# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:** A Phase 2 Open-label Randomized Study of V940 in Combination With BCG Versus BCG Monotherapy in Participants With High-risk Non-muscle Invasive Bladder Cancer (INTerpath-011)

**Short Title:** A Phase 2 Study of V940 Plus BCG Versus BCG Monotherapy in High-risk NMIBC

**Acronym:** INTerpath-011

**Hypotheses, Objectives, and Endpoints:**

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In individuals ≥18 years of age who have high-risk NMIBC and are BCG-naïve (Cohort A) or who have CIS +/- papillary high-risk NMIBC and are ineligible for, or refusing, any I-VESIC therapy and either BCG-naïve or BCG-exposed (Cohort B, exploratory):

| Primary Objective | Primary Endpoint |
|---|---|
| **Cohort A**<br>To compare V940 in combination with BCG to BCG monotherapy with respect to EFS<br><br>Hypothesis (H1): V940 in combination with BCG is superior to BCG monotherapy with respect to EFS | **Cohort A**<br>- EFS, defined as the time from randomization to the first occurrence of any of the following as determined by BICR:<br>• HG Ta or CIS in the bladder at the 24-week assessment or later<br>• Any T1 UC in the bladder<br>• Any T2 or greater UC in the bladder<br>• Presence of extravesical UC, defined as:<br>- UC involvement of the urethra or upper tract (ureters, renal pelvis) excluding LG Ta<br>- Invasion into the prostate, seminal vesicles, uterus, vagina, or pelvic or abdominal wall (T4)<br>- Regional lymph node metastasis of UC (N1 or greater)<br>- Distant metastasis of UC, including non-regional lymph nodes (M1)<br>• Death due to any cause |

| Secondary Objectives | Secondary Endpoints |
|---|---|
| **Cohort A**<br>To evaluate V940 in combination with BCG and BCG monotherapy with respect to:<br>• 12-month EFS rate<br>• 24-month EFS rate | **Cohort A**<br>- 12-month EFS rate, defined as the proportion of participants with EFS within 12 months from randomization<br>- 24-month EFS rate, defined as the proportion of participants with EFS within 24 months from randomization |
| **Cohort A**<br>To evaluate V940 in combination with BCG and BCG monotherapy with respect to:<br>• RFS<br>• DSS<br>• OS<br>• 12-month OS rate<br>• 24-month OS rate | **Cohort A**<br>- RFS, defined as the time from randomization to the first occurrence of any of the following as determined by BICR:<br>• Any event included in the definition of EFS<br>• Any other UC recurrence including LG Ta at any timepoint as well as HG Ta or CIS in the bladder before the 24-week assessment<br>- DSS, defined as the time from randomization to death due to bladder cancer<br>- OS, defined as the time from randomization to death due to any cause<br>- 12-month OS rate, defined as the proportion of participants with OS within 12 months from randomization<br>- 24-month OS rate, defined as the proportion of participants with OS within 24 months from randomization |
| **Cohort A**<br>To evaluate V940 in combination with BCG and BCG monotherapy in participants with CIS at baseline with respect to:<br>• CRR<br>• DOR | **Cohort A**<br>- CR, defined, for participants in the FAS population, as the absence of all of the following as determined by BICR:<br>• High-risk non-muscle invasive UC, defined as HG Ta, CIS, or any T1 UC in the bladder<br>• Any T2 or greater UC in the bladder<br>• Extravesical UC, defined as:<br>- UC involvement of the urethra or upper tract (ureters, renal pelvis) excluding LG Ta<br>- Invasion into the prostate, seminal vesicles, uterus, vagina, or pelvic or abdominal wall (T4)<br>- Regional lymph node metastasis of UC (N1 or greater)<br>- Distant metastasis of UC, including non-regional lymph nodes (M1) |

| | |
|---|---|
| | - DOR, defined, for participants in the analysis population of CR who demonstrate documented CR, as the time from the first documented CR to the end of response, defined as the first occurrence of any of the following as determined by BICR:<br>• High-risk non-muscle invasive UC, defined as HG Ta, CIS, or any T1 UC in the bladder<br>• Any T2 or greater UC in the bladder<br>• Extravesical UC as defined in the definition of CR<br>• Death due to any cause |
| **Cohort A**<br>To evaluate V940 in combination with BCG and BCG monotherapy with respect to time to cystectomy | **Cohort A**<br>- Time to cystectomy, defined as the time from randomization to the date of radical cystectomy |
| **Cohort A**<br>To evaluate the safety of all treatment arms | **Cohort A**<br>- AEs<br>- Discontinuations of study intervention due to AEs |

**Overall Design:**

| | |
|---|---|
| Study Phase | Phase 2 |
| Primary Purpose | Treatment |
| Indication | Bladder cancer |
| Population | Participants with high-risk NMIBC |
| Study Type | Interventional |
| Intervention Model | Parallel<br>This is a multi-site study. |
| Type of Control | Active comparator |
| Study Blinding | Unblinded open-label |
| Blinding Roles | Outcomes assessor |
| Estimated Duration of Study | The Sponsor estimates that the study will require approximately 7 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. |

# 5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age, race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

Refer to Appendix 7 for country-specific requirements.

## 5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

**Type of Participant and Disease Characteristics**

1. **Cohort A:** Is an individual with a BICR-confirmed histological diagnosis of high-risk non-muscle invasive (HG Ta, T1, and/or CIS) UC of the bladder.
   Note: Individuals with unifocal HG Ta ≤3 cm alone are not eligible. Clinical or pathology assessment can be used to confirm tumor size.

   **Cohort B:** Is an individual with a BICR-confirmed histological diagnosis of CIS +/- papillary non-muscle invasive UC of the bladder and is ineligible for, or refusing, any I-VESIC therapy.
   Note: Individuals who have HG Ta or T1 without CIS are not eligible.
   Note: Ineligibility for, or refusal of, I-VESIC therapy must be clearly recorded in the source documents. If ineligible for I-VESIC therapy, the cause of ineligibility must be documented.

   **Cohorts A and B:**
   - Confirmation of T1 stage requires the presence of detrusor muscle in the tumor tissue.
   - Individuals with tumors of mixed histology are eligible provided the conventional urothelial component is ≥50%.
   - Individuals whose tumors contain *any* neuroendocrine or small cell component are not eligible.

2. Is an individual whose most recent TURBT was performed within 12 weeks before randomization/allocation and showed BICR-confirmed high-risk NMIBC histology as detailed in Inclusion Criterion #1.
   For individuals with papillary tumors (Ta and T1), a complete TURBT must have been performed, as characterized by attainment of a visually complete resection of all papillary tumors (Ta and T1).
   Note: Individuals with residual CIS not amenable to complete resection are eligible.
   Note: Individuals with T1 disease must have undergone a restaging TURBT procedure within 12 weeks before randomization/allocation confirming complete resection and that the individual continues to meet eligibility criteria. Individuals who undergo restaging TURBT of BICR T1 lesion(s) are still eligible if the restaging TURBT:
   - Is performed within 12 weeks before randomization/allocation even if the previous TURBT was performed >12 weeks before randomization/allocation;
   - Is BICR-confirmed as absent of muscle-invasive tumor (≥T2) with or without a high-risk NMIBC diagnosis.

   Tumor samples from the most recent TURBT available before randomization/allocation, which includes the diagnostic and any restaging TURBT, as applicable, must be sent to the central pathology laboratory to confirm eligibility before randomization/allocation.
3. **Cohort A:** Is BCG-naïve defined as either having never received BCG or having received BCG more than 2 years before high-risk NMIBC recurrence. Recurrence must be at least 2 years from the last exposure to BCG with evidence of complete response during the 2-year period post BCG.
   **Cohort B:** Is either BCG-naïve (as defined above) *or* BCG-exposed who did *not* receive adequate dosing of BCG and experienced recurrence of high-risk NMIBC within 2 years of the last dose of BCG. Adequate dosing is defined as at least:
   - 5 of 6 doses of induction; *and*
   - 2 of 3 doses of the first maintenance cycle *or* 2 of 6 doses of a second induction.

   **Cohorts A and B:** For individuals who received I-VESIC therapy other than BCG (ie, more than a 1-time intravesical dose), the current high-risk NMIBC diagnosis should be diagnosed after the last dose of the regimen.

**Demographics**

4. Is an individual of any sex/gender who is at least 18 years of age at the time of providing documented informed consent.

**Assigned Male Sex at Birth**

Note: There are no contraceptive requirements for individuals assigned male sex at birth.

**Assigned Female Sex at Birth**

5. A participant assigned female sex at birth is eligible to participate if not breastfeeding during the study intervention period and for at least 15 days after the last dose of study intervention with V940 and 7 days after the last dose of study intervention with BCG.

6. A POCBP is eligible to participate if not pregnant and if a negative highly sensitive pregnancy test (urine or serum), as required by local regulations, has been obtained within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.
   Note: Since the first dose of study intervention in Cohort B will not be received within the time periods specified in this criterion, eligibility for individuals in Cohort B must be confirmed at the time of Screening and reverified before the first dose of V940.
7. A POCBP is eligible to participate if they use an acceptable contraceptive method or if they adhere to penile-vaginal intercourse abstinence as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5, during the intervention period and for at least 15 days after the last dose of study intervention with V940 and 7 days after the last dose of study intervention with BCG.
   Note: The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recent initiation) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the local contraception requirements for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed. Medical history, menstrual history, and recent sexual activity should be reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

**Informed Consent**

8. The individual (or legally acceptable representative) has provided documented informed consent for the study.

**Additional Categories**

9. Individuals must provide a tumor tissue sample that is suitable for the NGS required for this study.
   Note: Tissue from the diagnostic TURBT is mandatory to ensure QC checks are successful. If the diagnostic tissue fails QC checks, tissue from Screening/repeat or prior TURBT/biopsy is allowed as long as tissue requirements and Inclusion Criterion #2 are met.
   The tumor tissue sample must meet the following criteria:
   - The minimum standards for tissue quantity and quality as defined in the Procedure/Laboratory Manual.
   - Pass the required QC checks by the study Sponsor's vendor.
10. Individuals must provide blood samples as specified in the protocol to enable V940 generation.
11. Is an individual with a performance status of 0, 1, or 2 on the ECOG Performance Scale within 56 days before randomization/allocation.

12. Is an individual with adequate organ function as defined in Table 5. Specimens must be collected within 14 days before randomization/allocation except PT/INR, which must be collected within 28 days before randomization/allocation.
    Note: If laboratory assessments (except PT/INR) are obtained 14 to 28 days before randomization/allocation and the participant is eligible and has no reportable changes to health, the participant may be randomized/allocated but laboratory assessments (except PT/INR) must be repeated on Cycle 1, Day 1 before administration of study intervention to ensure continued eligibility.

Table 5 Adequate Organ Function Laboratory Values

| System | Laboratory Value |
|---|---|
| Hematological | |
| ANC | ≥1500/µL |
| Platelets | ≥100,000/µL |
| Hemoglobin | ≥9.0 g/dL or ≥5.6 mmol/L[a] |
| Renal | |
| Measured or calculated CrCl[b] | ≥30 mL/min |
| Hepatic | |
| Total bilirubin | ≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN |
| AST (SGOT) and ALT (SGPT) | ≤2.5 × ULN |
| Coagulation | |
| PT/INR | ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT/INR is within therapeutic range of intended use of anticoagulants |

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); ANC=absolute neutrophil count; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=creatinine clearance; GFR=glomerular filtration rate; INR=international normalized ratio; pRBC=packed red blood cell; PT=prothrombin time; ULN=upper limit of normal.
[a] Criteria must be met without erythropoietin dependency and without pRBC transfusion with the last 2 weeks.
[b] Creatinine clearance should be calculated per institutional standards. GFR can also be used in place of CrCl.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific therapies.

13. **Cohort B only:** HIV-infected individuals must have well controlled HIV on ART, defined as:
    a. Having a CD4+ T-cell count ≥350 cells/mm$^3$ at the time of Screening
    b. Having achieved and maintained virologic suppression, defined as confirmed HIV RNA level below 50 or the LLOQ using the locally available assay, at the time of Screening and for at least 12 weeks before Screening
    c. Absence of any AIDS-defining opportunistic infections within the past 12 months
    d. Being on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before randomization/allocation and agreeing to continue ART throughout the study

    HIV testing during the Screening Period is not required unless:

    - There is a known history of HIV infection
    - Mandated by local health authority

14. Individuals who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks, and have undetectable HBV viral load before randomization/allocation.
    Note: Participants should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

    Hepatitis B testing during the Screening Period is not required unless:

    - There is a known history of HBV infection
    - Mandated by the local health authority
15. Individuals with a history of HCV infection are eligible if their HCV viral load is undetectable at Screening.
    Note: Individuals must have completed curative antiviral therapy at least 4 weeks before randomization/allocation.

    Hepatitis C testing during the Screening Period is not required unless:

    - There is a known history of HCV infection
    - Mandated by the local health authority
16. **Cohort A only:** Agrees to use a barrier method for all sexual contact for 7 days post each BCG instillation (dose).

## 5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

### Medical Conditions

1. Has a history of or concurrent locally advanced (ie, T2, T3, T4) or metastatic UC.
2. Has concurrent extravesical (ie, urethra, ureter, renal pelvis) non-muscle invasive UC or a history of extravesical non-muscle invasive UC that recurred within the last 2 years.
    - Individuals with concurrent LG Ta of the prostatic urethra are eligible.
    - Individuals with prostatic ductal invasion regardless of histology are not eligible.

3. Has a known additional malignancy that is progressing or has required active treatment within the last 3 years.
   Note: Individuals with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, who have undergone potentially curative therapy are eligible.
   Note: Individuals with a history of prostate cancer (T2N0M0 or lower with a Gleason score ≤7) that was treated with definitive intent (surgically or through radiation therapy) at least 1 year before study entry are eligible, provided they are considered prostate cancer disease free and the following criteria are met: i) individuals who underwent radical prostatectomy must have an undetectable PSA for >1 year and during the Screening Period; and ii) individuals treated with radiation must have a PSA doubling time >1 year (based on at least 3 values taken more than one month apart) and a total PSA that does not meet Phoenix criteria for biochemical recurrence (ie, PSA must be <2.0 above nadir level). Individuals with untreated low-risk (Gleason 6 or less) prostate cancer on active surveillance with a PSA doubling time of >1 year (based on at least 3 values taken more than one month apart) are also eligible.
4. Has had a myocardial infarction within 6 months of randomization/allocation.
5. **Cohort A only:** Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.
   **Cohort B only:** HIV-infected individuals with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.

**Prior/Concomitant Therapy**

6. Has received any systemic anticancer therapy including investigational agents within 4 weeks before randomization/allocation.
   Note: Intravesical chemotherapy treatment given as part of the most recent cystoscopy/TURBT per local/regional practices is acceptable.
   Note: All AEs due to previous therapies must have recovered to Grade ≤1 or baseline.
   Note: Individuals must have recovered adequately from the toxicity and/or complications of major surgery before randomization/allocation.
7. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention.
   Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live-attenuated vaccines and are not allowed.
   Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as it is an mRNA vaccine, replication-incompetent adenoviral vaccine, or inactivated vaccine. These vaccines will be treated just as any other concomitant therapy.
   Note: No vaccine should be administered within 10 days before the first dose of V940.
   Note: Since the first dose of study intervention in Cohort B may not be received within the time periods specified in this criterion, eligibility for individuals in Cohort B must be confirmed at the time of Screening and reverified before the first dose of V940.
8. Has received prior treatment with a cancer vaccine.

### Prior/Concurrent Clinical Study Experience

9. Is currently participating in or has participated in a study of an investigational agent or has used an investigational agent or device within 4 weeks before randomization/allocation.
   Note: Individuals who have entered the Follow-up Phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent or device.

### Diagnostic Assessments

10. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before randomization/allocation.
11. Active autoimmune disease that has required systemic treatment in the last 2 years. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid) is allowed.
12. Active infection and/or diagnosis requiring systemic therapy at the time of randomization/allocation.
    Note: For Cohort A, treatment of latent tuberculosis is not allowed during Screening.

### Other Exclusions

13. **Cohort A only:** Has severe hypersensitivity (Grade ≥3) to V940 and/or BCG and/or any of their excipients.
    **Cohort B only:** Has severe hypersensitivity (Grade ≥3) to V940 and/or any of its excipients.
14. Has any contraindication to IV contrast *and* gadolinium or is otherwise unable to have imaging with either CTU or MRU.
15. Has a history of allogeneic tissue/solid organ transplant.
16. Has not adequately recovered from major surgery or has ongoing surgical complications.
17. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study, interfere with the individual's ability to cooperate with the requirements of the study, or interfere with the individual's participation for the full duration of the study, such that it is not in the best interest of the individual to participate, in the opinion of the treating investigator.
18. Individuals who are incapacitated are not eligible for this study.
19. **Cohort A only:** Has one or more of the following contraindications to BCG: prior BCG sepsis or systemic infection, total bladder incontinence, or an adverse experience to a previous BCG instillation that resulted in treatment discontinuation and precludes retreating with BCG.
20. **Cohort A only:** Has current active tuberculosis. Assessment method(s) per local standard-of-care and institutional guidelines.