Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 3, Randomized, Open-label, Multicenter Study Evaluating the Efficacy and Safety of TAR-210 Erdafitinib Intravesical Delivery System Versus Investigator's Choice of Intravesical Chemotherapy in Participants with High-risk Non-muscle-invasive Bladder Cancer with Susceptible FGFR Alterations Who Had Received Intravesical Bacillus Calmette-Guérin (BCG)

MoonRISe-3

Short Title

TAR-210 Versus Intravesical Chemotherapy in Recurrent High-risk Non-muscle-invasive Bladder Cancer (HR-NMIBC) After Bacillus Calmette-Guérin (BCG) with Susceptible FGFR Alterations

Protocol 42756493BLC3005; Phase 3
Version: Original

JNJ-42756493 (TAR-210)

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Studies conducted at sites in the United States (US) will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312). Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.

Regulatory Agency Identifier Number(s):
IND: 155255
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Participants who have been lost to follow-up or have withdrawn consent for study participation before the end of the follow-up phase will not be considered to have completed the study. Participants who prematurely discontinue study treatment for any reason will remain in the study and all efforts will be made to continue to follow those participants for assessments/procedures outlined for the follow-up phase (eg, recurrence, progression, OS, subsequent anticancer therapies, new malignancies, procedures [eg, cystectomy]; refer to Section 1.3 [SoA], Table 7). The only exception to this is when a participant specifically withdraws consent for any further contact with the participant or persons previously authorized by participant to provide this information. All reasonable efforts should be made to maintain the participant on study to ensure accurate assessment of all protocol-specified endpoints. Those participants who do prematurely discontinue study treatment for any reason before completion of the treatment phase will not be considered to have completed the study treatment.

5. STUDY POPULATION

Screening for eligible participants will be performed within 60 days before randomization. The screening period of 60 days may be extended exceptionally only by written sponsor approval (eg, in case of repeat screening procedures are necessary). Participants will sign study ICFs (molecular ICF for molecular eligibility, and full study ICF once molecular eligibility is met) prior to starting screening procedures (see also Section 8.1). Participants will be required to have a qualifying FGFR alteration (Section 10.9, Appendix 9: FGFR Alterations) before proceeding with additional study-specific screening assessments. If repeat TURBT/bladder biopsy and/or repeat imaging is conducted, the results must be available prior to randomization. Screening procedures (see Section 8.1) should be completed according to the timing provided in the SoA (Section 1.3, Table 1). Refer to Section 5.4 for conditions under which the repeat of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.5.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age

1. Be ≥18 years of age (or the legal age of majority in the jurisdiction in which the study is taking place, whichever is greater) at the time of informed consent.

Disease Characteristics

2. Histologically confirmed diagnosis by local histopathology of papillary-only HR-NMIBC (defined as HG Ta or any T1, no CIS).

   Mixed histology tumors are allowed if urothelial differentiation is predominant. However, neuroendocrine, and small cell variants will be excluded.

3. Have a susceptible FGFR mutation or fusion either by urine testing or tumor tissue testing (from TURBT tissue), as determined by central or local testing.

4. All visible tumor completely resected prior to randomization. Urine cytology must not be positive or suspicious for HG UC before randomization. For participants with lamina propria invasion (T1) on the screening biopsy/TURBT, muscularis propria must be present to rule out MIBC.

5. Participants must have:

   - Had adequate induction course of BCG (5 of 6 doses) and either 2 of 3 doses of maintenance BCG or 2 of 6 doses of second induction course of BCG, with HG T1 disease at first disease assessment after induction or HG Ta/any T1 disease within 6 months after last BCG (BCG-unresponsive population).

     OR

   - Had adequate induction course of BCG (5 or 6 doses) with or without maintenance BCG with HG Ta/any T1 disease within 12 months after last BCG excluding BCG-unresponsive (BCG-experienced population).

     OR

   - Been unable to complete an induction course of BCG with at least 5 doses due to Grade ≥2 toxicity requiring BCG discontinuation (BCG-intolerant population).

6. For participants with BCG-unresponsive or BCG-experienced disease:

   - Diagnosis of recurrence must be within 90 days prior to screening.
   - Participants with BCG-unresponsive disease (recurrence) must have HG T1 disease at first disease assessment after Induction or HG Ta/any T1 disease within 6 months after last BCG.
   - Participants with BCG-experienced disease (recurrence) must have HG Ta/any T1 disease within 12 months after last BCG.

For BCG-intolerant participants:

- For participants without recurrence after BCG: qualifying diagnosis must be within 180 days prior to screening and most recent BCG instillation was within 90 days prior to start of screening.
- For participants with recurrence: must have HG Ta/any T1 disease within 12 months after the last BCG instillation, and diagnosis of recurrence must be within 90 days prior to screening.

7. Participants must be ineligible for or refusing RC.

8. All AEs associated with any prior surgery and intravesical therapy must have resolved to CTCAE Version 5.0 Grade ≤2 prior to screening.

Participant Characteristics

9. Have an ECOG performance status Grade of 0, 1, or 2 (Oken 1982).

10. Adequate bone marrow, liver, and renal function:
    - Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks):
      - Platelet count $\geq 75 \times 10^3/\mu L$.
      - Hemoglobin ≥8 g/dL.
    - Liver function:
      - Total bilirubin <2 × ULN OR in participants with congenital nonhemolytic hyperbilirubinemia such as Gilbert's Syndrome isolated total bilirubin ≥2 × ULN with conjugated (direct) bilirubin <2 × ULN is allowed for those participants.
      - ALT/Serum glutamic-pyruvic transferase and AST/Serum glutamic-oxaloacetic transaminase ≤3 × institutional ULN.
    - Renal function:
      - eGFR of ≥30 mL/min, based on MDRD 4-variable formula (see Section 10.7, Appendix 7: Formulas for Estimating Glomerular Filtration Rate Using Modified Diet in Renal Disease Formula (in mL/min)).

Sex and Contraceptive/Barrier Requirements

11. While on study treatment and for 6 months after the last dose of study treatment (ie, 3 months after last TAR-210 removal in Group A), a participant must:
    - Not breastfeed or be pregnant.

- Not donate gametes (ie, eggs or sperm) or freeze for future use for the purposes of assisted reproduction.
- Wear an external condom.
- If of childbearing potential,
  - have a negative highly sensitive (eg, β-hCG) pregnancy test at screening and within 24 hours before the first dose of study treatment, and agree to further pregnancy tests,
  - practice at least 1 highly effective method of contraception; if oral contraceptives are used, a barrier method of contraception must also be used.
- If a participant's partner is of childbearing potential,
  - the partner must practice a highly effective method of contraception unless the participant is vasectomized.

See Section 10.4, Appendix 4: Contraceptive and Barrier Guidance for details.

Informed Consent

12. Participants must sign all applicable ICFs (or their legally designated representative must sign, if applicable) indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study and agreement to store samples when applicable.

13. Participants must be willing to comply with and able to undergo all study procedures (eg, multiple cystoscopies from screening through the end of study and TURBT/bladder biopsy for assessment of recurrence/progression) and willing and able to adhere to the lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Disease Characteristics

1. Presence of CIS at any point from time of diagnosis of papillary-only HR-NMIBC recurrence to randomization. Additionally, presence or history of histologically confirmed, muscle-invasive, locally advanced, nonresectable, or metastatic UC (ie, T2, T3, T4, N+, and/or M+).

2. Must not currently have UC or histological variant at any site outside of the urinary bladder. UC of the upper urinary tract (including renal pelvis and ureter) is allowable if treated with complete nephroureterectomy more than 24 months prior to randomization with no evidence of recurrence.

3. N+ and/or M+ per BICR of CT/MR Urography.

Medical Conditions

4. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. Allowed recent second or prior malignancies:

   - Any malignancy that was not progressing nor requiring treatment change in the last 12 months (and not considered at HR of recurrence requiring systemic therapy).
   - Malignancies treated within the last 12 months and considered at very low risk for recurrence:
     - Non-melanoma skin cancers treated with curative therapy or localized melanoma treated with curative surgical resection alone.
     - Noninvasive cervical cancer.
     - Breast cancer: adequately treated lobular CIS or ductal CIS, localized breast cancer and receiving antihormonal agents.
     - Localized prostate cancer (N0, M0) with a Gleason score ≤7a, treated locally only (RP/RT/focal treatment).
     - Other malignancy that is considered at minimal risk of recurrence.

   In the event of any questions, consult with the sponsor's medical monitor prior to enrolling a participant.

5. Presence of any bladder or urethral anatomic feature that, in the opinion of the investigator, may prevent the safe placement, indwelling use, or removal of TAR-210. Participants with tumors involving the prostatic urethra in men will be excluded.

6. A history of clinically significant polyuria with recorded 24-hour urine volumes >4,000 mL.

7. History of uncontrolled cardiovascular disease including any of the following in the preceding 3 months prior to screening: unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive New York Heart Association Class III-IV heart failure, cerebrovascular accident, or transient ischemic attack. History of pulmonary embolism or other venous thromboembolism within the preceding 2 months.

8. Pyeloureteral tube externalized to the skin is exclusionary. Unilateral nephrostomy tube or ureteral stent is permitted if it does not interfere with either insertion of TAR-210 into (or retention in) the bladder.

9. Participants who have not recovered from the effects of major surgery or significant traumatic injury at least 14 days before randomization (TURBT is not considered major surgery).

10. Indwelling catheters are not permitted; however, intermittent catheterization is acceptable.

11. Concurrent UTI, defined as a symptomatic infection with a positive urine culture with a bacterial count of $\geq 10^5$ CFU/mL in urine voided from women, or $\geq 10^4$ CFU/mL in urine voided from men, or in straight-catheter urine from women that cannot be cleared with antibiotic therapy.

12. Uncontrolled intercurrent illness including ongoing or active infection, or psychiatric illness/social situation that would limit compliance with study requirements.

13. As determined by the investigator, contraindications to the use of TAR-210, MMC, or gemcitabine per local prescribing information. Known hypersensitivity to any study component:

    - Erdafitinib (or other drug excipients) or chemically related drugs.
    - TAR-210 device constituent materials.
    - TAR-210 UPC materials.
    - Gemcitabine (or other drug excipients) or chemically related drugs.
    - MMC (or other drug excipients) or chemically related drugs.

    Refer to the latest version of the IB and Attachments for TAR-210 for complete information on excipients.

14. Received a live virus vaccine within 30 days prior to randomization. Inactivated (non-live or non-replicating) vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed.

Prior/Concomitant Therapy or Clinical Study Experience

15. Received serial intravesical therapy or systemic therapy from the time of histologic diagnosis of recurrent HR-NMIBC to date of randomization. Immediate post-TURBT single-dose per-operative intravesical chemotherapy is allowed in accordance with institutional guidelines.

16. Prior application of TAR-210 within 6 months of randomization or prior intravesical chemotherapy with gemcitabine or mitomycin within 6 months of randomization.

17. Currently participating or has participated in a study and received an investigational agent or investigational device within 4 weeks prior to screening.

Diagnostic Assessments

18. Evidence of bladder perforation which has not resolved prior to randomization.

19. Bladder PVR volume >350 mL at screening after second voided urine.

Other Exclusions

20. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: investigators must ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. Section 5.4, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

For inclusion/exclusion criteria for participants that would be eligible for the crossover, please refer to Section 10.11, Appendix 11: TAR-210 Crossover.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Participants are encouraged to follow current guidelines for lifestyle recommendations and adjustments for patients with UC.

2 Participants will be instructed to consume at least 1,500 mL of non-alcoholic and non-caffeinated liquid per day (about 6.5 cups) during the dosing period to ensure adequate urine production.

3 It has been confirmed that smoking increases the risk of tumor recurrence and progression in patients with NMIBC, and participants should be counseled to stop smoking.

4. Any blood donation is not allowed during treatment, up to 6 months after the last dose of study treatment, after which the rules of local blood donation organizations should be followed.

5. Refer to Section 6.9 for details regarding prohibited and restricted therapy during the study.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness. This study will use a RTSM system (eg, IWRS). The investigator will not generate screening and enrollment logs directly from a RTSM system. Any deviations from the use of sponsor recruitment and enrollment logs requires sponsor review and approval. The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. A participant who is a screen failure may be rescreened no more than 1 time, if in the opinion of the investigator, the participant would likely meet eligibility if available care were provided (eg, blood product provided for low hemoglobin or platelet count) and is deemed an appropriate candidate for study participation. Rescreened participants will sign a new consent, must be assigned new participant numbers, and will then restart the screening phase. Assessments performed before start of rescreening based on local SOC or during the first screening period do not need to be repeated during rescreening if they are within the allowable time window before randomization.

5.5. Criteria for Temporarily Delaying Administration of Study Treatment

Refer to Section 6.6.1.1.1 for recommendations on when to remove and delay a new placement of TAR-210.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

For this study, study treatments are considered IMPs and not an AxMP. The designation of the study treatments administered is provided in Table 11 below.