First subject first visit: Q3 2024
- Last subject last visit up to month 24 (treatment period):
  - If 454 subjects are randomised: Q2 2028
  - If 1,100 subjects are randomised: Q2 2030
- Last subject last visit (full length of the trial):
  - If 454 subjects are randomised: Q2 2031
  - If 1,100 subjects are randomised: Q2 2033

CLINICAL PHASE

3b

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

Nadofaragene firadenovec is a replication-deficient recombinant type 5 adenovirus vector containing the human interferon-α2b (IFN-α2b) gene and the excipient Syn3NODA.

Nadofaragene firadenovec was developed 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 tumors. Nadofaragene firadenovec is instilled quarterly into the bladder by intravesical instillation to deliver the IFN-α2b gene into the

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

A subject must meet all the following criteria to be eligible to participate in this trial.

1. Willing and able to provide written consent for the trial, obtained prior to any trial-related procedures
2. Age 18 years or older at the time of consent
3. Newly diagnosed or recurrent intermediate risk (IR) non-muscle invasive bladder cancer (NMIBC) at screening as defined by American Urological Association (AUA)/Society of Urologic Oncology [SUO] Guideline (2020)
4. Has undergone complete transurethral resection of bladder tumor (TURBT; with or without peri-operative intravesical chemotherapy) within 60 days prior to randomization, with 1 of the following confirmed by a diagnostic pathology report (which should indicate whether lamina propria and muscularis propria are present as well as the degree of involvement, if present):
   - Recurrence within 1 year, low-grade Ta
   - Solitary low-grade Ta >3 cm
   - Low-grade Ta, multifocal[a]
   - Solitary high-grade Ta, ≤3 cm
   - Low-grade T1[a]

   [a]Restage TURBT may be done at the discretion of the investigator.
5. Must adhere to applicable (regional or national) policies and procedures for the management and control of COVID-19
6. Life expectancy of >2 years
7. Have a normal upper urinary tract (as evidenced by ultrasound, computed tomography (CT) urography or other appropriate test within 1 year prior to randomization) and no evidence of tumor in prostatic urethra
8. Eastern Cooperative Oncology Group (ECOG) status of 2 or less
9. Subjects with prostate cancer on active surveillance at low risk for progression, defined as prostate-specific antigen (PSA) <10 ng/mL, Gleason score 6 and cT1 are permitted to be included into the trial at the discretion of the investigator
10. Subjects with prostate cancer which has previously been treated with radiation therapy are eligible, if the radiation therapy was complete at least 1 years prior to randomization and the subject has remained disease free
11. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of investigational medicinal product (IMP). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required

12. Female subjects of reproductive potential must be willing to use effective contraception during treatment with IMP 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.
13. Male subjects with female partners of reproductive potential must be surgically sterile or willing to use effective contraception during treatment with IMP and for 3 months following the last dose. Effective contraception is defined in inclusion criterion 12.
14. Adequate laboratory values defined as:
    - Hemoglobin ≥9 g/dL, without transfusion or erythroprotein dependency
    - White blood cells (WBC) ≥4 x 10^9/L
    - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    - Platelets ≥75 x 10^9/L
    - International Normalised Ratio (INR) or Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) ≤1.5 x upper limit of normal (ULN), unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
    - Aspartate aminotransferase (AST) ≤1.5 x ULN
    - Alanine aminotransferase (ALT) ≤1.5 x ULN
    - Total bilirubin ≤1.5 x ULN
    - Calculated creatinine clearance ≥30ml/min
    - Estimated glomerular filtration rate (eGFR) ≥30ml/min/1.73m^2

Inclusion criteria 3 and 4 are considered key.

Exclusion Criteria

A subject who meets any of the following criteria will be excluded from this trial.

1. Current or previous evidence of muscle-invasive (muscularis propria) or metastatic disease presented at the screening visit
2. High-risk NMIBC defined as:
    - High-grade T1
    - Any recurrent, high-grade Ta
    - High-grade Ta >3 cm (or multifocal)

- Any carcinoma in situ (CIS)
- Any Bacillus Calmette-Guérin (BCG) failure in high-grade subject
- Any variant histology
- Any prostatic urethral involvement

3. Low-risk NMIBC defined as:
   - First occurrence of low-grade solitary Ta ≤3 cm
   - Recurrence of low-grade solitary Ta ≤3 cm >12 months from previous occurrence
   - Papillary urothelial neoplasm of low malignant potential
4. Current systemic therapy for bladder cancer
5. Has significant urinary incontinence or known bladder instability
6. Current or prior pelvic external beam radiotherapy within 1 year of randomization
7. Use of other adenoviral vector-based medication, e.g. COVID-19 vaccines, within 2 weeks before and after IMP instillation
8. Current or prior use of nadofaragene firadenovec
9. Suspected hypersensitivity to interferon-α2b
10. Has an active or intractable infection requiring systemic therapy
11. Clinically significant and unexplained elevated liver tests
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening until 6 months (females) or 3 months (males) after the last IMP dose
13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator
14. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include:
    - Prior malignancy that has not progressed nor required active treatment in the past 2 years
    - Basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer
15. Cannot hold instillation for 1 hour

16. Peri-operative intravesical therapy during screening, except for any of the following: mitomycin C, doxorubicin, gemcitabine, or epirubicin when administered as a single instillation immediately following or within 24 hours after TURBT pre-trial or during screening (pre-trial/screening TURBT)
17. Any adjuvant pre-trial intravesical therapy within 8 weeks prior to beginning trial treatment except for the peri-operative intravesical therapy described in criterion 16
18. Any pre-trial adjuvant intravesical therapy > 8 weeks prior to beginning trial treatment, including induction and maintenance therapy, except any of the following:
    - 1 intravesical chemotherapy induction course (once weekly for 6 weeks) related to a prior occurrence of NMIBC administered within 12 months prior to pre-trial/screening TURBT
    - 1 intravesical induction course of BCG (once weekly for 5-6 weeks) related to a prior occurrence of NMIBC administered within 12 months prior to pre-trial/screening TURBT
19. Prior or current investigational therapy for NMIBC within 28 days or randomization
20. Immunocompromised persons, including those receiving immunosuppressant therapy, may be at risk for disseminated adenovirus infection because of the possible presence of low levels of replication-competent adenovirus in nadofaragene firadenovec. Individuals who are immunosuppressed or immune-deficient should not come into contact with nadofaragene firadenovec.
21. Has active uncontrolled clinically significant cardiovascular disease
22. Has known active Hepatitis B (e.g. HbsAg reactive) or Hepatitis C (e.g. Hepatitis C virus ribonucleic acid [qualitative] is detected)
23. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial
24. Concomitant participation in any other interventional studies, in which subject has received trial treatment (or used an investigation device), within 28 days of randomization

MEDICINAL PRODUCT

Nadofaragene firadenovec (3×10^{11} vp/mL), 75 mL suspension for quarterly intravesical installation, is a replication-deficient recombinant type 5 adenovirus vector containing the human interferon-α2b (IFN-α2b) gene and the excipient Syn3NODA.

DURATION OF TREATMENT

Treatment with nadofaragene firadenovec for up to 24 months in the absence of NMIBC disease recurrence or progression.

STATISTICAL METHODS

In total, 454 randomised subjects are required to accrue 163 events and achieve 90% power to yield a statistically significant (at α=0.025 1-sided test for superiority) difference between the