Objectives	Endpoints
• To evaluate changes in PD biomarkers for UGN-501	• Cytokine and other immune cell biomarker changes in urine, tumor tissues, serum, and/or plasma
• To evaluate viral replication of UGN-501	• Viral proteins such as YPet and/or anti-YPet antibodies in urine and/or serum
• To evaluate infectivity of UGN-501	• Infectivity of UGN-501 in urine
• To evaluate penetrance of UGN-501	• Level of UGN-501 in bladder tissue
• To identify markers of response or resistance to UGN-501	• CD46 expression in tumor tissue • Immune cell, DNA, RNA, and/or protein biomarkers in tumor tissue, serum, plasma, and/or urine

ADA = anti-drug antibodies; AUC = area under the concentration-time curve; CIS = carcinoma in situ; C_{max} = maximum plasma concentration; CR = complete response; CRR = complete response rate; C_{tau} = concentration in plasma at the end of a dosing interval; DLT = dose limiting toxicity; DNA = deoxyribonucleic acid; MTD = maximum tolerated dose; NMIBC = non-muscle invasive bladder cancer; PD = pharmacodynamic(s); PK = pharmacokinetic(s); RFS = recurrence-free survival; RNA = ribonucleic acid; RP2D = recommended Phase 2 dose; $t_{1/2}$ = terminal half-life; TEAE = treatment-emergent adverse event; t_{max} = time of maximum plasma concentration.

Overall Design Synopsis

This is a Phase 1, open-label, dose-escalation, multicenter study to investigate the safety, tolerability, immunogenicity, and PK of UGN-501 administered intravesically in participants with recurrent NMIBC. The study consists of a dose-escalation phase (Part A) and may include a dose-expansion phase (Part B) based on emerging data from Part A (Section 1.2.1).

This master protocol may comprise multiple study intervention arms designed to independently investigate UGN-501 (eg, alternative formulations, schedules, and/or combination regimens). The initial study intervention is a single-arm evaluation of UGN-501.

A SRC will review emerging safety data to inform dose escalation/de-escalation decisions.

Brief Summary:

The purpose of this study is to evaluate the safety and tolerability of UGN-501 administered intravesically in adult participants with recurrent NMIBC and to determine the RP2D.

Study details include:

- The maximum duration of study participation (from first UGN-501 instillation to last visit) is approximately 15 months (Section 1.2.2).
- The maximum duration of treatment is approximately 12 months.
- The visit frequency during the Induction and Maintenance Periods is:
    - Induction Period (Weeks 1 to 12): Participants will attend UGN-501 study intervention visits once weekly for 6 weeks and a disease assessment visit at the end of the period (Week 12).

- Maintenance Period (Months 3 to 15): Participants will attend UGN-501 study intervention visits once weekly for 3 weeks, quarterly through Month 12, and quarterly disease assessment visits through Month 15.

Number of Participants: The study may enroll up to 30 participants in Part A.

Note: Enrolled means participants', or their legally acceptable representatives', agreement to participate in the clinical study following completion of the informed consent process and confirmation of eligibility. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

Study Arms and Duration:

The study consists of:

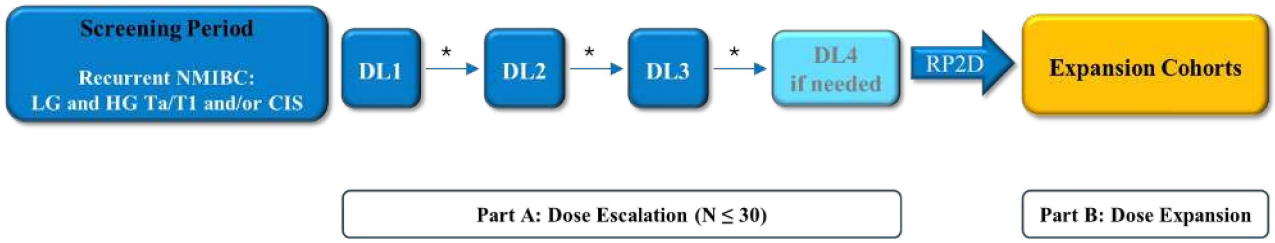
- A Screening Period of up to 28 days.
- A 12-week Induction Period during which participants will receive 6 once-weekly intravesical instillations of UGN-501 at their assigned dose level cohort.
- A Maintenance Period with a maximum duration of approximately 12 months (including the Month 15 Safety Follow-up Visit) for participants with no evidence of disease at Week 12. During this period, participants will receive 3 once-weekly intravesical instillations of UGN-501 (at the same dose administered in the Induction Period) quarterly from Month 3 and continuing through Month 12, or until disease recurrence, disease progression, or death is documented, whichever occurs first (Section 1.2.2).

Study intervention may be postponed for up to 4 weeks until resolution or improvement of significant clinical events or laboratory abnormalities (eg, UTI, irAE), if applicable.

Data Monitoring/Other Committee: Yes (SRC).

1.2 Schema

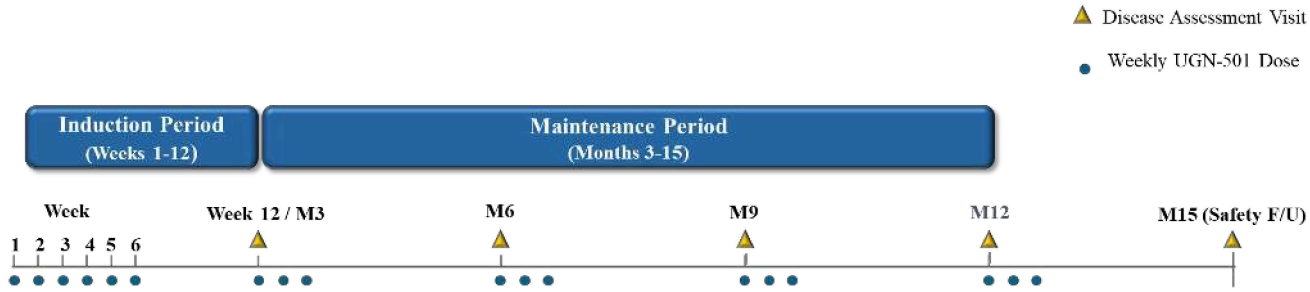
1.2.1 Overall Schema



CIS = carcinoma in situ; DL = UGN-501 dose level; LG = low-grade; HG = high-grade; NMIBC = non-muscle invasive bladder cancer; RP2D = recommended Phase 2 dose; SRC = Safety Review Committee.

* SRC informs dose escalation/de-escalation decisions.
Note: One or more expansion cohorts at the RP2D may be added by protocol amendment.

1.2.2 Dosing Schema



F/U = follow-up; M = Month.

2 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

2.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply. Refer to Section 5.4 for details on rescreening.

Age

1. Participant must be ≥ 18 years or older at the time of signing informed consent.

Type of Participant and Disease Characteristics

Participants who have:

2. Confirmed recurrent NMIBC with HG Ta/T1 disease and/or CIS, or recurrent LG Ta/T1disease.

3. HG Ta/T1 disease and/or CIS must meet one of the following criteria:

   - Have BCG-unresponsive disease, defined as 1) persistent or recurrent CIS alone or with recurrent Ta/T1 disease within 12 months of completion of adequate BCG therapy (defined below), or 2) recurrent HG Ta/T1 disease within 6 months of completion of adequate BCG therapy, or 3) HG T1 disease at the first evaluation following a BCG induction course.

     Notes: Adequate BCG therapy is defined as at least 5 of 6 doses of an initial induction course plus 1) at least 2 of 3 doses of maintenance therapy or 2) at least 2 of 6 doses of a second induction course (FDA, 2018). Participants with BCG-unresponsive disease also must be unwilling or unfit to undergo radical cystectomy.
   - Are BCG-exposed, defined as HG persistent or recurrent NMIBC within 24 months of the last dose of BCG but not meeting the definition of BCG-unresponsive disease and received at least 5 of 6 doses of an initial induction course of BCG (Roumiguié et al, 2022).
   - Are BCG intolerant, defined as the inability to tolerate at least one full induction course of BCG (Kamat et al, 2015).
   - HG Ta tumor ≤ 3 cm and failed at least 1 previous course of therapy (eg, TURBT plus adjuvant induction course of intravesical chemotherapy).

4. LG disease must meet one of the following criteria (Holzbeierlein et al, 2024):

   - Ta tumors recurring within 1 year.
   - Ta solitary tumor > 3 cm.
   - Ta multifocal tumors.
   - T1 tumors.

5. All visible papillary tumors resected and obvious areas of CIS fulgurated during Screening or within 6 weeks before Screening. Participants with T1 disease should have a re-staging TURBT during Screening or within 6 weeks before Screening.

   Note: Enhanced cystoscopy (eg, blue light cystoscopy or other locally accepted modalities) is permitted, but the same modality must be used for all subsequent disease assessments.

6. Eastern Cooperative Group performance status score ≤ 2.

7. Absence of concomitant UTUC or UC within the prostatic stroma. Freedom from upper tract disease (if clinically indicated) as indicated by no evidence of upper tract tumor by either IV pyelogram, retrograde pyelogram, computerized tomography urogram with or without contrast, magnetic resonance imaging urogram with or without contrast, or ureteroscopy with ureteral washing for cytology, performed within 6 months of enrollment. Participants with UC involving the prostatic urethra, where the carcinoma is confined to the ducts and/or epithelium, may be included after a restaging TURBT is performed to rule out more extensive disease (prostatic stroma).

8. Prostate cancer, and who after surgery or radiation do not meet the criteria for biochemical recurrence, or those on active surveillance at very low, low, or favorable risk for progression, defined as Gleason Grade Group 1 or 2, Gleason score ≤ 7, with prostate-specific antigen < 20 ng/dL, and cT1-cT2b (NCCN, 2025) are permitted in the study at the discretion of the investigator (exclusion criterion 11).

9. Adequate organ and bone marrow function within 14 days of treatment initiation as determined by routine laboratory tests outlined below:

    - Leukocytes ≥ 3000/µL (≥ 3×10^9/L).
    - Absolute neutrophil count ≥ 1500/µL (≥ 1.5×10^9/L).
    - Platelets ≥ 100,000/µL (≥ 100×10^9/L).
    - Hemoglobin ≥ 9.0 g/dL.
    - Total bilirubin ≤ 1.5 × ULN.
    - AST/ALT ≤ 2.5 × ULN.
    - ALP ≤ 2.5 × ULN.
    - Estimated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation (Cockcroft and Gault, 1976).

10. Has a life expectancy > 12 months.

Contraceptive/Barrier Requirements

11. Contraceptive use by participants or participant partners should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    a. Male participants:

    Must agree to the following during the study intervention period and for at least 12 weeks after the last study intervention instillation due to the risk of viral shedding and the potential for pregnancy in a partner of CBP (defined as premenopausal women who have not been sterilized):

    - Refrain from donating sperm.

      PLUS, either:

        - Be abstinent from sexual activity that could result in exposure to seminal fluid and agree to remain abstinent.

      OR

- Use an external condom when engaging in sexual activity with a partner. The participant should also be advised of the benefit for a partner of CBP to use an additional acceptable form of effective contraception (11b).

b. Female participants:

- Who are not pregnant or breastfeeding, and one of the following conditions applies:
  - Is of non-childbearing potential.

OR

  - Is of CBP and using 2 acceptable forms of effective contraception during the study intervention period and for at least 12 weeks after the last study intervention instillation.

    Acceptable methods of birth control considered to have a low failure rate (less than 1% per year) when used consistently and correctly include implants, injectable, combined (estrogen/progesterone) oral contraceptives, intrauterine devices (only hormonal), condoms with spermicide, sexual abstinence*, or vasectomized partner.

    * Sexual abstinence for CBP females is defined as refraining from intercourse. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is NOT an acceptable method of contraception.

- A participant of CBP must have a negative pregnancy test (serum or urine, as required by local regulations) upon entry into this study.

Informed Consent

12. Signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Diagnostic Assessments

1. Current or previous evidence of muscle invasive, locally advanced nonresectable, or metastatic UC (ie, T2, T3, T4, and/or stage IV).

Prior/Concomitant Therapy

2. Current systemic therapy for bladder cancer.

3. Prior treatment with any human adenovirus-based therapy (eg, nadofaragene firadenovec vcng [ADSTILADRIN®] or cretostimogene grenadenorepvec).

4. Intravesical therapy within 4 weeks before starting study intervention, including but not limited to BCG, chemotherapy, and nogapendekin alfa inbakicept (ANKTIVA®).

5. Has participated in a study of an investigational agent and received study therapy or received investigational device within 4 weeks before the first dose of study intervention.

6. Has received an immune modulator therapy within 5 half-lives of starting study intervention, including but not limited to, pembrolizumab, BCG, and nogapendekin alfa inbakicept.

7. Has received a vaccine or anti-viral agent within 2 weeks before starting study intervention.

Medical Conditions

8. Active infection requiring systemic therapy including UTI (once satisfactorily treated, participants can enter the study).

9. Immunocompromised state, including but not limited to, participants with HIV infection or any condition that required systemic immunosuppressive treatment in the past 2 years (eg, active systemic autoimmune disease, solid organ or stem cell transplant recipient). Short courses of steroids (≤ 14 days) for medical reasons without anticancer intent (eg, atopic dermatitis, psoriasis, infection, allergic reaction) are permitted if the last dose was ≥ 4 weeks before the first dose of study intervention.

10. Any medical psychological, familial, sociological, or geographical condition that, in the opinion of the investigator, would preclude participation in the study.

11. History of malignancy of other organ system within the past 5 years, except previously treated UTUC, basal cell carcinoma or squamous cell carcinoma of the skin, and/or prostate cancer (inclusion criterion 8).

12. Cannot tolerate intravesical dosing or intravesical surgical manipulation.

13. Has a known allergy or hypersensitivity to any of the study interventions or any of the study intervention excipients.