1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: Phase 1/2 Study of Intravesical MK-3120 in BCG-Naïve or BCG-Exposed High-Risk Non-muscle Invasive Bladder Cancer

Short Title: Phase 1/2 Study of Intravesical MK-3120 in HR NMIBC

Acronym: Not applicable.

Hypotheses, Objectives, and Endpoints:

There are no hypotheses for this study.

In BCG-naïve or BCG-exposed individuals with HR NMIBC:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of I-VESIC MK-3120 monotherapy	-DLT -AEs -Discontinuation of study intervention due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of I-VESIC MK-3120 with respect to CRR at 3 months based on local assessment	CR at 3 months, where CR is defined as the absence of all of the following as determined by local assessment using urine cytology, cystoscopy, biopsy and radiology assessments as applicable: • High-risk non-muscle invasive UC (defined as HG Ta, CIS, or any T1 disease of the bladder, urethra, or upper tract [ureters, renal pelvis]) • Any T2 or greater in the bladder, including transurethral prostate stromal invasion of UC, or in the upper tract (ureters, renal pelvis) • Metastatic UC, defined as: - Regional lymph node metastasis of UC (N1 or greater) - Distant lymph node or visceral metastasis of UC (M1)

Overall Design:

Study Phase	Phase 1/2
Primary Purpose	Treatment
Indication	Bladder cancer
Population	Participants with BCG-naïve or BCG-exposed HR NMIBC with CIS (+/- papillary tumors)
Study Type	Interventional
Intervention Model	Single Group This is a multi site study.
Type of Control	No Control
Study Blinding	Open Label
Blinding Roles	Not Applicable
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 38 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 45 participants will be enrolled in Part 1 of the study.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Part 1	MK-3120	100 mg/vial	300 mg 600 mg 900 mg	Intravesical	Induction: qw for 6 weeks Maintenance: q1month for 9 months	Test Product

qw=once weekly; q1month=once per month.

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.

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. Has histologically confirmed CIS +/- papillary HR NMIBC, confirmed locally
   Note: Individuals who have HG Ta or T1 without CIS are not eligible.
   Note: Individuals with tumors of mixed histology are eligible provided the conventional urothelial component is ≥50%.
   Note: 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 allocation and showed 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 confirming complete resection and that the individual continues to meet eligibility criteria. Individuals who undergo restaging TURBT of T1 lesion(s) are still eligible if the restaging TURBT:

- Is performed within 12 weeks before allocation even if the previous TURBT was performed >12 weeks before allocation
- Is absent of muscle-invasive tumor (≥T2).

3. Is either:

- BCG-naïve, defined as either having never received BCG or having received BCG more than 2 years before CIS +/- papillary HR NMIBC recurrence. Recurrence must be at least 24 months from the last exposure to BCG with evidence of complete response during the 2-year period post-BCG.

OR

- BCG-exposed and received adequate BCG therapy and had recurrence of CIS +/- papillary HR NMIBC >12 months but ≤24 months after the last BCG dose. Adequate BCG therapy is defined as at least:
  - 5 of 6 doses of initial induction BCG plus at least
    - 2 doses of subsequent maintenance OR
    - 2 of 6 doses of a second induction.

  Note: Participants should be disease-free after BCG induction and subsequently have a CIS +/- papillary recurrence outside the BCG-unresponsive window (>6 months for Ta/T1 and >12 months for CIS), but within 24 months.

Demographics

4. Is an individual of any sex/gender, ≥18 years of age at the time of providing the informed consent. Follow local regulatory requirements if the legal age of consent for participation is >18 years of age.

Assigned Male Sex at Birth

5. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for study intervention is: 120 days.

- Refrains from donating sperm
- Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant PLUS partner use of an additional contraceptive method (refer to Section 10.5.3), as a condom may break or leak

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Note: If the participant is azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview), no contraception is required.

Assigned Female Sex at Birth

6. A participant assigned female sex at birth is eligible to participate if not breastfeeding during the study intervention period and for at least 14 days after the last dose of study intervention.

7. A WOCBP 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 8.3.6.
8. A WOCBP is eligible to participate if they use a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, 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 the time needed to eliminate the study intervention after the last dose of study intervention. In addition, the participant agrees not to donate eggs (ova, oocytes) to others or freeze/store eggs during this period for the purpose of reproduction. The length of time required to continue contraception for the study intervention is: 210 days

- 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 WOCBPs 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 WOCBP with an early undetected pregnancy.

Informed Consent

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

Additional Categories

10. Able to provide a tissue sample for biomarker research from the diagnostic TURBT/biopsy procedure.
11. Participants who have AEs due to previous anticancer therapies must have recovered to ≤Grade 1 or baseline. Participants with endocrine-related AEs who are adequately treated with hormone replacement or participants who have ≤Grade 2 neuropathy are eligible.
12. Participants must agree to avoid donating blood or blood products for the duration of the study treatment period.
13. Participants must agree to avoid any penile or vaginal sexual contact for 2 days after drug instillation to prevent sharing of drug.
14. HIV-infected participants must have well controlled HIV on ART, defined as:
    a. Participants on ART must have a CD4+ T-cell count ≥350 cells/mm^3 at the time of screening

b. Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening
c. It is advised that participants must not have had any AIDS-defining opportunistic infections within the past 12 months
d. Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (Day 1) and agree to continue ART throughout the study
e. The combination ART regimen must not contain any antiretroviral medications that interact with CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)

15. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks, and have undetectable HBV viral load prior to 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 screening tests are not required unless:

    - Known history of HBV infection
    - As mandated by local guidelines

16. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.
    Note: Participants must have completed curative antiviral therapy at least 4 weeks prior to allocation.

    Hepatitis C screening tests are not required unless:

    - Known history of HCV infection
    - As mandated by local guidelines

17. An ECOG performance status of 0, 1, or 2 assessed within 14 days before allocation.
18. Adequate organ function as defined in the following table (Table 6). Specimens must be collected within 14 days before the start of study intervention.

Table 6 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
eGFR per local institutional standard	≥60 mL/min/1.73 m^2
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 (≤5 × ULN for participants with liver involvement)
Coagulation	
International normalized ratio (INR)/prothrombin time (PT), or activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); eGFR=estimated glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

5.2 Exclusion Criteria

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

Medical Conditions

1. History of or current locally advanced (ie, T2, T3, T4) or metastatic UC.
2. Has concurrent extravesical (ie, urethra, ureter, renal pelvis) non-muscle invasive UC or history of extravesical non-muscle invasive UC that recurred within the last 2 years.

   Note: Individuals with concurrent LG Ta of the prostatic urethra are eligible.

   Note: Individuals with prostatic ductal invasion regardless of histology are not eligible.
3. Has active total bladder incontinence, active UTI, neurogenic bladder, or urethral stricture
4. Has a condition that would prohibit normal voiding (or holding bladder voiding for 1 to 2 hours)
5. Has uncontrolled, significant cardiovascular disease or cerebrovascular disease, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, uncontrolled symptomatic arrhythmia, prolongation of QTcF interval to >470 ms, and/or other serious cardiovascular and cerebrovascular diseases within the 6 months preceding study intervention.
6. Has history of documented severe dry eye syndrome, severe Meibomian gland disease and/or blepharitis, or severe corneal disease that prevents/delays corneal healing.

7. HIV-infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.

Prior/Concomitant Therapy

8. Received prior treatment with a Nectin-4-targeted ADC or a topoisomerase 1 inhibitor, including ADCs.
9. Received strong CYP3A4 inhibitors, inducers, or substrates within 2 weeks before the first dose of study intervention or within 5 half-lives of drug elimination, whichever is longer.
   Note: A list of strong inhibitors or inducers of CYP3A4 can be found at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.
10. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed.
11. Received prior systemic and/or I-VESIC anticancer therapy within 4 weeks or 5 half-lives (whichever is shorter) and has not recovered to grade ≤ 1 or baseline from AE associated with anticancer therapy before allocation.
    Note: A single dose of I-VESIC chemotherapy following TURBT/biopsy is permitted without a washout.

Prior/Concurrent Clinical Study Experience

12. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

Diagnostic Assessments

13. Known additional malignancy that is progressing or has required active treatment within the past 3 years.
    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded. Participants with low-risk early-stage prostate cancer (T1-T2a, Gleason score ≤6, and PSA <10 ng/mL) either treated with definitive intent or untreated in active surveillance with stable disease are not excluded.
14. Known active CNS metastases and/or carcinomatous meningitis.
15. Active infection requiring systemic therapy other than those permitted in Section 5.1.
16. History of (noninfectious) pneumonitis/ILD that required steroids or has current pneumonitis/ILD.
17. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's ability to cooperate with the requirements of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
18. A known severe hypersensitivity reaction to MK-3120 and/or any of its excipients

Other Exclusions

19. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.
20. Participants who are incapacitated are not eligible for this study.

See Appendix 7 for country-specific requirements.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Foods or alternative supplements that affect CYP3A4 activity should be avoided while receiving study intervention (Section 6.5).

Participants should be advised to modify their diet to avoid foods that may cause damage to the mucosa (eg, pretzels and chips) and foods that are acidic.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study and are deemed ineligible or are 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 CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Retesting may be performed only within the screening/rescreening periods; see Section 8.11.1 for details. Participants who are retested will retain their original screening number.

Individuals who fail screening may be rescreened one time for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management; see Section 8.11.1.

5.5 Participant Replacement Strategy

For safety monitoring in Part 1, all enrolled participants are required to meet safety evaluation criteria during the DLT evaluation window (first I-VESIC dose to the fourth I-VESIC dose +1 week). Replacement of a nonevaluable participant will occur if the participant is:

- Allocated, but not treated with study intervention
- Discontinued from study treatment without completing required DLT safety evaluations (excluding treatment-related AE discontinuations)