- Do not receive treatment due to any of the following reasons:
  - HG disease or progression
  - Completion of month 24 visit

Follow-up data will be collected on SAEs, type and frequency of bladder cancer therapy, overall survival, lesion development (including pathological staging) in the bladder, upper tract and/or prostatic urethra and, date of cystectomy and pathological staging at cystectomy.

Disease Evaluation

Evidence of disease will be assessed using urine cytology, cystoscopy and for-cause biopsy during the treatment period. Biopsy is mandatory at month 11 day 15, i.e. 12 months after first IMP treatment.

The assessments will be done once quarterly up to 14 days prior to next scheduled instillation with nadofaragene firadenovec.

End-of-treatment Assessments

Subjects discontinued from treatment will have end-of-treatment assessments preferably within 30 days of the decision to withdraw. The subjects will be offered other treatment (e.g., standard therapy) at the discretion of the investigator.

NUMBER OF SUBJECTS

Per previous protocol versions, a total sample size of 250 subjects in a 2:2:1 randomization ratio was planned (Arm 1: 100 subjects, Arm 2: 100 subjects, and Arm 3: 50 subjects). Following the DMC recommendation to stop randomising subjects into Arm 3, the sponsor has elected to close further enrolment into Arm 3 and maintain the sample size of n=100 subjects in Arms 1 and 2.

CRITERIA FOR INCLUSION / EXCLUSION

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 within 6 months of enrolment
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. Females must meet at least 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
    - Be postmenopausal (no menstrual period for a minimum of 12 months, as confirmed by follicle-stimulating hormone levels)

- 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.

12. 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 10.

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)[c] 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

[c] 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.

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 2 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