ISRCTN72352492 https://doi.org/10.1186/ISRCTN72352492

A research study of an investigational drug delivery system for adults with high-risk non-muscle invasive bladder cancer

Submission date 17/01/2024	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol
Registration date 18/03/2024	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 01/05/2024	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
High-Risk Non-Muscle Invasive Bladder Cancer (HR-NMIBC) is an early stage of bladder cancer, in the inner lining of the bladder. Bacillus Calmette-Guerin (BCG) therapy is used for the prevention of recurrence of HR-NMIBC. While BCG therapy is often successful at preventing early tumor recurrences in patients with HR-NMIBC, many patients do not maintain sustained remissions. BCG treatment eventually fails in up to 50% of participants. TAR-200 is a drug delivery system designed to slowly deliver gemcitabine directly into the bladder.
The purpose of this study is to compare disease-free survival (the length of time during which a patient survives post-treatment without any signs or symptoms of a specific disease) in participants treated with TAR-200 therapy versus intravesical chemotherapy* (mitomycin C [MMC] or gemcitabine) in participants with recurrence papillary-only HR-NMIBC within 1 year of last dose of BCG therapy and who refused or are unfit for bladder removal surgery.
*Intravesical chemotherapy is a therapy that involves instilling chemotherapy medication directly into the bladder through a catheter placed in the urethra.

Who can participate?
Patients aged 18 years and older diagnosed with HR-NMIBC

What does the study involve?
This study will consist of:
1. Screening phase (up to 60 days)
2. Induction phase
3. Maintenance phase (up to week 99) and
4. Follow-up phase
Participants will be assigned to either of the two groups below:
Group A: TAR-200 will be inserted into the bladder every 3 weeks during an induction phase and every 12 weeks during a maintenance phase.
Group B: Either MMC or gemcitabine will be instilled directly into the bladder every week during an induction phase and every 4 weeks during a maintenance phase.
Study assessments will include questionaries, vital signs, electrocardiogram (ECG), blood and

urine laboratory tests, pregnancy tests, bladder examinations and other safety evaluations. The total duration of the study can be up to 6 years and 7 months.

What are the possible benefits and risks of participating?
There is no established benefit to participants of this study. Based on scientific theory treatment with TAR-200 may slow down bladder cancer progression and lower the rate of tumor recurrence. However, this cannot be guaranteed because TAR-200 is still under investigation as a treatment.
Participants may experience some benefit from participation in the study that is not due to receiving study drug, but due to regular visits and assessments monitoring overall health. Participation may help other people with HR-NNIIBC in the future.
Participants may have side effects from the drugs or procedures used in this study that may be mild to severe and even life-threatening, and they can vary from person to person. Potential risks include urinary tract infections, renal and urinary disorders, bleeding, and risks associated with the insertion and removal of the TAR-200 drug delivery system. Known risks or side effects associated with PANIC or gemcitabine include but not limited to skin disorders, bladder pain, urinary urgency, vomiting and nausea.
The participant information sheet and informed consent form, which will be signed by every participant agreeing to participate in the study, includes a detailed section outlining the known risks to participating in the study.
Not all possible side effects and risks related to TAR-200 are known at this moment. During the study, the sponsor may learn new information about TAR-200. The study doctor will tell participants as soon as possible about any new information that might make them change their mind about being in the study, such as new risks.
To minimize the risk associated with taking part in the study, participants are frequently assessed for any side effects and other medical events. Participants are educated to report any such events to the study doctor who will provide appropriate medical care. Any serious side effects that are reported to the sponsor are thoroughly reviewed by a specialist drug safety team.
There are no costs to participants to be in the study. The sponsor will pay for the study drug and tests that are part of the study. The participant will receive reasonable reimbursement for study-related costs (e.g., pregnancy testing kits for testing between study visits and travel costs).

Where is the study run from?
Janssen-Cilag International NV (Netherlands)

When is the study starting and how long is it expected to run for?
January 2024 to August 2031

Who is funding the study?
Janssen Research and Development (USA)

Who is the main contact?
Participate-In-This-Study@its.jnj.com

Contact information

Type(s)
Scientific

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Clinical Trials Information System (CTIS)
2023-507685-10

Integrated Research Application System (IRAS)
1009453

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
17000139BLC3004, IRAS 1009453, CPMS 60216

Study information

Scientific Title
A Phase III, randomized, open-label, multi-center study evaluating the efficacy and safety of TAR-200 versus investigator's choice of intravesical chemotherapy in participants who received Bacillus Calmette-Guérin (BCG) and recurred with high-risk non-muscle-invasive bladder cancer (HR-NMIBC) and who are ineligible for or elected not to undergo radical cystectomy

Acronym
SunRISe-5

Study objectives
Main objectives:
To compare disease free survival in participants receiving TAR-200 versus MMC or gemcitabine

with recurrence of papillary-only high-risk non-muscle-invasive bladder cancer (HR-NMIBC) within 1. year of last dose of bacillus calmette-guerin (BCG) therapy and who refused or are unfit for radical cystectomy (RC).

Secondary objectives
To compare recurrence-free survival (RFS), time to next intervention (TTNI), time to disease worsening (TTDW), time to progression (TTP), overall survival (OS), safety and tolerability of TAR-200, and patient-reported disease and treatment related symptoms and impacts on the functioning in participants receiving TAR-200 versus MMC or gemcitabine with recurrence of papillary-only high-risk non-muscle-invasive bladder cancer (HR-NMIBC) within 1 year of last dose of bacillus calmette-guerin (BCG) therapy and who refused or are unfit for radical cystectomy (RC).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/03/2024, Greater Manchester South Research Ethics Committee (3 Piccadilly Place, Manchester, M1 3BN, United Kingdom; +44 (0)2071048014; gmsouth.rec@hra.nhs.uk), ref: 24 /NW/0028

Study design
Open randomized controlled trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Recurrent high-risk non-muscle-invasive bladder cancer

Interventions
Group A:
Participants will receive TAR-200 (225 mg gemcitabine intravesical drug delivery system) every 3 weeks through Week 24 (8 induction doses), with the last with the last TAR-200 insertion at Week 21 and removal at Week 24. Maintenance dosing (six doses) of TAR-200 will then occur every 12 weeks. Beginning at week 36, through Week 99 (Year 2), with the last TAR-200 insertion at Week 96 and removal at Week 99.
TAR-200 drug delivery system containing 225 mg gemcitabine will be administered to the participant intravesically

Group B:
For participants in Group B, Mitomycin C (MMC) or gemcitabine will be dosed weekly through Week 5 (6 induction doses). Maintenance dosing (10 doses) of MMC or gemcitabine will then occur QM, beginning at Week 8, through Week 44. This may be followed by an optional second year of additional maintenance at the Investigator’s discretion.
Gemcitabine (2000 mg) or MMC (40 mg) will be administered to the participant intravesically

Intervention Type

Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Gemcitabine hydrochloride, mitomycin C

Primary outcome(s)
Disease-free survival (DFS), measured as the time from randomisation to the time of the first recurrence of HR-NMIBC (HG Ta, any T1 or CIS), progression, or death due to any cause, whichever occurs first. Recurrence or progression of DFS events will be determined by central disease assessments of urine cytology, bladder biopsy, or imaging, as applicable.

Key secondary outcome(s))
1. Recurrence-Free Survival (RFS): The time from randomisation to the first recurrence of HR-NMIBC, or death due to any cause, whichever occurs first.
2. Time to Next Intervention (TTNI): The time from randomisation to the time of the next intervention for the treatment of bladder cancer.
3. Time to Disease Worsening (TTDW): The time from randomisation to cystectomy, systemic therapy, or radiation therapy
4. Time to Progression (TTP): The time from randomisation to the time of first documented evidence of disease progression, or death due to disease progression, whichever occurs first.
5. Overall Survival (OS): The time from randomisation to death, due to any cause.
6. Disease-free survival (DFS) rate at 12 and 24 months: Percentage of participants with DFS at 12 /24 months.
7. Number of participants with adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) from the time the participant signs the consent form through to 30 days after the last treatment
8. Number of participants with change from baseline in laboratory abnormalities at 12, 24, 36, 48, 60, 72, 84, 96, End of Treatment visit, 30-day safety follow-up visit
9. Number of participants with change from baseline in vital signs abnormalities at 12, 24, 36, 48, 60, 72, 84, 96, End of Treatment visit, 30 day safety follow-up visit
10. Change from baseline in quality of life measured using the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire (EORTC QLQ) - C30 scores at [timepoints] 9, 12, 24, 36, 48 and 96 weeks during treatment, End of Treatment and during post-treatment follow-up
11. Change from baseline in quality of life measured using the EORTC QLQ- Non-Muscle-Invasive Bladder Cancer (NMIBC) 24 scores at 9, 12, 24, 36, 48 and 96 weeks during treatment, End of Treatment and during post-treatment follow-up
12. Proportion of participants with meaningful change in quality of life measured using the EORTC QLQ-C30 and EORTC QLQ-NMIBC24 scores at 9, 12, 24, 36, 48 and 96 weeks during treatment, End of Treatment and during post-treatment follow-up

Completion date
30/08/2031

Eligibility

Key inclusion criteria

1. 18 or more years of age at the time of informed consent.
2. Histologically confirmed diagnosis by local pathology (within 90 days of documented informed consent) of recurrent, papillary-only high-risk non-muscle-invasive bladder cancer (HR-NMIBC; defined as high-grade [HG] Ta or any T1; no carcinoma in situ [CIS]).
3. Participants with variant histologic subtypes are allowed if tumour(s) demonstrate urothelial (transitional cell histology) predominance. However, neuroendocrine and small cell variants will be excluded.
4. All visible tumour completely resected prior to randomisation. Urine cytology must not be positive or suspicious for HG urothelial carcinoma (UC) before randomisation. For participants with lamina propria invasion (T1) on the Screening biopsy/ transurethral resection of bladder tumour (TURBT), muscularis propria must be present to rule out muscle-invasive bladder cancer (MIBC).
5. Participants must have received at least 5 of 6 induction doses of Bacillus Calmette-Guérin (BCG; adequate induction) with or without maintenance therapy.
6. Diagnosis of recurrent, papillary-only HR-NMIBC (defined as HG Ta or any T1; no CIS) must be within 12 months of the last dose of BCG therapy.
7. Participants must be ineligible for or have elected not to undergo radical cystectomy (RC).
8. All adverse events (AEs) associated with any prior surgery and intravesical therapy must have resolved to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Grade less than or equal to 2 prior to Screening.
9. Have an Eastern Cooperative Oncology Group (ECOG) performance status Grade of 0, 1, or 2.
10. Adequate bone marrow, liver, and renal function, as defined in the study protocol.
11. While on study treatment and for 6 months after the last dose of study treatment, a participant must: not breastfeed or be pregnant; not donate gametes (i.e., 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 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 vasectomised.
12. Participants must sign an Informed Consent Form (ICF; or their legally acceptable representative must sign) 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 and willing and able to adhere to the lifestyle restrictions specified in the protocol.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Presence of carcinoma in situ (CIS) at any point from time of diagnosis of papillary-only high-risk non-muscle-invasive bladder cancer (HR-NMIBC) recurrence to randomisation. Additionally, presence or history of histologically confirmed, muscle-invasive, locally advanced, nonresectable, or metastatic urothelial carcinoma (UC).
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 randomisation with no evidence of recurrence.
3. N+ and/or M+ per blinded independent central review (BICR) of CT/MR Urography.
4. Active malignancies other than the disease being treated under study. Allowed recent second or prior malignancies are detailed in the protocol.
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-200. Participants with tumours involving the prostatic urethra in men will be excluded.
6. A history of clinically significant polyuria with recorded 24-hour urine volumes greater than 4,000 millilitres (mL).
7. History of uncontrolled cardiovascular disease in the preceding 3 months prior to Screening.
8. Pyeloureteral tube externalised to the skin is exclusionary. Unilateral nephrostomy tube or ureteral stent is permitted if it does not interfere with either insertion or retention of TAR-200 into the bladder. Bilateral ureteral stents are exclusionary.
9. Participants who have not recovered from the effects of major surgery or significant traumatic injury at least 14 days before randomisation (transurethral resection of bladder tumour [TURBT] is not considered major surgery).
10. Indwelling catheters are not permitted; however, intermittent catheterisation is acceptable.
11. Concurrent urinary tract infection (UTI) as defined within the protocol.
12. Uncontrolled intercurrent illness.
13. As determined by the Investigator, contraindications to the use of TAR-200, mitomycin C (MMC), or gemcitabine per local prescribing information. Known hypersensitivity to any study component.
14. Received a live virus vaccine within 30 days prior to randomisation. Inactivated (non-live or non-replicating) vaccines approved or authorised for emergency use (e.g., for COVID-19) by local health authorities are allowed.
15. Received serial intravesical therapy or systemic therapy from the time of histologic diagnosis of recurrent HR-NMIBC to date of randomisation. Immediate post-TURBT single-dose per-operative intravesical chemotherapy is allowed in accordance with institutional guidelines.
16. Previous treatment with TAR-200.
17. Currently participating or has participated in a study and received an investigational agent or investigational device within 4 weeks prior to Screening.
18. Participants with evidence of bladder perforation during cystoscopy. Participants are eligible if perforation has resolved prior to dosing.
19. Bladder post-void residual (PVR) volume greater than 350 mL at Screening after second voided urine.
20. Any condition for which, in the opinion of the Investigator, participation would not be in the best interest of the participant (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

Date of first enrolment

25/04/2024

Date of final enrolment
13/11/2026

Locations

Countries of recruitment
United Kingdom

England

Argentina

Belgium

Brazil

China

France

Germany

Italy

Japan

Mexico

Poland

Romania

Spain

Study participating centre
St. Bartholomews Hospital
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Study participating centre
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Sponsor information

Organisation
Janssen-Cilag International NV

Funder(s)

Funder type
Industry

Funder Name
Janssen Research and Development

Alternative Name(s)
Janssen R&D, Janssen Research & Development, Janssen Research & Development, LLC, Janssen Research & Development LLC, Janssen Pharmaceutical Companies of Johnson & Johnson, Research & Development at Janssen, JRD, J&J PRD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing policy of the Janssen Pharmaceutical Companies of Johnson and Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at yoda.yale.edu.

IPD sharing plan summary
Available on request