5. Study Population

This study will enroll male and female participants at least 18 years of age with centrally confirmed HG NMIBC with CIS (±Ta/T1).

Participants must have high-grade non-muscle invasive bladder cancer (HG NMIBC) with CIS (±Ta/T1) and be BCG-naïve, defined as:

- Never exposed to BCG, or
- Previously exposed, but have not received intravesical BCG for ≥24 months prior to the most recent CIS diagnosis, or
- Received ≤2 doses of BCG within the 24 months prior to the most recent CIS diagnosis

Additionally, participants must meet at least one of the following conditions:

- Documented intolerance to BCG
- Documented ineligibility for BCG due to contraindications
- Documented refusal of BCG treatment (including reduced or partial dosing regimens)
- Documented inability to access BCG (including reduced or partial dosing regimens)

Participants who refuse or are ineligible for cystectomy per Investigator's judgement are eligible for this study, provided they fulfill all inclusion/exclusion criteria.

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participants who have voluntarily given written informed consent (including reconsent for crossover participants) after the nature of the study has been explained according to applicable requirements prior to study entry, including willingness to be randomized to either study arm.
2. Male or female participants must be 18 years of age or older at the time of signing the informed consent.
3. BCG-naïve: defined as those who were never exposed to BCG, those who are BCG exposed and have not received intravesical BCG for at least 24 months prior to most recent CIS diagnosis, or those who have received ≤2 doses of BCG within the 24 months prior to the most recent CIS diagnosis. Additionally, participants must meet at least one of the following conditions:
   a. Documented intolerance to BCG
   b. Documented ineligibility for BCG due to contraindications
   c. Documented refusal of BCG treatment (including reduced or partial dosing regimens)
   d. Documented inability to access BCG (including reduced or partial dosing regimens)
4. Central histologic confirmation of HG CIS (±Ta/T1) NMIBC with active disease.

- Note: CIS with active disease is defined as CIS (±Ta/T1) present on the most recent tumor evaluation within 3 months prior to signing the ICF or during Screening. The specimen containing CIS should be submitted for central review to determine eligibility. Historic/archived tissue may be used for central confirmation of CIS if the specimen is from the most recent tumor evaluation and the participant has not received treatment for NMIBC (except for single-dose post-operative intravesical chemotherapy after TURBT, which is allowed) during the intervening time from diagnosis of CIS to signing of ICF. Historic/archived tissue is recommended to be $\leq$ 3 months old unless otherwise approved by the Sponsor.
- Note: Sites are encouraged to ensure that pathological specimens have been specifically evaluated by the local pathologist for the presence or absence of CIS. There should be documentation by the local pathologist in the medical record that this evaluation has been performed as well as documentation of the findings prior to submitting the samples for central confirmation.
- Note: All papillary disease must be completely resected, and obvious areas of CIS should be fulgurated or cauterized if technically feasible prior to study intervention initiation.
- Note: Participants with CIS+T1 without muscle present in the specimen should undergo a re-staging TURBT to confirm eligibility.
- Note: Participants CIS+T1 with muscle present in the specimen should undergo a re-staging TURBT to confirm eligibility if they did not have a repeat resection within 6 weeks of their initial TURBT.
- Note: During Screening, if TURBT/biopsy shows worsening stage of disease per local/Investigator's assessment (eg, $\geq$ T2 [carcinoma invading the muscle layer]), then the participant is ineligible for study intervention.
- Note: In instances of significant discrepancies between local and central pathological reads, a central adjudication process may be implemented.

5. Participants with an ECOG performance status of 0, 1, or 2.
6. Adequate organ and bone marrow function based on central laboratory defined as: Hemoglobin > 8.0g/dL, Absolute neutrophil count > 1.5 x 10^9/L, Platelet count > 80 x 10^9/L, Aspartate aminotransferase (AST)/aspartate transaminase (SGOT) and/or alanine aminotransferase (ALT)/alanine transaminase (SGPT) < 2.5 x upper limit of normal (ULN), Total bilirubin $\leq$ 1.5 x ULN, Creatinine Clearance > 30 mL/min.
   - Note: Participants with known Gilbert's syndrome may be included if total bilirubin is $\leq$ 3.0 × ULN and direct bilirubin is within normal limits.
7. Contraceptive use by participants or participant partners should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   - If sexually active with male partners, females of childbearing potential agree to use a medically acceptable method of contraception for the duration of the study and for at least 120 days after the last dose of study intervention. Females are considered of childbearing potential if they are post-menarche, have not been surgically sterile for at least 6 weeks (ie, total hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation) and are pre-menopausal (menopause is defined as complete cessation of menstruation for

at least 12 months).
Acceptable methods of contraception include:
- The simultaneous use of stable hormonal contraception in conjunction with a double-barrier method (eg, condom with spermicide or diaphragm with spermicide), or;
- The use of an intrauterine device in place for at least 12 weeks, in conjunction with a double barrier method, or;
- Abstinence if this is the participant's usual lifestyle and preferred contraception.

- If sexually active with female partners, nonsterile males agree to use a medically acceptable method of contraception and abstain from donating sperm for the duration of the study and for at least 4 weeks after the last dose of investigational product. Males are considered surgically sterile if they have undergone bilateral orchiectomy or vasectomy at least 12 weeks prior to signing the ICF.
  Acceptable methods of contraception include:
  - The simultaneous use of stable hormonal contraception by the female partner in conjunction with a double-barrier method (eg, condom with spermicide or diaphragm with spermicide), or;
  - The female partner's use of an intrauterine device in place for at least 12 weeks, in conjunction with a double barrier method, or;
  - The female partner is surgically sterile for at least 6 weeks or is at least 12 months postmenopausal, or;
  - Abstinence if this is the participant's usual lifestyle and preferred contraception.

8. Females of childbearing potential with a negative pregnancy test per local read.

5.2. Exclusion Criteria

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

1. Penicillin allergy.
   - Note: Participants with a questionable history of allergy to penicillin will undergo penicillin blood allergy testing via central laboratory. If the penicillin blood allergy test is negative, and the participant meets all other protocol required eligibility requirements, the participant is eligible for the study.
2. Any known hypersensitivity reaction to gemcitabine or MMC or any of their excipients.
3. Significant urinary incontinence or otherwise unable to hold intravesical immunotherapy in the bladder for 1.5 hours (±30 minutes), per the Investigator's assessment.
   - Note: Participants with baseline urinary incontinence that is well-controlled by behavior modification, medication, or other therapies are allowed.
4. Concurrent malignancy diagnosed within 6 months prior to signing the informed consent.
   - Note: Basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, in situ cervical cancer, or low or very low-risk prostate cancer is allowed, provided no systemic treatment is ongoing for the malignancy.
   - Note: History of prior malignancy is allowed so long as it is not concurrent, no ongoing systemic treatment and is stable for more than 6 months per the Investigator's assessment and should be documented in chart.

- Note: Any participant with a history of pulmonary nodules must have a chest computed tomography (CT) scan within the last 6 months which demonstrates stability of disease and is not suggestive of malignancy or active infection OR provide biopsy pathology results that demonstrate a benign process. Either or both chest CT and lung nodule biopsy must be negative for malignancy or active infection. Purified Protein Derivative (PPD) test is required for pulmonary nodules that are negative for malignancy and the PPD must also be negative. Participants who received a BCG vaccine to prevent tuberculosis must provide documentation to rule out a false positive PPD test and such cases must be discussed with the medical monitor.

5. A current indwelling ureteral stent. Exceptions to this exclusion are listed below:
   - Note: If the stent is anticipated to be removed prior to study intervention administration, the participant is eligible.
   - Note: Nephrostomy tubes are allowed as long as they do not contain a ureteral stent (nephroureteral).
   - Note: Nephrostomy tubes with Fogarty ballons that occlude the ureter and prevent reflux from the bladder are allowed.
   - Note: Participants with chronic indwelling foley catheter are allowed.
   - Note: Participants with chronic indwelling suprapubic tube (SPT) are allowed as long as urethral incontinence is not present.
6. Any significant systemic or localized active uncontrolled, untreated, or suspected infection.
7. Known human immunodeficiency virus (HIV) infection or other immunodeficiency disorders, either primary or acquired.
   - Note: Exceptions include participants requiring use of inhaled or intranasal corticosteroids or local steroid injections.
8. Treatment for NMIBC administered between the most recent CIS diagnosis and planned initiation of study intervention.
   - Note: Single-dose post-operative intravesical chemotherapy after TURBT is allowed during Screening if it is the site's standard of care.
9. Receipt of any other anti-cancer therapy (including investigational agents) or any type of investigational treatment within 6 weeks prior to signing informed consent.
   - Note: Single-dose post-operative intravesical chemotherapy after TURBT is allowed during Screening if it is the site's standard of care.
10. Concurrent or planned immunosuppressive therapy, hormonal therapy (other than oral contraception), systemic chemotherapy, surgery (other than TURBT, biopsy, or otherwise approved by the Sponsor), or other cancer therapy during study period.
    - Note: Concurrent or planned hormonal therapy refers to hormone treatment for cancer or immunosuppression and does not refer to routine medications for chronic disease (eg, diabetes, hypothyroidism, osteoporosis).
    - Note: Low-dose prednisone (≤ 10 mg daily) or equivalent low corticosteroid is acceptable.
    - Note: Participants receiving non-biologic immunosuppressants to manage active autoimmune diseases, such as ulcerative colitis or rheumatoid arthritis are generally excluded, provided the dosing levels are high enough to achieve immunosuppression.
    - Note: Sites may reach out to the Sponsor for case-by-case clarification.

- Note: Single-dose post-operative intravesical chemotherapy after TURBT is allowed during Screening if it is the site's standard of care.

11. Any variant pathology or histological variants (or metastatic disease to bladder) according to central histologic review.
    - Note: Variant pathology includes adenocarcinoma or squamous cell carcinoma.
    - Note: Histological variants include plasmacytoid, sarcomatoid, squamous components, or micropapillary components.
12. Concomitant prostatic or upper tract urothelial involvement per Investigator's assessment.
13. Nodal and/or metastatic disease if they existed at any time (whether present or in the past).
    - Note: The determination of nodal and/or metastatic disease is based on the Investigator's review of local imaging results and clinical evaluation. A diagnosis of nodal and metastatic disease is not solely based on radiographic imaging; a clinical judgment and/or a histological investigation (if applicable) are factors the Investigator may use to assist in diagnosis of nodal or metastatic disease.
14. Any history of ≥ T2 bladder cancer that existed at any point in time per Investigator's assessment.
15. In the opinion of the treating Investigator, the participant has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study (eg, plans to move), or participation in the study is not in the best interest of the participant.

5.3. Lifestyle Considerations

Participants will be instructed to avoid alcohol for 24 hours prior to treatment visits where study intervention is administered.

Participants will abstain from strenuous exercise (eg, jogging, exercise bike, cardio) for 12 hours before each blood collection for clinical laboratory tests but may participate in light recreational activities during that time (eg, watching television, reading).

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened with Sponsor approval. Rescreened participants should be assigned a new participant number for every screening/rescreening event. Participants may be re-screened no more than 2 times.

Specified assessments from the participant's first screening may be carried over in the event that they are rescreened. The site should follow the study-specific Rescreen Plan for guidance on time frames for all assessments.