5. Study Population

This Phase 2 study will include male and female subjects 18 years of age or older with CIS (± Ta/T1) NMIBC with active disease (defined as disease present at last tumor evaluation prior to signing ICF).

This study will enroll subjects into 2 cohorts (Cohort A or Cohort B) based on their BCG experience:

Cohort A (Section 5.1, Inclusion Criteria; Criterion #4):

- Subjects with CIS (± Ta/T1) who are BCG naïve, or
- Subjects with CIS (± Ta/T1) who are BCG exposed and have not received intravesical BCG for at least 24 months prior to the most recent CIS diagnosis.

Cohort B (Section 5.1, Inclusion Criteria; Criterion #5):

- Subjects with persistent or recurrent CIS (± Ta/T1) who are BCG unresponsive within 12 months of completion of adequate BCG therapy (at least 5 of 6 doses of an initial induction course plus either at least 2 of 3 doses of maintenance therapy or at least 2 of 6 doses of reinduction)

BCG exposure must be clearly documented in the source for Sponsor and/or designee review. The timepoint for which "adequate BCG therapy" is achieved is the day, month, year that 2 of 3 doses of maintenance or 2 of 6 doses of a second induction course (reinduction) is completed. If the precise date for the maintenance or reinduction is unavailable, at least the month and year of the associated treatment cycle will be utilized for BCG exposure verification purposes, See Appendix 6: ADVANCED-2 Prior BCG Exposure Verification Form for further details.

5.1. Inclusion Criteria

To participate in this study, all subjects must meet all inclusion criteria described.

1. Male or female subjects 18 years of age or older at the time of signing the ICF
2. Subjects who have voluntarily given written informed consent after the nature of the study has been explained according to applicable requirements prior to study entry
3. Central histologic confirmation of high-grade non-muscle invasive CIS (± Ta/T1) with active disease
   - CIS with active disease is defined as CIS (± Ta/T1) present on last tumor evaluation prior to signing the ICF. The specimen containing CIS should be submitted for central review to determine eligibility. If re-staging TURBT was performed prior to signing informed consent, CIS with active disease may be determined from ANY specimen during this tumor evaluation period (i.e., staging or re-staging).
   - Subjects with CIS + T1 without muscle in the specimen should undergo re-staging TURBT to confirm eligibility (e.g., absence of muscle invasion). If re-staging was not completed prior to signing ICF, re-staging cystoscopy/cytology/TURBT can be performed in the same setting during Screening. Local interpretation of re-staging is

acceptable to confirm eligibility. Study visits may be delayed by up to 28 days after TURBT/biopsy procedure only if required per the site's standard of care.
- All papillary disease should be completely resected prior to dosing.
- During Screening, if TURBT/biopsy shows worsening stage of disease per local/Investigator's assessment (e.g., ≥ T2), then the subject is ineligible for study treatment.

4. Cohort A only: Subjects with CIS (± Ta/T1) who are BCG naïve or subjects with CIS (± Ta/T1) who are BCG exposed and have not received intravesical BCG for at least 24 months prior to the most recent CIS diagnosis.
   - Non-BCG therapy for the treatment of NMIBC after last BCG therapy but prior to most recent CIS diagnosis is permitted.
5. Cohort B only: BCG unresponsive CIS
   - Persistent or recurrent CIS (± Ta/T1) within 12 months of completion of adequate BCG therapy (at least 5 of 6 doses of an initial induction course plus either at least 2 of 3 doses of maintenance therapy or at least 2 of 6 doses of reinduction). Note: to qualify for adequate BCG therapy, maintenance or reinduction should occur within the same treatment period as initial induction.
   - The 12-month period calculation for inclusion into the study starts from the last time point that BCG was administered until the date of the CIS diagnosis used to establish BCG-unresponsive disease. This time frame must be less than or equal to 12 months.
   - Any subject with a history of BCG unresponsive CIS at any time in their bladder cancer history, despite recurrent/persistent CIS after receiving subsequent therapy since their initial diagnosis of BCG unresponsive CIS disease, is considered BCG unresponsive (i.e.,"once unresponsive always unresponsive"). These subjects should be enrolled in Cohort B. Under these circumstances, the time point for CIS with active disease will differ from the time point for establishment of BCG-unresponsive CIS. For example, a subject receiving 3 years of BCG therapy with CIS ± Ta/T1 recurrence at 3.5 years may achieve "adequate BCG therapy" status at Month 3 after initiating BCG, but "completion of adequate BCG" is at Year 3, and establishment of BCG-unresponsive CIS is Year 3.5.
6. Subjects enrolled in other investigational treatment studies should have received their last treatment at least 6 weeks prior to the time of signing the informed consent (i.e., 6-week washout period).
   - Treatment for NMIBC (other than single-dose post-operative chemotherapy) administered between most recent CIS diagnosis and planned TARA-002 therapy is not permitted.
   - Note: Subjects with prior TARA-002 exposure under the Ph1b/2 protocol (Protocol TARA-002-101-Ph1b/2, Version 3.0) are allowed to re-consent to this study. All other subjects with prior TARA-002 exposure in any other Protara sponsored protocol are not allowed to re-consent to this study.
7. Subjects who the Investigator believes can and will comply with the requirements of the protocol.
8. Subjects with an ECOG performance status of 0, 1 or 2.

9. 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 4 weeks after the last dose of investigational product. Females are considered of childbearing potential if they are post-menarche, have not been surgically sterile for at least 6 weeks (i.e., 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 (e.g., 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 subject's usual lifestyle and preferred contraception.
10. If sexually active with female partners, sexually mature, 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 (e.g., 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 subject's usual lifestyle and preferred contraception.
11. Females of childbearing potential with a negative pregnancy test per local read
12. Subjects whose treating physician must confirm availability and access to TARA-002
13. Subjects who have not completed vaccination against COVID-19 should be negative for COVID-19 infection (according to local site requirements, e.g., rapid test, polymerase chain reaction [PCR] within the 42-day screening window PRIOR to receiving their first dose of TARA-002 at Treatment Day 1). Results can be read and interpreted locally.

5.2. Exclusion Criteria

To participate in this study, subjects must not meet ANY exclusion criteria described below:

1. Penicillin allergy (subjects with a questionable history of allergy to penicillin will undergo penicillin blood allergy testing via central laboratory. If penicillin blood allergy test is negative, the subject is eligible for the study).
2. Central histologic review, predominant (defined as > 50%) adenocarcinoma, squamous cell carcinoma, or histological variants including plasmacytoid, sarcomatoid, or squamous

components (Note: If predominant histology is urothelial, the subject is eligible for the study). Subjects with any micropapillary component will be excluded.

3. Concomitant prostatic or upper tract urothelial involvement per Investigator's assessment
   - Prior history of prostatic and upper tract disease is acceptable as long as there is no evidence of disease in these areas at the time of dosing.
4. Nodal and metastatic disease are excluded if they existed at any time (whether present or in the past). The determination of nodal and metastatic disease is determined by the Investigator after reviewing local imaging results. Note: 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).
5. Any history of ≥ T2 bladder cancer that existed at any point in time in the subject's history is excluded. This determination is based on the Investigator's assessment.
6. Life expectancy of less than 5 years.
7. ECOG performance status 3 or 4.
8. The subject has significant urinary incontinence or is otherwise unable to hold intravesical immunotherapy in the bladder for 2 hours, per the Investigator's assessment.
9. Concurrent or planned immunosuppressive therapy, hormonal therapy (other than oral contraception), systemic chemotherapy, surgery (other than TURBT and/or biopsy), 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 e.g. diabetes, hypothyroidism, osteoporosis. Low Prednisone (< 10 mg daily or 5 mg bid) or equivalent low corticosteroid is acceptable. Subjects 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. Sites may reach out to the Sponsor for case-by-case clarification.
   - Note: single-dose post-operative chemotherapy is allowed during the study if it is the site's standard of care.
10. Concurrent malignancy diagnosed within 6 months prior to the time of signing the informed consent. Exceptions include 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. Note: history of prior malignancy is allowed so long as it is not concurrent or is stable for more than 6 months per the Investigator's assessment.
11. Receipt of any other anti-cancer therapy (including investigational agents) within 6 weeks prior to signing informed consent.
    - Note: Subjects receiving single-dose post-operative chemotherapy are exempt from this exclusion.
12. Inadequate 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 > 1.0 x ULN
- Creatinine Clearance ≤ 30 mL/min (as calculated by central laboratory)

13. Subjects with a current indwelling ureteral stent. If the stent is anticipated to be removed prior to drug administration, the subject is eligible.
14. A woman who is nursing, pregnant, or intending to become pregnant during the study period.
15. Known human immunodeficiency virus (HIV) infection or other immunodeficiency disorders, either primary or acquired. Exceptions include subjects requiring use of inhaled or intranasal corticosteroids or local steroid injections.
16. In the opinion of the treating Investigator, the subject 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.

5.3. Lifestyle Considerations

Subjects will be instructed to avoid alcohol for 24 hours prior to treatment visits where TARA-002 is administered. Additionally, for these visits, subjects will be instructed to maintain consistent consumption of diuretics, including coffee, tea, and all types of juice for 24 hours prior to and during study visits (e.g., amount and frequency should remain the same on a daily basis).

Subjects will abstain from strenuous exercise (e.g., 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 (e.g., watching television, reading).

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects 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.

Subjects who do not meet eligibility criteria for participation in this study (screen failure) during the initial screening process may be rescreened within 28 days and do not need to be reconsented unless there was a substantive Protocol Amendment that required ICF revisions in the interim.

Rescreened subjects will be assigned a new subject number for every screening/rescreening event. Subjects may be rescreened no more than 2 times. Specified assessments from the subject'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.