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

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Regulatory Agency Identifier Number(s):
IND: 155255
EU TRIAL NUMBER: 2024-519493-39

1. PROTOCOL SUMMARY

1.1. Synopsis

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)

IND: 155255
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Short Title: TAR-210 Versus Intravesical Chemotherapy in High-Risk Non-muscle-invasive Bladder Cancer (HR-NMIBC) After Bacillus Calmette-Guérin (BCG) with Susceptible Fibroblast Growth Factor Receptor (FGFR) Alterations

This study will evaluate the erdafitinib intravesical delivery system (referred to as TAR-210) in BCG-experienced, unresponsive, or intolerant participants with HR-NMIBC harboring susceptible FGFR alterations and who are ineligible or refusing radical cystectomy. TAR-210 is an investigational drug delivery system, which comprises erdafitinib minitablets and a drug delivery constituent.

BENEFIT-RISK ASSESSMENT

Participants will receive TAR-210 or investigator's choice of either intravesical mitomycin C (MMC) or gemcitabine, which are recommended treatment options for patients with papillary-only HR-NMIBC (high-grade [HG] Ta or any T1, no carcinoma in situ [CIS]) recurrence after BCG therapy. As local delivery of treatment in the bladder via TAR-210 yields very low systemic exposure based on preclinical and Phase 1 study data, risks are expected to pertain mainly to placement and removal procedures, and local drug exposure. Considering the measures taken to minimize risk to participants, the potential risks identified in association with TAR-210 and intravesical MMC or gemcitabine are justified by the potential benefits that may be afforded to participants. The benefit-risk profiles of intravesical MMC and gemcitabine are expected to be similar.

OBJECTIVES

The primary objective is to compare disease-free survival (DFS) in participants receiving TAR-210 versus investigator's choice of single agent intravesical chemotherapy. Key secondary objectives are to compare recurrence-free survival (RFS), time to next intervention (TTNI), time to disease worsening (TTDW), time to progression (TTP), and overall survival (OS).

Hypothesis: The primary hypothesis is that TAR-210 therapy will prolong DFS to a greater extent than compared with investigator's choice of single agent intravesical chemotherapy in the target population.

OVERALL DESIGN

This is a Phase 3, randomized, open-label, active-controlled, multicenter study evaluating the efficacy and safety of intravesical TAR-210 (Group A) versus investigator's choice of either intravesical MMC or gemcitabine (Group B) in the target population. To be eligible, participants must have BCG-unresponsive, BCG-experienced, or BCG-intolerant disease (defined in the table below).

	Minimum BCG Therapy	Timing of Recurrence
BCG-unresponsive	Adequate Induction (5 of 6 doses) **AND** either 2 of 3 doses of Maintenance **OR** 2 of 6 doses of second Induction	HG T1 disease at first disease assessment after Induction **OR** HG Ta/any T1 disease within 6 months
BCG-experienced (excluding BCG-unresponsive)	Adequate Induction (5 of 6 doses) With or without Maintenance therapy	HG Ta/any T1 disease within 12 months
BCG-intolerant	Unable to receive adequate BCG induction (5 of 6 doses) due to Grade ≥2 toxicity requiring permanent BCG discontinuation	

Participants will be stratified based on T-stage (HG Ta or any T1), prior BCG treatment (BCG-unresponsive, BCG-experienced, or BCG-intolerant), and choice of intravesical chemotherapy (MMC versus gemcitabine), and randomly assigned (1:1) to Group A or B. An Independent Data Monitoring Committee (IDMC) will be commissioned to review safety data and the preplanned interim efficacy analysis. In the event of a positive result at a planned analysis with statistically significant difference in primary endpoint, the IDMC may recommend the option of crossover for participants in the control arm.

NUMBER OF PARTICIPANTS

Approximately 220 participants will be randomized in this study.

TREATMENT GROUPS AND DURATION

Group A: TAR-210 every 12 weeks with the last TAR-210 insertion at Week 84 and removal at Week 96.
Group B: MMC or gemcitabine once weekly for 6 induction doses. Maintenance dosing (10 monthly doses + optional additional 12 monthly doses at investigator's discretion) will begin at Week 8. The duration of individual participation will be approximately 5 years.

EFFICACY EVALUATIONS

Primary Efficacy Evaluation (DFS): The primary efficacy endpoint is DFS, which is measured as the time from randomization to the date of the first documented recurrence of HR-NMIBC (HG Ta, any T1 or CIS), progression, or death due to any cause, whichever occurs first.

***Additional Efficacy Evaluations*:** Key secondary endpoints include RFS and TTP based on urine cytology, bladder biopsy, and imaging as applicable. TTNI, TTDW, OS will also be assessed as key secondary endpoints. Any procedures and subsequent anticancer therapies will also be evaluated. Patient impact will be evaluated using patient-reported outcome questionnaires.

SAFETY EVALUATIONS

Safety assessments will be based on medical review of adverse event (AE) reports and the results of vital sign measurements, physical examination, clinical laboratory tests, and other safety evaluations at specified timepoints. Concomitant medication usage will be recorded. AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

STATISTICAL METHODS

The primary efficacy analysis for DFS will be performed after approximately 104 DFS events have been observed. Based on current literature and analyses of the FGFR-selected population, the 1-year DFS rate in the control group is anticipated to be 50%. Assuming approximately 21% absolute improvement in the

1-year DFS rate as compared with the control arm that corresponds to a hazard ratio of 0.50 under the exponential distribution assumption, this study will provide over 90% power to achieve a statistically significant difference between the treatment groups (2-sided alpha = 0.05). This assumes an 18-month accrual, 12 months of follow-up, and a 5% annual dropout rate. If the testing for the primary endpoint of DFS is statistically significant, key secondary endpoints will be sequentially tested, by utilizing a hierarchical testing approach.

One interim analysis is planned for the primary endpoint when approximately 78 DFS events have been observed (approximately 75% of the target number of events).

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 ≥75×10^3/μL.
  - 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.