NUMBER OF SUBJECTS

Total (Subjects Randomized)	Arm 1: Nadofaragene Firadenovec	Arm 2: Observation
454	227	227

An unblinded sample size reassessment will be performed during the conduct of the trial with the possibility to increase the sample size up to a maximum of 1,100 subjects.

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[a]):
   - Low-grade Ta, <12 months
   - Low-grade Ta, solitary and >3 cm
   - Low-grade Ta, multifocal[b]
   - High-grade Ta, solitary and ≤3 cm
   - Low-grade T1[a,b]

   [a] Patients with T1 disease should undergo resection at the base of the lesion and biopsies should contain muscle fibres.

   [b] 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 2 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. Females of reproductive potential must meet 1 of the following conditions:

    - Have a negative highly sensitive urine or serum pregnancy test upon entry into this trial and be willing to use highly effective contraception[a] during treatment with the IMP and for 6 months following the last dose.

      For sites in **Japan only**, contraception should be approved in Japan.

    - Be postmenopausal (no menstrual period for a minimum of 12 months, as confirmed by follicle-stimulating hormone levels).

      For sites in **Japan only**, postmenopausal women should be 45 years or older.

    - Be surgically sterile[b].

      [a] Highly effective methods of contraception include: combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, and sexual abstinence.
      Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the female subject and that the vasectomised partner has received medical assessment of the surgical success.
      Sexual abstinence is defined as refraining from heterosexual intercourse. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

      [b] The methods acceptable for surgical sterility are hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
13. Male subjects must be willing to use a male condom and effective contraception during sex throughout the treatment period 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 erythropoietin 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 2 years 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. Any intravesical therapy within 8 weeks prior to randomization, except any of the following: mitomycin C, doxorubicin, gemcitabine, epirubicin, or pirarubicin, when administered as a single peri-operative intravesical 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 more than 8 weeks prior to randomization, except any of the following:
    - Peri-operative single instillation intravesical therapy related to a prior occurrence(s) of NMIBC
    - 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

18. Prior or current investigational therapy for NMIBC within 28 days or randomization
19. 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.
20. Has active uncontrolled clinically significant cardiovascular disease
21. Has known active Hepatitis B (e.g. HbsAg reactive) or Hepatitis C (e.g. Hepatitis C virus ribonucleic acid [qualitative] is detected)
22. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial
23. 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 instillation, 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 randomized 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 arms. This is based on assuming a true hazard ratio of 0.6 (of nadofaragene firadenovec relative to observation), a recurrence rate of 45% by month 24 in the observation arm, a dropout rate of 10% by month 24 in both treatment arms, and 1:1 randomization.

The primary efficacy endpoint, RFS, will be analyzed via a stratified log-rank test based on the intention-to-treat (ITT) analysis set, defined as all randomized subjects. Subjects will be included in the analysis according to the planned (randomized) intervention.

The null hypothesis tested with the log-rank test is that the 2 treatment arms have identical hazard functions. The alternative hypothesis is that the hazard function is lower for the nadofaragene