Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 2, Open-Label, Multi-Center, Randomized Study of TAR-200 in Combination with Cetrelimab and Cetrelimab Alone in Participants with Muscle-Invasive Urothelial Carcinoma of the Bladder who are Scheduled for Radical Cystectomy and are Ineligible for or Refusing Platinum-Based Neoadjuvant Chemotherapy

SunRISe-4

Protocol 17000139BLC2002; Phase 2
Version: Amendment 2

JNJ-17000139 (TAR-200)
JNJ-63723283 (Cetrelimab)

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United States (US) sites of this study will be conducted under US Food & Drug Administration (FDA) Investigational New Drug (IND) regulations (21 CFR Part 312).

Regulatory Agency Identifier Number(s):

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Status:	Approved
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Prepared by:	Janssen Research & Development, LLC
EDMS number:	CCI [redacted]

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	20 April 2023
Amendment 1	19 September 2022
Original Protocol	06 April 2021

Amendment 2 (20 April 2023)

Overall Rationale for the Amendment: The primary focus of the protocol amendment is to provide greater clarity for Investigators, to harmonize shared protocol elements within the protocol and across SunRISe protocols for the TAR-200/cetrelimab program, and to align with the latest Sponsor protocol template.

The changes made to this clinical protocol 17000139BLC2002 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections, Changes made in previous protocol amendments are listed in Section 10.19 Appendix 19: Protocol Amendment History.

In the following table, new text added to the protocol is shown in **bold**. Deleted text is shown in ~~strike through~~.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updates made to harmonize with changes in the protocol body	For consistency with the protocol
1.3 Schedule of Activities Table 1 (Cohort 1) and Table 2 (Cohort 2) 4.1 Overall Design 5. Study Population 5.1 Inclusion Criteria (Criterion 2)	90-day window extended to 120-day from diagnostic TURBT to randomization	To increase feasibility of enrollment due to concern from investigators that 90 days is not practical in all cases
1.3 Schedule of Activities Table 1 (Cohort 1) and Table 2 (Cohort 2)	Clarifications to footnote for Revised Cardiac Risk Index (RCRI): 1-2 weeks prior to radical cystectomy (RC) updated to "1-3 weeks prior to RC" Added cross-reference for further information on vital sign monitoring	To improve clarity
1.3 Schedule of Activities Table 1 (Cohort 1) and Table 2 (Cohort 2) 10.2 Appendix 2 (Clinical Laboratory Tests)	Hematology, Blood, Chemistry. Footnote text amended as HbA1c testing must be performed at Screening through Week C post RC, and fasting glucose will be captured at baseline but does not need to be done during treatment. Text added: **HbA1c results can replace the requirement for fasting blood glucose prior to each dose; however, if fasting glucose results are available, the HBA1c result does not need to be reviewed prior to dosing, but should still be collected**	To align with other SunRISe protocols
1.3 Schedule of Activities Table 1 (Cohort 1) and Table 2 (Cohort 2)	Urine and blood biomarkers analyses. Text added to footnote that urine and blood is collected at Week C if radical cystectomy is not performed at this visit Footnote text amended to state that urine sample collection is not required immediately prior to radical cystectomy at Screening	To clarify biomarker collection requirements

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities Table 1 (Cohort 1)	Cystoscopy, Cetrelimab, and TAR-200 Removal with Cystoscopy updated: To mitigate the risk of UTI's, participants must receive at least one dose of periprocedural prophylactic antibiotics ~~for any intravesical study procedures.~~**at time of TAR200 insertion and/or removal.** Note added to Week C cystoscopy - ****An assessment cystoscopy for participants in Cohort 1 and Cohort 2 may be performed at Week C if clinically indicated.**	To clarify use of periprocedural prophylactic antibiotics
6.1.1 TAR-200 Insertion (Cohort 1); 6.5.1.1 Management of Adverse Events Related to TAR-200 and Procedures 6.8 Concomitant Therapy	Sections updated to clarify that periprocedural prophylactic antibodies are for TAR-200 insertion and/or removal and not for any intravesical procedure	
1.3 Schedule of Activities Table 2 (Cohort 2)	Cystoscopy: Text updated: ~~To mitigate the risk of UTI's, participants must receive at least one dose of peripredural prophylactic antibiotics for any intravescial study procedures~~ Week C cystoscopy updated - ****An assessment cystoscopy for participants in Cohort 1 and Cohort 2 may be performed at Week C if clinically indicated.**	Prophylactic antibodies are for TAR-200 insertion and removal (Cohort 1 only) To align with Table 1
2 Introduction 6.1 Study Treatment (s) Administered	Language to describe TAR-200 and Urinary Placement Catheter (UPC) updated	To improve clarity and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program
2. Introduction	Language for the term "study drug" and "study treatment(s)" updated	To clarify the definitions of study drugs and study drug combinations used in this study
2.2.2 Cetrelimab Clinical Studies 2.2.2.1 IV Cetrelimab	Section 2.2.2 updated to include total number of participants who have received cetrelimab monotherapy or in combination. New Section 2.2.2.1 describing clinical study results for IV cetrelimab	To provide updated clinical study results for IV cetrelimab
2.2.3.1 TAR-200 + IV Cetrelimab Combination	New Section 2.2.3.1 includes details of the ongoing studies with TAR-200 + IV cetrelimab: the Phase 3 Study 17000139BLC3001, the Phase 3 Study 17000139BLC3002, and the Phase 2 Study 17000139BLC2001; and is updated with outcomes from Independent Data Monitoring Committee (IDMC). Reference to Investigator's Brochure (IB) for safety results included	To provide an overview of clinical studies for TAR-200 in combination with cetrelimab.
3. Objectives and Endpoints	Name of Cohort (1 or 2) added to each objective (where applicable).	To improve clarity.
3. Objectives and Endpoints	Exploratory objective and endpoint, respectively updated: To determine whether the baseline immune status, molecular subtype **or mutational status**	Reference to mutational profiling added to support exploratory objectives

Section Number and Name	Description of Change	Brief Rationale
	influences treatment response; and **mutational status by DNA sequencing**	
4.1 Overall Design	TAR-200 removal visit schedule updated for Cohort 1: **A cystoscopy is not required at these visits if TAR-200 removal is not needed**	To improve clarity for cystoscopy requirements in Cohort 1
4.3 Justification for Dose	Justification for dose selection for IV cetrelimab updated	To expand the justification of dose selection provided in the protocol
4.4. End of Study Definition	Participant End of Study Definition and Completion of Study Definition has been updated	For consistency across protocols for the TAR-200/cetrelimab program
5.1 Inclusion Criteria	Inclusion criterion 2 modified per Amendment 2: Histologically proven, cT2-T4a N0, M0 infiltrating urothelial carcinoma (AJCC 2017) of the bladder. Initial diagnosis must have been within ~~90~~ **120** days of randomization date. Participants with variant histologic subtypes ~~(eg squamous differentiation)~~ are allowed ~~if urothelial (transitional cell) differentiation is predominant (eg, <20% variant histologic subtype~~) **if tumor(s) demonstrate urothelial predominance.** However, the presence of ~~any~~ **small cell or** neuroendocrin~~e, micropapillary, signet ring cell, plasmacytoid, or sarcomatoid features~~ **variants** will make a participant ineligible.	To ensure patients who may derive benefit from this therapeutic regimen are included in this study
5.1 Inclusion Criteria 8.7.1.1 TURBT Biopsies, Cystoscopy, and Radical Cystectomy Pathology (Disease Assessments) 8.7.2.1 TURBT Biopsies, Cystoscopy, and Radical Cystectomy Pathology (Response Assessments)	Inclusion criterion 3 modified per amendment 2 to include: Participants **with no residual tumor, or** ~~an individual~~ intravesical tumor size of ≤3 cm following TURBT are eligible; **debulking TURBT for any residual disease is encouraged but not mandated.** Participants with persistent ~~multifocal~~ tumors **>3 cm** at screening must undergo a second debulking, re-staging TURBT. ~~to reduce the tumor burden.~~ Participants will be ineligible if any individual tumor is >3 cm **after debulking TURBT.** Text amended: **If screening cystoscopy demonstrates any residual mucosal disease, debulking TURBT is encouraged to attain complete resection, but not mandated if all individual residual tumors are <3 cm**. ~~All individual residual tumors should be ≤ 3 cm.~~ Text added: **A debulking re-TURBT is encouraged if there is residual mucosal disease ≤3 cm.**	To encourage debulking for tumors ≤3 cm
5.1 Inclusion Criteria	Inclusion criterion 6 modified per amendment 2 to include "**Note: If thyroid stimulating hormone (TSH) is not within normal limits, the participant may still be eligible if T3 (either total or free) and free T4 are within normal limits.**	To clarify eligibility criteria for participants with TSH not within normal limits
5.1 Inclusion Criteria	Inclusion criterion 7 modified per amendment 2 to include link to Section 10.17, Appendix 17,	Inclusion criteria for study participants is ≥30 mL/min

Section Number and Name	Description of Change	Brief Rationale
	Cockroft-Gault formula – Calculated and Measured Creatinine Clearance	based on Cockcroft -Gault formula
10.17: Appendix 17: Cockcroft-Gault Formula	New Appendix	
5.1 Inclusion Criteria	Inclusion criterion 8 modified per amendment 2 to include link to Section 10.18, Appendix 18, CKD-EPI Creatinine Equation (2021)	To determine ineligibility to platinum therapy the CKD-EPI equation is used
10.18: Appendix 18: CKD-EPI Creatinine Equation (2021)	New Appendix	
5.1 Inclusion Criteria	Inclusion criterion 11 modified per amendment 2 to include **Investigators will advise participants on the options for banking of sperm and ova for reproductive conservation.** and: • not be breastfeeding (**including temporarily withholding breastfeeding in order to participate in the study**) and not planning to become pregnant during the study and for at least 6 months after the last dose of study treatment. Female participants should consider preservation of eggs prior to study **treatment as anti-cancer treatments may impair fertility. Investigators will advise female participants on the options for banking of ova for reproductive conservation.** • not plan to father a child while enrolled in this study or within 6 months after the last dose of study ~~drug~~ **treatment. Male participants should consider preservation of sperm prior to study treatment as anti-cancer treatments may impair fertility. Investigators will advise male participants on the options for banking of sperm for reproductive conservation.**	For consistency across protocols for the TAR-200 /cetrelimab program
5.2 Exclusion Criteria	Exclusion criterion 13 modified per Amendment 2 Participants with an active, ~~known or suspected~~ autoimmune disease **that has required systemic treatment in the past 2 years are excluded**. Participants with autoimmune disorders not requiring systemic treatment ~~(eg, skin conditions such as vitiligo or alopecia)~~ or conditions requiring hormonal replacement therapies such as type 1 diabetes mellitus or hypothyroidism are permitted to enroll.	To provide further clarification by combining with Exclusion criterion 27
5.2 Exclusion Criteria	Exclusion criterion 16 modified per Amendment 2 to include: Evidence of active **or chronic** hepatitis B or C infection	To clarify exclusion criteria for participants with hepatitis B or C infection
5.2 Exclusion Criteria	Exclusion criterion 17 updated per Amendment 2: Urinary tract infection (UTI), defined as a symptomatic infection with a positive urine culture with a bacterial count of $\geq 10^5$ colony forming units (CFU)/mL in urine voided from women, or $>10^4$ CFU/mL in urine voided from men, or in straight catheter urine from women, **that cannot be cleared**	To clarify exclusion criteria for participants with UTI

Section Number and Name	Description of Change	Brief Rationale
	with adequate antibiotic therapy. ~~Symptoms may include dysuria, urgency, frequency, and/or systemic symptoms such as fever, chills, elevated white blood cell, and/or abdominal/flank pain. Participants free from symptoms for 7 days with no culture evidence of $\geq 10^5$ CFUs may be eligible.~~	
5.2 Exclusion Criteria	Exclusion criterion 18 deleted per Amendment 2 ~~Active, uncontrolled urogenital bacterial, viral or fungal infections, including UTI. Skin/nail fungal infections are not exclusionary. Participants with active shingles (varicella zoster infection) will be excluded from the study.~~	Details of exclusion criteria for participants with UTI is covered separately in exclusion criterion 17; and for consistency across protocols for the TAR-200 /cetrelimab program
5.2 Exclusion Criteria	Exclusion criterion 21 updated per Amendment 2 Participants ~~who have had a history of~~ **with current** acute diverticulitis, intra-abdominal abscess, gastrointestinal obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation, **and participants who have a history immune-mediated colitis**	To update exclusion criteria and to exclude participants with a history immune-mediated colitis
5.2 Exclusion Criteria	Exclusion criterion 22 deleted per Amendment 2 ~~Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions~~	Delay or arrest of wound healing not associated with TAR-200 or cetrelimab administration
5.2 Exclusion Criteria	Exclusion criterion 26 to include that, in addition to non-live vaccines, **non-replicating** vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed. Added link to Section 6.8 (Concomitant Therapy)	For consistency throughout the protocol and to improve clarity on types of vaccines allowed
5.2 Exclusion Criteria	Exclusion criterion 27 deleted per Amendment 2 ~~Active autoimmune disease that has required systemic treatment in the past 2 years~~	The exclusion of participants with active autoimmune disease is covered separately in Exclusion Criterion 13
5.2 Exclusion Criteria	Exclusion criterion 39 updated per Amendment 2 ~~Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.~~	To update exclusion criteria for participants with planned surgical procedures
5.1 Inclusion Criteria 5.2 Exclusion Criteria	Minor edits/clarifications incorporated	To improve clarity
6.1 Study Treatment(s) Administered	Table 8 updated to include route of administration, Use, IMP, and NIMP information. Added details on the liquid formulation product for IV cetrelimab Dosing instructions were updated in Table 8 to include that flexible cystoscope is preferred for the removal process; the same clarifications were added to Section 6.1.2 TAR-200 Removal. Section 6.1.2 includes additional clarifications to guidance for removal: 'The TAR-200 should be grasped fully **(wireform and tubing)** ...' and	To improve clarity and align with the Sponsor oncology protocol template and for consistency across protocols for the TAR-200/cetrelimab program

Section Number and Name	Description of Change	Brief Rationale
	'trained credentialed medical professional' updated to '**healthcare professional**'	
	Section 6.1.1 TAR-200 Insertion, note added to indicate **the bladder should not be completely empty when TAR-200 is inserted.** Bladder analgesics corrected: ~~phenopyrazidine~~ replaced by **phenazopyridine**	
	New Section 6.1.3 Cetrelimab Administration	To clarify dosing instructions
	Section 6.2 Subheading "Accountability of Study Treatment", '~~Treatment accountability form~~' replaced by '**treatment administration form'**. The following statement was deleted: '~~The return to the Sponsor of unused study treatment will be documented on the applicable return form'~~	To ensure correct reporting requirements are provided and to improve clarity
6.5 Management of Adverse Events and Dose Modification	Heading 6.5 updated to include **Management of Adverse Events**. Structure of Section 6.5 and subheadings updated to include the 2 study treatments (6.5.1 TAR-200, 6.5.2 Cetrelimab), and to describe management of adverse events (AEs) prior to dose modification. Cross-reference to Section 7.1 Discontinuation of Study Treatment included	To improve clarity and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program
	Section 6.5.2 list of cetrelimab-related immune-related AEs (irAEs) requiring delay or discontinuation updated	To align with irAEs reported in the Cetrelimab IB Annual Update
6.8 Concomitant Therapy	Text updated: '**non-live or non-replicating vaccines such as** annual inactivated influenza, COVID-19, **and monkeypox vaccine are allowed**'	For consistency with exclusion criterion 7, to include non-replicative vaccines like monkeypox
7.1 Discontinuation of Study Treatment	Text included: '**The Investigator believes that for safety reasons or tolerability reasons (eg, due to an AE, laboratory abnormality or intercurrent illness) it is in the best interest of the participant to discontinue study treatment.** '	To harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program
7.3.1 Withdrawal From the Future Use of Research Samples and Appendix	Section 7.3.1, duplicated information about long-term retention of samples deleted	This information is presented in Section 10.3.5 (Long-Term Retention of Samples for Additional Future Research)
8. Study Assessments and Procedures	'Home Health Care and Telehealth Visits' subsection incorporated. Study-Specific Materials list updated to include TAR-200 IFU, cetrelimab IPPI, PRO questionnaire(s) and ePRO completion guidelines, and eCOA manual	To clarify operational aspects within the protocol
8.2 Treatment	(Cohort 1and Cohort 2): Instructions for vital signs monitoring during IV cetrelimab infusion updated to: For the first infusion, vital signs should be monitored before the start of the infusion, **during infusion**, ~~every 15 to 20 minutes during the infusion~~, at the end of infusion **(+10 minutes),** and 2 hours (±15 min) after the completion of infusion. After the	To harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program

Section Number and Name	Description of Change	Brief Rationale
	completion of the first infusion, the participant may be discharged if considered clinically stable and all other study procedures have been completed. During subsequent infusions of cetrelimab, vital signs should be monitored **before the start of the infusion**. ~~pre-dose, once during infusion, and at the end of infusion.~~	
	TAR-200 text (Cohort 1) updated to: 'All Investigators **or healthcare professional designees** must have training completed ~~per~~ **and documented in accordance with** TAR-200 training guidance'	To align with TAR-200 training guidance and instructions for use
	Text added for Cohort 1 and Cohort 2 Early Disease Progression: **In cases of discordance or equivocal findings, additional imaging may be obtained at Investigator's discretion to adjudicate; these cases must be discussed with Sponsor**	To provide further operational aspects for CT/MRI-assessed response to treatment
	Minor edits incorporated	To improve clarity
8.7.1.2 Computed Tomography/Magnetic Resonance Imaging (CT/MRI)	Updated instructions for CT/MRI assessments: **Eligibility is determined by central read of CT/MRI at screening**. All **on-**study treatment decisions should be based on the Investigator's assessment of the CT/MRI images and not on the central review. **In cases of discordance between local and central review of CT/MRI images, the Investigator should consult with Sponsor for support**.	To provide further operational aspects for CT/MRI-assessed response to treatment
8.8.1. Specification of Safety Parameters	Updates made to clarify reporting of AEs and serious AEs (SAEs) relative to the 100-day safety follow-up visit	To ensure alignment of safety reporting across protocols in the TAR-200/cetrelimab program
	Statement added: '**In the event that a participant complains of unexpected fever, shortness of breath/dyspnea, or dry cough, a thorough evaluation for interstitial pneumonitis is recommended per institution standard of care.**'	For consistency across protocols for the TAR-200/cetrelimab program
8.9.5. Pregnancy	Text added: '**Any participant who becomes pregnant during the study must discontinue further study treatment.**' '**Because the effect of the study drugs on sperm is unknown, pregnancies in partners of male participants included in the study will be reported as noted above.**'	To align with the Sponsor oncology protocol template
8.9 Adverse Events, Serious Adverse Events, and Other Safety Reporting; 9.4.5 Safety Analysis; 10.4.6 Product Quality Complaint (PQC) Handling; 10.10 Adverse Events, Adverse Device	Text regarding PQC and Device Deficiency reporting updated and cross-references to Appendices included when applicable. Headings of sections modified with updated terminology Section 8.9.8, text added: '**If a PQC or Device Deficiency is reported, the TAR-200, cetrelimab, or UPC, respectively, must be retained by the site**	Per the latest Sponsor template/Standard Operating Procedures (SOPs) and regulatory reporting requirements

Section Number and Name	Description of Change	Brief Rationale
Effects, Serious Adverse Events, Serious Adverse Device Effects, Unanticipated Serious Adverse Device Effects, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device, and 1.3 Schedule of Activities	**under the correct storage conditions until a shipment request is received from the Sponsor.**' Same note added to SoA tables, PQC Assessments Section 10.10, Appendix 10 updated: title of appendix updated, subsections created, headings modified	
8.10. Pharmacokinetics 8.10.1 Evaluations	Subheading: Sparse Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 only) Text deleted: ~~Labeled urine collection containers will be stored in the refrigerator during each 24-hour collection interval and then transferred to the study clinic where the samples will be stored at -20°C or colder.~~ Text added: **The 20 participants in Cohort 1 in the serial urine sampling are not required to complete Week 0 and Week** CCI **sparse timepoints as the serial sampling will meet these requirements** Subheading: Serial Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 Only) Text deleted: ~~For these 20 participants, the sparse pre-dose time points at Week 0 and Week~~ CCI ~~do not need to be collected as this serial urine sampling will meet these requirements~~ Text deleted: ~~Labeled urine collection containers will be stored at room temperature during each 24-hour collection interval.~~	Detailed instructions for urine PK sample collection and storage are provided in the Laboratory Manual For consistency across protocols for the TAR-200/cetrelimab program Detailed instructions for urine PK sample collection and storage are provided in the Laboratory Manual
8.12 Biomarkers	Section updated to include DNA mutation profiling to explore molecular markers of response and resistance Circulating tumor DNA: paragraph describing the role of ctDNA fragments removed	To support exploratory objective Superfluous text
9.4.2 Primary Endpoint	Text added: **Additionally, 95% exact confidence interval will also be calculated for each cohort based on binomial distribution**	To provide further details of statistical analyses
9.4.4 Exploratory Endpoint(s)	80% exact confidence interval amended to 95%	To update statistical analysis for pOR rate
9.4.6 Other Analyses	Text added to TAR-200 PK Analyses: **For serial urine PK, PK parameters will be listed and summarized using descriptive statistics. Details of the analyses will be described in the Clinical Pharmacology Analysis Plan.** New Subsection added: **Pharmacokinetic/pharmacodynamic Analyses**	To improve clarity To align across the TAR-200/cetrelimab

Section Number and Name	Description of Change	Brief Rationale
	Pharmacokinetic/pharmacodynamic models may be explored to understand and characterize the exposure-response relationship for key efficacy, safety, and pharmacodynamic/biomarker data parameters, to detect the influence of covariates, and to identify inter-individual variability in response. The details will be provided in a separate analysis plan and the results of the analyses will be summarized in a separate report	program for the FDA Diversity Plan
9.5 Interim Analysis (Cohort 1 and Cohort 2)	Section updated: 1 interim analysis was originally planned for this study but as per Amendment 2, there are now 2 interim analyses planned	To update the statistical considerations sections with the 2 planned interim analyses
10.2 Appendix 2: Clinical Laboratory Tests	Text deleted in Protocol-Required Safety Laboratory Assessments Table: ~~Red blood cell count (RBC), Hematocrit, Monocytes, Eosinophils, Basophils~~ ~~Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.~~ Text added to HIV antibody testing: '**if positive, further testing of CD4 count and HIV viral load should be carried out.**'	To harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program
10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	In Section 10.3.3, statement about impartial witness updated from '~~should~~' to '**must'** personally date and sign the ICF	To improve clarity
10.5 Appendix 5: Contraceptive and Barrier Guidance	Removed footnote b regarding susceptibility of hormonal contraception to interaction with study treatment as it is not applicable to the study treatments administered	To remove misinformation on study treatment interactions
10.9 Appendix 9: Guidelines for Management of Immune-Related Adverse Events and Adverse Events of Clinical Interest	Section 10.9.1. Table 11: Management of Immune-Related Gastrointestinal Adverse Events: Text added to Grade 3-4 events: Persistence >3 days**, high-risk endoscopic features (large deep ulceration, multiple ulcers, extensive colitis beyond left colon),** or recurrence: add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis)	To harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program
10.13 Appendix 10.13: Cytokine Release Syndrome – Severity Grading and Management	Appendix updated using NCI-CTCAE (Version 5.0) grading systems	To align with NCI-CTCAE Version 5.0
10.19 Appendix 19: Protocol Amendment History	Text revised to note that the Protocol Amendment Summary of Changes Table for this amendment is located directly before the Table of Contents	Changes for Protocol Amendment 2
Throughout the protocol	Protocol template-driven updates were made where applicable	To align with updates to the Sponsor oncology protocol template

Section Number and Name	Description of Change	Brief Rationale
	Language containing potential Company Confidential Information and considered not essential for the protocol has been deleted	In accordance with the European Union (EU) Clinical Trial Regulations (CTR) effective as of 31 January 2022
	Minor clarifications including grammatical, formatting, or spelling changes were made, and links and cross-references corrected/updated. Abbreviations added to tables where applicable within the document, and the list of abbreviations and definitions updated (Section 10.1, Appendix 1).	Minor errors were corrected

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LIST OF IN-TEXT TABLES AND FIGURES

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2, Open-Label, Multi-Center, Randomized Study of TAR-200 in Combination with Cetrelimab and Cetrelimab Alone in Participants with Muscle-Invasive Urothelial Carcinoma of the Bladder who are Scheduled for Radical Cystectomy and are Ineligible for or Refusing Platinum-Based Neoadjuvant Chemotherapy

The Gemcitabine 225 mg intravesical delivery system (JNJ-17000139) product (hereafter, TAR-200) is an investigational integral drug-device combination product with a drug primary mode of action being the drug constituent, consisting of two components as described below:

- The drug constituent consists of gemcitabine minitablets (225 mg, free base equivalent) and osmotic minitablets containing CCI as the osmotic agent.
- The device constituent is comprised of a dual lumen CCI part with a CCI and a CCI wire. The large lumen of the CCI part contains the gemcitabine and CCI minitablets and serves as an elementary osmotic pump to release drug in a controlled manner. The smaller lumen contains the CCI wire in a predefined form to provide retention of the system in the bladder during the indwelling period.

TAR-200 is inserted into the bladder using a co-packaged device, the Urinary Placement Catheter, also known as "the Inserter" (hereafter referred to as "UPC"). TAR-200 is removed from the bladder transurethrally via cystoscopy and endoscopic graspers.

The UPC is a sterile, single-use, transient contact medical device, which has been specifically developed for the transurethral placement of TAR-200 into the bladder. Refer to Appendix 2 of the Investigator's Brochure for further details regarding the UPC.

Cetrelimab is an investigational drug product available in intravenous (IV) and subcutaneous formulations. Cetrelimab, a fully human immunoglobulin G4 (IgG4) kappa monoclonal antibody (mAb) containing the hinge-stabilizing S228P mutation, binds to programmed-cell death protein 1 (PD-1) with high affinity and specificity. Cetrelimab blocks binding to the programmed-cell death ligands 1 and 2 (PD-L1 and PD-L2), enhances pro-inflammatory cytokine production from ex-vivo stimulated T cells, and reduces tumor volume in human PD-1 knock-in (hPD-1KI) mice bearing MC38 murine colon carcinoma tumors.

BENEFIT-RISK ASSESSMENT

The standard of care in muscle invasive bladder cancer (MIBC) includes radical cystectomy (RC) with urinary diversion and is considered the preferred treatment option for patients who are considered surgical candidates. Systemic neoadjuvant chemotherapy for these patients is associated with increased overall survival (OS). Specifically, pathologic partial and complete responses, as well as negative lymph node status, correlate with meaningful disease-free and OS benefits. However, systemic chemotherapy is associated with significant toxicity, and up to 80% of patients may refuse or be ineligible for neoadjuvant and/or adjuvant regimens. There is a significant unmet need for efficacious and more tolerable neoadjuvant treatments, specifically for patients who are ineligible for cisplatin-based chemotherapy. A clinical benefit has been demonstrated in this platinum-ineligible patient population utilizing checkpoint inhibitor monotherapy (anti-PD1/PDL-1). It is postulated that the sustained antineoplastic local therapy of TAR-200, in combination with an efficacious anti-PD1 immunotherapy, could potentially provide comparable complete response (CR) rates to neoadjuvant chemotherapy, without an overlapping toxicity profile.

Intravesical gemcitabine has consistently exhibited activity and a favorable toxicity profile in bladder cancer, albeit in the setting of non-muscle invasive disease. Ongoing clinical studies in MIBC and NMIBC have demonstrated good tolerability of intravesical dosing. Prior clinical trials evaluating the safety of TAR--200 itself have noted an excellent tolerability and safety profile.

For safety details of intravesical gemcitabine and the TAR-200 drug-device combination product, refer to the most recent version of the IB.

Overall, the safety profile of IV cetrelimab monotherapy is well-tolerated and generally consistent across completed and ongoing clinical trials. Most adverse events (AEs) were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to cetrelimab dose level.

For the recognized pattern of immune-related AEs (irAEs) that are defined, management algorithms and treatment plans have been developed. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. Additional details on the safety profile of cetrelimab, including results from other clinical studies, are also available in the cetrelimab IB.

Overall, for participants who are ineligible for cisplatin-based treatment, the treatment of TAR-200 in combination with IV cetrelimab (hereafter referred to as "TAR-200 + IV cetrelimab"), or IV cetrelimab alone, has the potential to increase disease-free and survival periods relative to patients who are unable to receive neoadjuvant chemotherapy.

Accounting for the measures taken to minimize AEs in participants of this study, the identified potential risks of TAR-200 in combination with IV cetrelimab are justified by the anticipated benefits that may be afforded to participants with MIBC who are scheduled for RC and ineligible for platinum chemotherapy.

From a risk-based alternative treatment perspective, chemoradiotherapy has been proposed as an alternative to RC. Several organizations, including the AUA and the EAU, have updated their guidelines to support chemoradiotherapy as an alternative to RC in patients with muscle invasive disease. However, chemoradiotherapy has been associated with both acute and latent toxicity, including local and systemic symptoms. Such acute toxicities include anemia, fatigue, colitis, and cystitis, while latent longer-term toxicities and side effects may include bladder contracture, hemorrhagic cystitis, secondary malignancy, and urethral or rectal stricture. Therefore, while participants in this clinical study should be counseled on all treatment options, RC remains a standard of care.

More detailed information about the known and expected benefits and risks of TAR-200 and cetrelimab may be found in the respective IBs for these study drugs.

OBJECTIVES

The primary objective is to determine the anti-tumor effects, as assessed by pathologic complete response (pCR) at RC) of TAR-200 + IV cetrelimab (Cohort 1) and IV cetrelimab alone (Cohort 2). Secondary objectives are to evaluate the safety and recurrence-free survival (RFS) in participants receiving TAR-200 + IV cetrelimab (Cohort 1), and IV cetrelimab alone (Cohort 2).

Hypothesis

The primary hypothesis is that the treatment with TAR-200 + IV cetrelimab (Cohort 1) and IV cetrelimab alone (Cohort 2) will produce a pCR rate CCI . The statistical evaluation of the hypothesis will use a Bayesian approach to assess the likelihood of whether a true pCR rate CCI can be ruled out.

OVERALL DESIGN

This is a randomized, open-label, multicenter, Phase 2 clinical study of intravesical gemcitabine delivered via the TAR-200 drug-device combination product in combination with neoadjuvant IV cetrelimab and neoadjuvant IV cetrelimab alone in participants with muscle-invasive urothelial carcinoma of the bladder (clinically referred to as MIBC [muscle invasive bladder cancer]) who are scheduled for RC and are ineligible for or refusing platinum-based neoadjuvant chemotherapy. The transurethral resection of bladder tumor (TURBT) demonstrating an initial pathologic diagnosis of cT2-T4a MIBC must have been completed

within 120 days of randomization. All enrolled participants who have confirmed MIBC with absence of nodal or metastatic disease at screening and have met all eligibility criteria will be randomly assigned (5:3) to receive intravesical TAR-200 + IV cetrelimab (Cohort 1) or IV cetrelimab alone (Cohort 2). Two stratification factors for analysis will be completeness of TURBT (visibly complete vs incomplete and ≤3 cm) and tumor stage (cT2 vs. cT3-4a) at initial diagnosis. Participants must have tumor volume ≤3 cm prior to randomization. Participants in screening must undergo a cardiovascular risk assessment based on available guidelines for cardiac and surgical risk assessment and must not be enrolled if not considered eligible for RC.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study.

NUMBER OF PARTICIPANTS

A target of approximately 160 participants will be enrolled and be randomly assigned in a 5:3 ratio in this study with 100 participants planned to be randomized into Cohort 1 and 60 participants into Cohort 2.

TREATMENT GROUPS AND DURATION

The Treatment Phase will begin following random assignment into the study and continue with dosing every 21 days for 4 consecutive cycles. The RC should occur within [redacted] weeks following the Week [redacted] visit. Treatment should continue unless the participant has metastatic progression, intolerable toxicity, withdraws consent, there is a decision by the Investigator to discontinue study treatment, or the study is terminated, whichever occurs first.

All scheduled non-dosing assessments should be completed prior to dosing of any treatment.

At the initial treatment visit, study treatments will be administered as follows:

- TAR-200 + IV cetrelimab (Cohort 1): TAR-200 will be placed intravesically via the UPC and cetrelimab will be dosed IV at 360 mg approximately every 21 days for 4 consecutive cycles, with cycles starting at Week 0, Day 1.
- IV cetrelimab (Cohort 2): Cetrelimab alone will be dosed intravenously at 360 mg approximately every 21 days for 4 consecutive cycles, with cycles starting at Week 0, Day 1.

For both cohorts, Week 0, Day 1 will be defined as the day of the first dose of the first study drug administered. During Week [redacted] the participants will undergo an imaging assessment via computed tomography/magnetic resonance imaging (CT/MRI). If metastatic progression is noted on local report and confirmed by central radiology review, the participant will be discontinued from the Treatment Phase of the study. If local progression is suspected from cystoscopy or clinical symptoms warrant, the participant will proceed with immediate RC and urinary diversion, at local Investigator's discretion. Alternatively, if the RC is delayed due to clinical symptoms, TAR-200 will be removed at the regularly scheduled Week [redacted] visit. The date of the RC surgery will become the protocol specified 'RC visit.' All participants should undergo pre-operative cardiac and risk stratification prior to RC per institutional guidelines.

Following the RC and urinary diversion, all participants will have regular follow-up study visits from Week 4 to Week 108 (End of Study) post RC.

EFFICACY EVALUATIONS

The rate of pCR (ypT0N0) within the bladder at the RC as well as analysis of residual tumor stage, ypTa-ypT4 will be performed as an outcome assessment for Cohort 1 and Cohort 2. Participants who develop metastatic disease at any timepoint within the study will be discontinued from the efficacy (imaging) follow-up and continued to be followed for survival status, subsequent anti-cancer therapies, and other malignancies. If a participant develops imaging consistent with pelvic nodal disease, radical cystectomy and/or percutaneous biopsy should proceed at Investigator's discretion. Participants with

evidence of pelvic nodal disease will be followed with radiographic imaging per the Schedule of Activities. All participants should be followed for survival status.

The presence of radiographic nodal and metastatic disease involvement will be assessed at Week [redacted] and during post RC follow up visits (every [redacted] weeks). At the Week [redacted] visit, imaging will be performed for assessment of response and confirmed with central radiology review. If local progression is suspected from cystoscopy or based on clinical signs, participant will proceed with immediate RC, if clinically indicated. At post RC follow up imaging assessment timepoints, if metastatic progression is confirmed, the participant should be discontinued from further imaging assessments and continued to be followed for survival status, subsequent anti-cancer therapies, and other malignancies. Percutaneous biopsy may proceed at Investigator's discretion.

PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER EVALUATIONS

For those participants in Cohort 1, one single timepoint urine sample at baseline as well as one pooled 24-hr cumulative urine collection following either Week [redacted] study visit will be collected from participants over the course of the study. Additionally, serial urine PK sampling will be collected from up to 20 participants in Cohort 1. Participants in the serial urine PK sampling are not required to complete the Week 0 and Week [redacted] sparse timepoints. These urine samples will be collected for assessment of gemcitabine and 2′,2′-difluorodeoxyuridine (dFdU) concentrations in urine.

Blood samples will be collected from participants at multiple time points which coincide with sparse urine PK time points in Cohort 1 only. These blood samples will be collected for assessment of gemcitabine and dFdU concentrations in plasma.

Sparse blood samples for IV cetrelimab PK and immunogenicity will be collected at predose at Week 0, [redacted], [redacted] and [redacted] prior to RC. One additional post RC blood sample will also be collected between Week [redacted] and Week [redacted] if RC is performed prior to Week [redacted] or any time between Day 0 and Day 5 if RC is performed between Week [redacted] and Week [redacted] in both cohorts. In addition, end of infusion blood samples will be collected for IV cetrelimab PK only (both cohorts). Samples for biomarker collections will be obtained at multiple time points during the study.

SAFETY EVALUATIONS

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, clinical laboratory tests, and other safety evaluations at specified time points.

All adverse events will be collected from the time of the informed consent form signature to the end of the 100-day safety follow-up visit. All drug-related serious adverse events (SAEs) beyond 100 days after last dose of study drug(s) must be reported for participants during the Follow-up Phase. The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol. Any clinically significant abnormalities or toxicities persisting at the end of the study/early withdrawal will be followed by the Investigator until resolution or until reaching a clinically stable condition.

Safety oversight will be performed by the study Sponsor's Medical Monitor and IDMC, which will be composed of individuals with the appropriate expertise. The IDMC will operate under an approved charter and will meet as outlined in the IDMC charter. An IDMC will review safety data periodically during the study in accordance with the IDMC charter.

STATISTICAL METHODS

This study will randomize approximately 160 participants in a 5:3 randomization ratio to receive TAR-200 + IV cetrelimab (n=100) (Cohort 1) or IV cetrelimab alone (n=60) (Cohort 2). Each cohort will be analyzed separately to determine the CCI Bayesian credible interval, utilizing a Bayesian approach. Assuming the true pCR rate is CCI for the combination of TAR-200 + IV cetrelimab, Cohort 1, has more than 90% power to rule out CCI pCR rate with the lower limit of the Bayesian credible interval (or 80% power to rule out CCI pCR rate). Assuming the true pCR rate is CCI for IV cetrelimab alone (Cohort 2 only), the monotherapy cohort has approximately 65% power to rule out CCI pCR rate with the lower limit of the Bayesian credible interval.

A side-by-side descriptive summary of efficacy will be provided to illustrate the contribution of TAR-200 to the efficacy of the combination therapy.

1.2. Schema

Figure 1: Schematic Overview of the Study

CCI

CCI

1.3. Schedule of Activities (SoA)

Table 1: Cohort 1 (TAR-200 + IV Cetrelimab)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZA-TION	Treatment Phase (Week)				TAR-200 Removal	**RC (may coincide with TAR-200 removal)	Post Radical Cystectomy Follow Up					Notes
Study Week												CCI		*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). Imaging should occur prior to dosing. **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. **If RC is performed at Week C then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
Window	C D	Wk 0 – 7 D	N/A					CCI						
SCREENING- ONLY ASSESSMENTS (Section 8.1)														
Informed Consent	X													Must be obtained prior to performing any screening procedures.
Eligibility Confirmation	X													Must be assessed during screening period and confirmed prior to randomization.
Medical History including prior therapies	X													
Height	X													
Demographics	X													
Bladder Post Void Residual (PVR)	X													Per site's standard of care method (ie, bladder scan, catheterization).
Serology – HIV, HBsAg, HepB core antibody, HCV antibody	X													
Obtain TURBT biopsy	X													Biopsy slides should be from specimen taken within 120 days of randomization. Note: Specimens will be submitted for central review. Re-reading and confirmation of diagnostic slides required for participants referred from an outside institution.
De-bulking re-TURBT/biopsy (applicable for tumors >3 cm)	X													De-bulking completion TURBT is needed during screening for intravesical residual tumors >3 cm on assessment cystoscopy. Local pathology review.
Serum Pregnancy Test (POCBP)*	X													All pregnancy tests will be conducted by study site or local laboratory. *If urine is positive at any point during study, repeat with serum pregnancy testing
Randomization		X												

Table 1: Cohort 1 (TAR-200 + IV Cetrelimab)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZA-TION	Treatment Phase (Week)				TAR-200 Removal	**RC (may coincide with TAR-200 removal)	Post Radical Cystectomy Follow Up					Notes
Study Week												CCI		*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). Imaging should occur prior to dosing. **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. **If RC is performed at Week C then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
Window	C D	Wk 0 – 7 D	N/A	±				CCI						
SAFETY ASSESSMENTS (Section 8.1 and Section 8.8)														
Physical Exam	X*				X**							X**	X**	*Full PE to be done at screening **targeted PE to be done at disease assessment visits and any time on study if clinically indicated
ECOG	X				X							X	X	ECOG assessment to be done at screening, disease assessment visits, and any time on study if clinically indicated
Vital Signs with weight	X		X*	X	X	X	X	X	X	X	X	X	X	See Section 8.2 for further details on vital signs collections during IV cetrelimab
Electrocardiogram	X													To be done at screening and then if clinically indicated.
Adapted Revised Cardiac Risk Index for Pre-Operative Risk (RCRI)	X					*X								Must be performed at Screening and *at approximately 1-3 weeks prior to the anticipated RC date. Refer to Section 10.15, Appendix 15
Hematology, Blood Chemistry, (see Section 10.2, Appendix 2)	X*		X	X	X	X	X	X**	X	X	X	X	X	*Screening labs must be within 30 days of randomization. If collected within 5 days of Week 0, Week 0 labs may be omitted. For details see Section 10.2, Appendix 2 (Clinical Laboratory Tests). Glucose must be fasting at Screening. HbA1c must be performed at Screening through Week C post RC. HbA1c results can replace the requirement for fasting blood glucose prior to each dose; however, if fasting glucose results are available, the HbA1c result does not need to be reviewed prior to dosing, but should still be collected. T3 at screening, then only as clinically indicated. **Only necessary if Week C visit was done >3 weeks prior. Note: Inpatient lab assessments should be done per institutional standard of care.
Coagulation Panel			X				X							
Urinalysis	X		X	X	X	X								For details see Section 10.2, Appendix 2 (Clinical Laboratory Tests) Urinalysis to be performed prior to each TAR-200 insertion

Table 1: Cohort 1 (TAR-200 + IV Cetrelimab)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZA-TION	Treatment Phase (Week)				TAR-200 Removal	**RC (may coincide with TAR-200 removal)	Post Radical Cystectomy Follow Up					Notes
Study Week												CCI		*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). Imaging should occur prior to dosing. **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. **If RC is performed at Week C then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
Window	C D	Wk 0 – 7 D						CCI						
Urine Culture	X													For details see Section 10.2, Appendix 2 (Clinical Laboratory Tests) Recommend obtaining urine culture with adequate time for treatment of potential positive urine culture prior to Week 0. Urine culture only required for symptomatic patients (eg. urinary frequency, urgency, or dysuria) while on treatment.
Urine Pregnancy Test (POCBP)			X*	X	X	X	X	X	X**	X**	X**	X***		To be completed prior to each dose of study drug. If positive, repeat in serum. All pregnancy tests will be conducted by study site or local laboratory. *urine pregnancy test must be completed within 72 hours of the first dose of study treatment. **only if uterus/ovaries are not removed in POCBP ***Week 24 post RC visit only Note: Continued more frequent local pregnancy testing for POCBP should occur per local country regulations (eg, CTFG guidance).
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	
Adverse Events/SAE	X		X	X	X	X	X	X	X	X	X	X	X	AEs/SAEs will be captured from the informed consent (screening) until 100 days after last dose of study drug. Beyond 100 days after last dose, all study drug-related serious adverse events should be reported while participant is in study follow-up.
Product Quality Complaint (PQC) and Device Deficiencies			X	X	X	X	X	X*						Identified PQCs and device deficiencies should be reported at any time throughout the Treatment Phase. All initial PQCs (including Device Deficiencies) must be reported to the Sponsor by the study site personnel immediately, without undue delay or within 24 hours after being made aware of the event, as required by local regulations. If a PQC (including Device Deficiency) is reported, the TAR-200, cetrelimab or UPC must be retained under the correct storage conditions until a shipment request is received

Table 1: Cohort 1 (TAR-200 + IV Cetrelimab)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZA-TION	Treatment Phase (Week)				TAR-200 Removal	**RC (may coincide with TAR-200 removal)	Post Radical Cystectomy Follow Up					Notes
Study Week			CCI											*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). Imaging should occur prior to dosing. **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion.
Window	C D	Wk 0 – 7 D	N/A	CCI										**If RC is performed at Week C then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
														from the Sponsor. Instructions will be provided in the Study Reference Manual. *if TAR-200 removed at time of RC
Relevant Procedures (including GU events and procedures)	X		X	X	X	X	X	X	X	X	X	X	X	
DISEASE ASSESSMENTS (Section 8.7.1)														
Cystoscopy	X*		X	X	X**	X	X	X***						To mitigate the risk of UTI's, participants must receive at least one dose of periprocedural prophylactic antibiotics at time of TAR-200 insertion and/or removal *Repeat cystoscopy/TURBT within Screening is required for participants referred from an outside institution, different health care provider from study Investigator, known residual tumor >3 cm, and/or if previous assessment was not done within 42 days of randomization. **An assessment cystoscopy for participants in Cohort 1 and Cohort 2 may be performed at Week C if clinically indicated. *** If TAR-200 removed at RC
CT/MRI with contrast (chest, abdomen, and pelvis)	X				X						X	X	X	Should be performed prior to dosing. All imaging must be performed and confirmed by central review.
Radical Cystectomy Surgery							X*	X						*RC can be done at same visit of Week C TAR-200 removal Note: Specimens will be submitted for central review.
Survival Status Follow-up	X*													*To be completed every C weeks beginning after a patient discontinues from treatment and/or disease assessment follow up visits until end of study. May be obtained via telephone or other locally approved methods of contact. Other methods to obtain data per institutional SOC policy are acceptable. OS will be documented in the eCRF.
Subsequent anti-cancer therapies	X													To be completed every C weeks beginning after a patient discontinues from treatment and/or disease assessment follow up visits until end of study.

Table 1: Cohort 1 (TAR-200 + IV Cetrelimab)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZA-TION	Treatment Phase (Week)				TAR-200 Removal	**RC (may coincide with TAR-200 removal)	Post Radical Cystectomy Follow Up					Notes
Study Week												CCI		*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). Imaging should occur prior to dosing. **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. **If RC is performed at Week C then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
Window	C D	Wk 0 – 7 D						CCI						
Other Malignancies	X													To be completed every C weeks beginning after a patient discontinues from treatment and/or disease assessment follow up visits until end of study. Malignancy that is not related to the study indication. Other Malignancies can be recurrence of a prior malignancy or a tumor of completely new etiology. Metastases of the disease under study are not considered new malignancies. Benign neoplasms should not be reported on this form.
PATIENT-REPORTED OUTCOMES (Section 8.7.4)														
FACT-B1			X	X	X	X	X							Questionnaires should be completed prior to other assessments on the same day, in countries where approved and available. The PGIS and PGIC should be administered prior to other PRO assessments. The PGIC will not be administered at the first visit because it captures change.
PGIS			X	X	X	X	X							
PGIC				X	X	X	X							
HEATHCARE RESOURCE UTILIZATION AND HEALTH ECONOMICS (Section 8.14)														
Healthcare Resource Utilization		X	X	X	X	X	X	X	X	X	X	X	X	
STUDY DRUG (Section 8.2)														
TAR-200 Insertion			X	X	X	X								Insertion of TAR-200 and administration of IV cetrelimab do not need to occur on the same day but should occur no more than CCI of each other. On days in which both TAR-200 and IV cetrelimab will be administered. TAR-200 will be inserted at least CCI before the start of IV cetrelimab infusion, or at least CCI after the completion of IV cetrelimab infusion. If one treatment is held the other may still be administered in consultation with the sponsor. To mitigate the risk of UTI's, participants must receive at least one dose of periprocedural prophylactic antibiotics at time of TAR-200 insertion and/or removal.
Cetrelimab Administration (IV)			X	X	X	X								

Table 1: Cohort 1 (TAR-200 + IV Cetrelimab)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZA-TION	Treatment Phase (Week)				TAR-200 Removal	**RC (may coincide with TAR-200 removal)	Post Radical Cystectomy Follow Up					Notes
Study Week			[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI	[redacted]	*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). Imaging should occur prior to dosing. **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. **If RC is performed at Week C, then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
Window	C D	Wk 0 – 7 D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TAR-200 Removal with Cystoscopy				X	X*	X	X	X**						To mitigate the risk of UTI's, participants must receive at least one dose of periprocedural prophylactic antibiotics at time of TAR-200 insertion and/or removal *An assessment cystoscopy for participants in Cohort 1 and Cohort 2 must be performed at Week C if clinically indicated. TAR-200 will be removed at Week C visit CCI RC may be performed on the same day, provided TAR-200 is removed cystoscopically prior to cystectomy, but should occur no later than C weeks from CCI infusion visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. If participant discontinues treatment prior to Week C visit, please ensure the participant returns to clinic for TAR-200 removal within CCI of insertion. Used TAR-200 to be removed prior to insertion of new TAR-200. **if removed at time of RC
BIOMARKERS (Section 8.12) *Refer to Tables 3-7 for PK sample collection*														
Urine biomarker analyses	X*		X	X	X	X	X**							Note: Sample to be collected upon disease progression *Urine sample collection must occur immediately prior to TURBT, as applicable **Collection at CCI if RC is not performed at this visit
Biomarker in blood	X		X	X	X	X	X*		X	X	X	X	X	Note: Sample to be collected upon disease progression. *Collection at CCI if RC is not performed at this visit
Tumor biopsy/biomarker in tumor tissue	X*	X*	X*				X	X**						*Any pre-dose sample (1 collection) **if removed at time of RC

Abbreviations: AE=adverse event; CT=computed tomography; ctDNA= circulating tumor deoxyribonucleic acid; CTFG=Clinical Trial Facilitation and Coordination Group; D=day;

ECOG=Eastern Cooperative Oncology Group; FACT-Bl= Functional Assessment of Cancer Therapy – Bladder; MRI=magnetic resonance imaging; PE=physical exam; PGIC= Patient Global Impression of Change, PGIS= Patient Global Impression of Severity; POCBP=participants of childbearing potential; PQC=product quality complaint; PVR=post void residual; RC=radical cystectomy; SAE=serious adverse event; TURBT=transurethral resection of bladder tumor; UPC=Urinary Placement Catheter; Wk=week

Table 2: Cohort 2 (IV Cetrelimab Alone)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZATION	Treatment Phase (Week)				Week C Clinic Visit	**Radical Cystectomy	Post Radical Cystectomy Follow Up					Notes
Study Week			[redacted]				[redacted]	[redacted]	[redacted]			CCI		*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. **If RC is performed at Week C then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
Window	C days	Wk 0 – 7 D	N/A	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SCREENING- ONLY ASSESSMENTS (Section 8.1)														
Informed Consent	X													Must be obtained prior to performing any screening procedures.
Eligibility Confirmation	X													Must be assessed during screening period and confirmed prior to randomization.
Medical History including prior therapies	X													
Height	X													
Demographics	X													
Bladder Post Void Residual (PVR)	X													Per site's standard of care method (ie, bladder scan, catheterization).
Serology – HIV, HBsAg, HepB core antibody, HCV antibody	X													
Obtain TURBT biopsy	X													Biopsy slides should be from specimen taken within 120 days of randomization Note: Specimens will be submitted for central review. Re-reading and confirmation of diagnostic slides required for participants referred from an outside institution.
De-bulking re-TURBT/biopsy (applicable for tumors >3 cm)	X													De-bulking completion TURBT is needed during screening for intravesical residual tumors >3 cm on assessment cystoscopy. Local pathology review.
Serum Pregnancy Test (POCBP)*	X													All pregnancy tests will be conducted by study site or local laboratory. *If urine is positive at any point during study, repeat serum.
Randomization		X												
SAFETY ASSESSMENTS (Section 8.1 and Section 8.8)														
Physical Exam	X*				X**							X**	X**	*Full PE to be done at screening **targeted PE to be done at disease assessment visits and any time on study if clinically indicated

Table 2: Cohort 2 (IV Cetrelimab Alone)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZATION	Treatment Phase (Week)				Week C Clinic Visit	**Radical Cystectomy	Post Radical Cystectomy Follow Up					Notes
Study Week			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI	[redacted]	*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. **If RC is performed at Week C, then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
Window	C days	Wk 0 – 7 D	N/A	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ECOG	X				X							X	X	ECOG assessment to be done at screening, disease assessment visits, and any time on study if clinically indicated
Vital Signs with weight	X		X	X	X	X	X	X	X	X	X	X	X	See Section 8.2 for vital signs collection.
Electrocardiogram	X													To be done at screening and then if clinically indicated.
Adapted Revised Cardiac Risk Index for Pre-Operative Risk (RCRI)	X					*X								Must be performed at Screening and *at approximately 1-3 weeks prior to the anticipated RC date. Refer to Section 10.15, Appendix 15.
Hematology, Blood Chemistry, (see Section 10.2 Appendix 2)	X*		X	X	X	X	X	X**	X	X	X	X	X	*Screening labs must be within 30 days of randomization; If collected within 5 days of Week 0, Week 0 labs may be omitted. For details see Section 10.2, Appendix 2 (Clinical Laboratory Tests). Glucose must be fasting at Screening. HbA1c must be performed at Screening and through Week C post RC. HbA1c results can replace the requirement for fasting blood glucose prior to each dose; however, if fasting glucose results are available, the HBA1c result does not need to be reviewed prior to dosing, but should still be collected. T3 at screening, then only as clinically indicated. **Only necessary if Week C visit was done >3-weeks prior. Note: Inpatient lab assessments should be done per institutional standard of care.
Coagulation Panel			X				X							
Urinalysis	X		X	X	X	X								For details see Section 10.2, Appendix 2 (Clinical Laboratory Tests)
Urine Culture	X													For details see Section 10.2, Appendix 2 (Clinical Laboratory Tests) Recommend obtaining urine culture with adequate time for treatment of potential positive urine culture prior to Week 0. Urine culture only required for symptomatic patients (eg. urinary frequency, urgency, or dysuria) while on treatment.

Table 2: Cohort 2 (IV Cetrelimab Alone)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZATION	Treatment Phase (Week)				Week C Clinic Visit	**Radical Cystectomy	Post Radical Cystectomy Follow Up					Notes
Study Week			[redacted]				[redacted]	[redacted]	[redacted]			CCI		*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. **If RC is performed at Week C then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
Window	C days	Wk 0 – 7 D	N/A	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Urine Pregnancy Test (POCBP)			X*	X	X	X	X	X	X**	X**	X**	X***		To be completed prior to each dose of study drug. If positive, repeat in serum. All pregnancy tests will be conducted by study site or local laboratory. *urine pregnancy test must be completed within 72 hours of the first dose of study treatment. **only if uterus/ovaries are not removed in POCBP ***Week C post RC visit only Note: Continued more frequent local pregnancy testing for POCBP should occur per local country regulations (eg, CTFG guidance).
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	
Adverse Events/SAE	X		X	X	X	X	X	X	X	X	X	X	X	AEs/SAEs will be captured from the informed consent (screening) until 100 days after last dose of study drug. Beyond 100 days after last dose, all study drug-related serious adverse events should be reported while participant is in study follow-up.
Product Quality Complaint			X	X	X	X								
Relevant Procedures (including GU events and procedures)	X		X	X	X	X	X	X	X	X	X	X	X	
DISEASE ASSESSMENTS (Section 8.7.1)														
Cystoscopy	X*				--**									*Repeat cystoscopy/TURBT within Screening is required for participants referred from an outside institution, different health care provider from study Investigator, known residual tumor >3 cm, and/or if previous assessment was not done within 42 days of randomization. **An assessment cystoscopy for participants in Cohort 1 and Cohort 2 may be performed at Week C if clinically indicated.
CT/MRI with contrast (chest, abdomen, and pelvis)	X				X						X	X	X	Should be performed prior to dosing. All imaging must be performed and confirmed by central review
Radical Cystectomy Surgery							X*	X						*RC can be done at same visit of Week C however, it must be completed within 3 weeks of Week C visit.

Table 2: Cohort 2 (IV Cetrelimab Alone)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZATION	Treatment Phase (Week)				Week C Clinic Visit	**Radical Cystectomy	Post Radical Cystectomy Follow Up					Notes
Study Week			[redacted]				[redacted]	[redacted]	[redacted]			CCI		*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. **If RC is performed at Week C then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
Window	C days	Wk 0 – 7 D	N/A	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
														Note: Specimens will be submitted for central review.
Survival Status Follow-up	X*													*To be completed every C weeks beginning after a patient discontinues from treatment and/or disease assessment follow up visits until end of study. May be obtained via telephone or other locally approved methods of contact. Other methods to obtain data per institutional SOC policy are acceptable. OS will be documented in the eCRF.
Subsequent anti-cancer therapies	X													To be completed every C weeks beginning after a patient discontinues from treatment and/or disease assessment follow up visits until end of study.
Other Malignancies	X													To be completed every C weeks beginning after a patient discontinues from treatment and/or disease assessment follow up visits until end of study. Malignancy that is not related to the study indication. Other Malignancies can be recurrence of a prior malignancy or a tumor of completely new etiology. Metastases of the disease under study are not considered new malignancies. Benign neoplasms should not be reported on this form.
PATIENT-REPORTED OUTCOMES (Section 8.7.4)														
FACT-B1			X	X	X	X	X							Questionnaires should be completed prior to other assessments on the same day, in countries where approved and available. The PGIS and PGIC should be administered prior to other PRO assessments. The PGIC will not be administered at the first visit because it captures change.
PGIS			X	X	X	X	X							
PGIC				X	X	X	X							
HEALTHCARE RESOURCE UTILIZATION AND HEALTH ECONOMICS (Section 8.14)														
Healthcare Resource Utilization		X	X	X	X	X	X	X	X	X	X	X	X	
STUDY DRUG														
Cetrelimab Administration (IV)			X	X	X	X								

Table 2: Cohort 2 (IV Cetrelimab Alone)

*Procedures, Tests, & Evaluations	SCREENING	RANDOMIZATION	Treatment Phase (Week)				Week C Clinic Visit	**Radical Cystectomy	Post Radical Cystectomy Follow Up					Notes
Study Week			[redacted]				[redacted]	[redacted]	[redacted]			CCI		*It is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, any type of blood draw, and dosing to be conducted last (refer to Section 8). **Radical Cystectomy may be performed at Week C visit but should occur no later than 3 weeks from Week C visit. Radical Cystectomy surgery should not take place prior to Week C unless at Investigators discretion. **If RC is performed at Week C then additional RC visit (within table) is not required. Assessments at time of RC supersede Week C clinic visit assessments.
Window	C days	Wk 0 – 7 D	N/A	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BIOMARKERS (Section 8.12) *Refer to Tables 3-7 for PK sample collection*														
Urine biomarker analyses	X*		X	X	X	X	X**							Note: Sample to be collected upon disease progression *Urine sample collection must occur immediately prior to TURBT, as applicable. **Collection at CCI if RC is not performed at this visit
Biomarker in blood	X		X	X	X	X	X*		X	X	X	X	X	Note: Sample to be collected upon disease progression *Collection at CCI if RC is not performed at this visit
Tumor biopsy/biomarker in tumor tissue	X*	X*	X*				X	X**						*Any pre-dose sample (1 collection) ** If removed at time of RC

Abbreviations: AE=adverse event; CT=computed tomography; ctDNA= circulating tumor deoxyribonucleic acid; CTFG=Clinical Trial Facilitation and Coordination Group; D=day; ECOG= Eastern Cooperative Oncology Group; FACT-Bl=Functional Assessment of Cancer Therapy – Bladder; MRI=magnetic resonance imaging; PE=physical exam; PGIC= Patient Global Impression of Change, PGIS= Patient Global Impression of Severity; POCBP=participants of childbearing potential; PQC=product quality complaint; PVR=post void residual; RC=radical cystectomy; SAE=serious adverse event; TURBT=transurethral resection of bladder tumor; Wk=week

Pharmacokinetics

Table 3: Sparse Urine Pharmacokinetic Sampling for Gemcitabine and dFdU Analysis (Cohort 1 Only)

VISIT	PRIOR TO TAR-200 INSERTION	POST TAR-200 INSERTION
Within 24 Hours Pre-dose at Week 0 Visit	X	
Anytime between Days 2 to 7, following TAR-200 insertion on either CCI		X One pooled 24-hour Collection

Abbreviations: dFdU=2′,2′-difluorodeoxyuridine
Note: Sample collections and analyses will only be performed as local regulations permit.
Participants in the serial urine PK sampling are not required to complete the Week 0 and Week CCI sparse timepoints

Table 4: Serial Urine Pharmacokinetic – (up to 20 Participants in Cohort 1)

VISIT	PRIOR TO TAR-200 INSERTION	POST TAR-200 INSERTION
Within 24 Hours Pre-dose at Week 0	X	
Beginning at Week 0, on all days from Day 1 through Day 5, and from Day 8 through Day 12		X One pooled 24-hour Collection per day
Beginning at Week CCI on all days from Days 1 through Day 5, and from Day 8 through Day 12		X One pooled 24-hour Collection per day

Note: It is anticipated that up to 20 participants in Cohort 1 will participate in the serial urine sampling. Sample collections and analysis will only be performed as local regulations permit.

Table 5: Plasma Pharmacokinetic for Gemcitabine and dFdU Analysis (Cohort 1 Only)

VISIT	PRIOR TO TAR-200 INSERTION	POST TAR-200 INSERTION
Within 24 Hours Pre-dose at Week 0 Visit	X	
Anytime between Days 2 to 7, following TAR-200 insertion on either Week CCI		X One Sample Collection (Coincide with sparse urine PK)

Abbreviations: PK=pharmacokinetics
Note: Sample collections and analyses will only be performed as local regulations permit.

Table 6: Serum Pharmacokinetics for Cetrelimab (Cohort 1 and Cohort 2)

Time Points	[redacted]	[redacted]	CCI	[redacted]	**Post RC - Only 1 post RC sample below should be taken** depending on timing of RC	
					Post RC if RC performed prior to Wk C	Post RC if RC performed between Wk CCI Wk C
Pre-dose (trough) Draw within 30-minutes and before cetrelimab Infusion	X	X	X	X	X Sample should be taken anytime between Wk C and Wk C	X Sample should be taken anytime between Day 0 to Day 15 post RC
End of Infusion (EOI) CCI CCI [redacted]	X	X	X	X		

Abbreviations: EOI=end of infusion; RC=radical cystectomy; Wk=week

Note: RC should not be done prior to Week C unless at PI discretion (eg, pelvic nodal disease)

Note: Sample collections and analyses will only be performed as local regulations permit.

Table 7: Serum Immunogenicity Samples for Cetrelimab (Cohort 1 and Cohort 2)

Time Points	CCI	[redacted]	[redacted]	[redacted]	Post RC - Only 1 post RC sample below should be taken depending on timing of RC	
					Post RC if RC performed prior to Wk C	Post RC if RC performed between Wk C and Wk C
Pre-dose (trough) Draw within 30-minutes and before cetrelimab Infusion	X	X	X	X	X Sample should be taken anytime between Wk C and Wk C	X Sample should be taken anytime between Day 0 to Day 15 post RC

Abbreviations: RC=radical cystectomy
Note: Sample collections and analyses will only be performed as local regulations permit.
No additional blood sample will be collected for immunogenicity. Aliquot(s) from serum PK samples will be used for immunogenicity assessments. No separate blood sample collection required when samples are collected for PK serum also.

2. INTRODUCTION

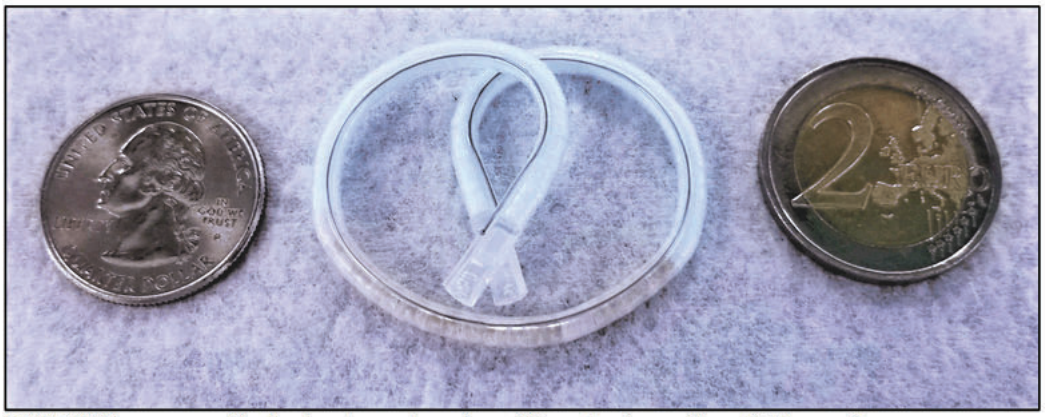
The Gemcitabine 225 mg intravesical delivery system (JNJ-17000139) product (hereafter, TAR-200) is an investigational intravesical drug-device combination product with a drug primary mode of action being the drug constituent, consisting of two components as described below:

- The drug constituent consists of gemcitabine minitablets (225 mg, free base equivalent) and osmotic minitablets containing CCI as the osmotic agent.
- The device constituent is comprised of a dual lumen CCI part with a CCI CCI and a CCI wire. The large lumen of the CCI part contains the gemcitabine and CCI minitablets and serves as an elementary osmotic pump to release drug in a controlled manner. The smaller lumen contains the CCI wire in a predefined form to provide retention of the system in the bladder during the indwelling period.

TAR-200 is inserted into the bladder using a co-packaged device, the Urinary Placement Catheter, also known as "the Inserter" (hereafter referred to as "UPC"). TAR-200 is removed from the bladder transurethrally via cystoscopy and endoscopic, non-cutting graspers.

TAR-200 is flexible and bi-oval in shape. The product size (less than 5-cm on the long axis), is visually comparable to the size of an American 25-cent coin or a European 2-euro coin (Figure 2) which is partially submerged, and freely mobile in the urine while indwelling in the bladder.

Figure 2: TAR-200



TAR-200 is comparable in size to an American 25-cent coin and/or a 2-Euro coin.

The UPC is a sterile, single-use, transient contact medical device, which has been specifically developed for the transurethral placement of TAR-200 into the bladder (Figure 3 and Figure 4). Refer to the TAR-200 Investigator's Brochure for further details regarding the UPC.

Cetrelimab

Cetrelimab (JNJ-63723283) is a fully human immunoglobulin G4 (IgG4) kappa monoclonal antibody (mAb) containing the hinge-stabilizing S228P mutation. Cetrelimab binds to programmed-cell death protein 1 (PD-1) with high affinity and specificity, blocks binding to the programmed-cell death ligands 1 and 2 (PD-L1 and PD-L2), enhances pro-inflammatory cytokine production from ex-vivo stimulated T cells, and reduces tumor volume in human PD-1 knock-in

(hPD-1KI) mice bearing MC38 murine colon carcinoma tumors. Two recommended Phase 2 doses (RP2Ds) were recently established in Study 63723283LUC1001, an ongoing, multicenter, Phase 1/2 First in Human study of cetrelimab in participants with advanced solid tumor malignancies. In this study, cetrelimab was administered intravenously (IV) at doses ranging from 80 mg once every 2 weeks (Q2W) up to 800 mg once every 4 weeks (Q4W). Doses of 240 mg Q2W and 480 mg Q4W were comparable in maintaining trough serum cetrelimab concentrations and saturation of PD-1 receptor occupancy throughout continued treatment with cetrelimab. The planned dose in this Phase 2b study is 360 mg once every 3 weeks (Q3W).

Note the definition of the following key terms used throughout this protocol:

- The term "Sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.
- The term "participant" throughout the protocol refers to the common term "subject".
- The term “study drug” throughout the protocol refers to TAR-200, or cetrelimab.
- The term “study treatment(s)” throughout the protocol refers to TAR-200 in combination with systemic IV cetrelimab (hereafter referred to as TAR200 + IV cetrelimab, Cohort 1), and IV cetrelimab alone (Cohort 2).

General abbreviations can be found in Section 10.1, Appendix 1, Abbreviations and Definitions.

2.1. Study Rationale

Bladder cancer is the tenth most common type of cancer worldwide (WCRF 2020) and sixth most common type of cancer in the US (National Cancer Institute 2019). Approximately 550,000 new bladder cancer cases occurred worldwide in 2018 (WCRF 2020). In the US, the prevalence of people living with bladder cancer was 708,444 in 2015 (National Cancer Institute 2019), and the National Cancer Institute estimated that 81,190 new cases and 17,240 deaths occurred in 2018.

Approximately 25% of all new bladder cancer patients present with muscle invasive bladder cancer (MIBC) at the time of diagnosis (Scarpato 2015), and roughly 50% will ultimately develop distant metastases (Milowsky 2016). The standard treatment generally involves neoadjuvant platinum-based chemotherapy, followed by radical cystectomy (RC) with bilateral lymph-node dissection (Scarpato 2015). Despite the aggressive nature of this standard treatment, the 5-year survival rates for patients with localized, regional, or distant disease are 69%, 35%, and 5%, respectively (American Cancer Society 2020). When measured as a cumulative per patient cost from diagnosis until death, the cost to treat bladder cancer exceeds all other forms of cancer (Kemp 2005). In 2017, the estimated national expenditure in the United States (US) on bladder cancer was $4.6B (Cancer Trends Progress Report 2019).

These findings illustrate the relatively poor efficacy of current therapies and the significant need for new treatment approaches for MIBC. Further, approximately 40% of patients with MIBC do not receive potentially curative therapy, consisting of neoadjuvant chemotherapy and RC or chemoradiotherapy, due to the high level of patient burden associated with these standards of care

(Gray 2013, Westergren 2019); these patients have a very poor overall prognosis, with median survival of less than one year (Duchesne 2000; Guerrero 2017).

The National Comprehensive Cancer Network (NCCN), American Urological Association (AUA), and European Association of Urology (EAU) guidelines for the management of MIBC are founded upon treatment paradigms that provide both local definitive therapy in combination with systemic control. There is substantial clinical evidence that effective targeting and eradication of primary bladder tumors significantly improves outcomes in MIBC patients with organ-confined disease. This is believed to be due to tumor debulking and the inhibition of disease dissemination deeper into the bladder wall, the lymph nodes of the pelvis, and beyond. Thus, combination treatment regimens affording local and systemic disease control, without concomitant overlapping toxicity, may result in improved overall survival (OS), as well as prolonged recurrence- and metastasis-free survival.

Radical cystectomy remains the standard of care in the management of MIBC, and systemic neoadjuvant chemotherapy is associated with increased OS. Specifically, pathologic partial and complete responses (pPR and pCR), as well as negative lymph node status at RC, correlate with meaningful disease-free and OS benefits (Sonpavde 2009). Systemic chemotherapy, however, is associated with significant toxicity, risks overtreatment in a significant proportion of patients, and up to 80% of patients may refuse or be ineligible for neoadjuvant and/or adjuvant regimens (Haseebuddin 2015). In this Phase 2 study, the approximate CCI window to RC is congruent with neoadjuvant treatment strategies that have been employed in other MIBC studies. There is a significant unmet need for efficacious and more tolerable neoadjuvant treatments, specifically for patients who are ineligible for cisplatin-based chemotherapy.

In recent years, new immunotherapeutic options have been developed for locally advanced and metastatic MIBC patients, specifically checkpoint inhibitors (PD-1/PDL-1 inhibitors). Integrating courses of pre-RC immunotherapy in nonmetastatic MIBC has the potential to become a new strategy for neoadjuvant therapy (Necchi 2018, Powles 2019) particularly in those patients unable to receive or refusing chemotherapy. The PURE-01 (pembrolizumab) and ABACUS (atezolizumab) neoadjuvant studies were designed to assess the efficacy of neoadjuvant anti-PD-1 antibody administration in patients with MIBC who were scheduled for RC and unable to receive platinum-based chemotherapy. Following dosing of systemic checkpoint blockade in the neoadjuvant period (PURE-01, 3 doses; ABACUS, 2 doses), both studies demonstrated significant improvements in pathologic downstaging rates at RC as compared to historical controls of transurethral resection of bladder tumor (TURBT) alone (Grossman 2003, Brant 2017). However, these response rates were not appreciably different from those previously demonstrated with classic platinum-based neoadjuvant chemotherapy regimens (Grossman 2003). The overall response rates to these immunotherapies remains approximately 30% (Powles 2019). There is a clear clinical need to identify treatment strategies that provide benefit for more patients with MIBC, potentially through a combination of systemic and local therapies, without significant additive toxicity (Stenehjem 2018; Bellmunt 2017).

Gemcitabine, an anti-metabolite routinely used in the systemic treatment of various forms of cancer, has demonstrated activity across all stages of urothelial cancer, from organ-confined recurrent low-grade tumors to metastatic disease (Calabro 2002; Grossman 2003; Messing 2018; Skinner 2013). TAR-200 is a passive, non-resorbable investigational drug-device combination product whose primary mode of action is the controlled release of gemcitabine into bladder urine. The novel design of TAR-200 provides continuous delivery of gemcitabine at an average of 24 mg/day over the first 7 days for a maximum of 225 mg delivered over 21 days.

By continuously administering gemcitabine at significantly lower doses than those employed in standard bladder instillations (~2 g/100 mL normal saline over 1 hour), Gemcitabine HCl Tablets 225 mg Intravesical Delivery System (TAR-200), or TAR-200, increases the effective tumor exposure 150‑fold (multi-day versus 1-hour instillation) and optimizes tumor uptake by maintaining intravesical concentrations approximating the human nucleoside transporter (HNT) 1,9's maximum saturable concentrations of 1- to 25-µg/mL. Prolonged gemcitabine delivery ensures uniform tumor contact, regardless of location within the bladder, as drug concentrations are maintained over many voiding cycles. Finally, because TAR-200 delivers extremely low, yet continuous and potent doses of gemcitabine to the bladder tissue (approximately 1% of the standard intravenous or intravesical instillation doses), such directed anti-tumor treatment significantly limits both systemic drug exposure and local bladder toxicity relative to standard dosing schemas employed today.

In this clinical study (17000139BLC2002), we hypothesize that metronomic gemcitabine dosing via TAR-200, in combination with cetrelimab, a PD-1 inhibitor, will not only have marked local cytotoxic effects on bladder tumors, but will have a systemic priming effect, increasing tumor antigen presentation as well as tumor antigen specific T-cell activation and maintenance. When these T cells are activated by co-treatment with cetrelimab, this systemic anti-tumor activity could potentially result in material benefits in patients with MIBC, including those groups that are not suitable for platinum-based chemotherapy.

2.2. Background

2.2.1. TAR-200 Clinical Studies

Rationale for TAR-200 Regimen

TAR-200 is available in one dose only (containing 225 mg free base equivalents of gemcitabine). Each TAR-200 releases gemcitabine into the bladder during the indwelling period, with the majority of drug being delivered within the first 7 days. TAR-200 maintains therapeutic gemcitabine urine concentrations, exceeding the EC_{90} of many bladder tumor cell lines in the bladder urine over the first 5 to 10 days (Jeon 2011). Studies have also demonstrated that prolonged gemcitabine exposure increases intracellular concentrations of the active di- and tri-phosphorylated metabolites, enhancing overall drug potency compared to short duration dosing (Cattel 2006).

Four prospective, open-label Phase 1b clinical studies evaluating TAR-200 have been completed in bladder cancer participants. Three of these studies were performed in MIBC patients; NCT02722538 evaluated TAR-200 neoadjuvant to RC in patients ineligible to receive or who refused cisplatin-based systemic chemotherapy, NCT03404791 evaluated those participants who were unfit for RC and ineligible to receive or refused cisplatin-based systemic chemotherapy; NCT03518320 evaluated TAR-200 in combination with nivolumab in patients with MIBC who were scheduled for RC and ineligible for or refused platinum-based neoadjuvant chemotherapy. One prior study, NCT02720367, has been performed in participants with non-muscle invasive bladder cancer (NMIBC). As of 26 February 2021, CC participants have attempted to undergo insertion with TAR-200, and C participants have undergone at least one dosing cycle across all four studies. Each of these studies were designed to evaluate safety, tolerability, PK, and preliminary efficacy following dosing with TAR-200. Additionally, gemcitabine pharmacokinetics following insertion of TAR-200 in MIBC patients scheduled for RC was evaluated in participants before or after TURBT (NCT02722538). Gemcitabine was not detected in plasma samples before or after TURBT, suggesting maximal tumor resection did not increase gemcitabine systemic exposure. Gemcitabine metabolites such as plasma 2′,2′-difluorodeoxyuridine (dFdU) concentrations were observed infrequently, with low but measurable concentrations found in CC of the CCI plasma samples analyzed, ranging from CCI (median CCI The frequency of positive dFdU samples was higher in participants administered TAR-200 before TURBT compared to after TURBT (CCI suggesting the tumor is the main source of plasma dFdU.

The Phase 1b clinical study NCT02722538 demonstrated that TAR-200 had encouraging anti-tumor activity in MIBC. This study of platinum-ineligible patients with bulky (>3 cm) muscle invasive urothelial carcinoma of the bladder (cT2 and T3), dosed with two 7-day cycles over 28 days prior to RC, complete ablation or substantial downstaging of the gross tumor was observed visually at the time of bladder removal in 8 of 10 patients (80%) (Daneshmand 2017). Furthermore, TAR-200 was well tolerated, with no exacerbation of urinary symptoms or hematuria, demonstrated no measurable systemic levels of gemcitabine, and did not result in bone marrow suppression or delay of RC. Moreover, CCI showed no nodal involvement on final histopathologic analysis and no patients were upstaged on final pathology.

In a separate study evaluating the safety and preliminary efficacy of TAR-200 in MIBC patients ineligible for curative intent therapy (NCT03404791), the complete response (CR) rate at 3 months following 4-cycles of TAR-200 was found to be 37.9%. These initial responses have been durable, with disease control rates of 67%. TAR-200 has been well-tolerated in this frail population with MIBC.

Please refer to the IB for further details on the ongoing TAR-200 clinical studies and published clinical studies investigating intravesical gemcitabine.

2.2.2. Cetrelimab Clinical Studies

Clinical experience with cetrelimab in humans to date is based on data from 7 clinical studies: 3 monotherapy studies (63723283LUC1001, 63723283LUC1002 [Part 1]), and

63723283HPB1001, and 5 combination studies, excluding those with TAR-200 (63723283LUC1002 [Part 2], 54767414MMY2036, 64091742PCR2002, 42756493BLC2002, and 56021927PCR2032). As of the clinical efficacy data cutoff date of 01 September 2022, a total of CCI participants have received at least 1 dose of cetrelimab as monotherapy (CCI participants) or in combination (CCI participants). Of the participants treated with cetrelimab monotherapy, CCI participants were evaluable for response.

Study 63723283LUC1001 is an ongoing First in Human, open-label, multicenter, Phase 1/2 study in participants with selected solid tumor types who previously received or were ineligible for standard treatment options. Safety and efficacy data available to date for participants receiving IV cetrelimab (Parts 1 and 2) are summarized below:

2.2.2.1. IV Cetrelimab

Part 1 of Study 63723283LUC1001, initiated on 21 November 2016, evaluated dose escalation cohorts and PK/pharmacodynamics cohorts. Part 1 established the RP2D, which may be administered at either 240 mg Q2W or 480 mg Q4W. In Part 2, initiated on 03 May 2017, this RP2D has been evaluated in selected solid tumor types, including non-small cell lung cancer (NSCLC), melanoma, renal cancer, bladder cancer, SCLC, gastric/esophageal cancer, and high-level microsatellite instability or mismatch-repair deficiency colorectal cancer. The purposes of dose expansion in Part 2 were to further characterize the safety and to assess the antitumor activity of the RP2D.

Part 1 (dose escalation) included CC participants, and Part 2 included CCI participants, for a total enrollment of CCI participants. The overall response rate (ORR) by RECIST 1.1 for all 204 treated participants was CCI , with CC participants having a confirmed response of complete response (CR) or partial response. The complete benefit rate by RECIST 1.1 for all treated participants was CCI with CC participants having a confirmed response of CR, partial response, or stable disease for at least 24 weeks from the start of treatment. CCI experienced at least 1 treatment-emergent AE, and CCI participants CCI experienced at least 1 treatment-related AE. In summary, the overall efficacy and safety profile for cetrelimab was consistent with that of other marketed anti-PD-1 antibodies such as pembrolizumab and nivolumab. However, the sample size for various tumor histologies included in the current study is small: (NSCLC=C participants; melanoma=C participants; bladder=C participants; renal cell C participants; SCLC: CC participants; MSI H/dMMR colorectal cancer (CRC)=C participants; other=C participants) (CSR 63723283LUC1001 2020).

As of the pharmacokinetic data cut-off date of 03 December 2019 the pharmacokinetic analysis included a total of CCI PK-evaluable participants. Cetrelimab clinical PK with IV administration was linear and dose proportional with moderate variability. The model-derived half-life of the terminal phase was approximately C days, indicating that steady state of serum cetrelimab concentration would be reached around approximately CCI weeks in advanced cancer patients, similar to endogenous immunoglobulins. Full PD-1 receptor occupancy with JNJ-63723283 was sustained for both 240 mg IV Q2W and 480 mg IV Q4W. The IV RP2Ds for JNJ-63723283 (both

240 mg Q2W and 480 mg Q4W) are considered comparable in maintaining trough concentration and receptor occupancy saturation and T cell maximal stimulation throughout the dosing interval.

The overall incidence of antibodies to IV cetrelimab in this study was low, CCI The CCI participants with positive antibody titers were part of Part 2 who were treated with CCI IV cetrelimab CCI participants had a sample positive for anti-drug antibody (ADA) with a titer of 1:25 at Dose 3, but had samples negative for ADA thereafter. CCI participant had a positive status for ADA with a titer of 1:25 starting at Dose 5 and maintained a positive status for ADA with the same titer thereafter.

2.2.3. Combination Therapy

One hypothesis to enable treatment durability, prevent immune evasion, and enhance anti-tumor immunity is to use metronomic chemotherapies that have been shown to have beneficial immunomodulatory effects, without causing significant toxicity, including lymphopenia. One such chemotherapy is gemcitabine, an anti-metabolite that is routinely used in conjunction with cisplatin in the treatment of muscle-invasive and metastatic urothelial carcinoma. Once internalized into the tumor cell via the hENT 1,9 transporter, gemcitabine becomes di- and tri-phosphorylated intracellularly, acting as an inhibitor of ribonucleotide reductase and as an anti-metabolite respectively, resulting in impaired deoxyribonucleic acid replication and cellular apoptosis (Massacesi 2005). In addition, preclinical studies show that gemcitabine may augment the anti-tumor T-cell response in a variety of ways eg, the following recently published and unpublished preclinical data discuss:

1. Gemcitabine-related apoptosis causes increased dendritic cell dependent antigen presentation to T cells (Nowak 2003);
2. In BALB mice bearing mesothelioma, gemcitabine led to depletion of B cells causing a relative increase in T cells (Nowak 2002);
3. Partial restoration of immune visibility of tumor cells by T cells may be caused by an upregulation of human leukocyte antigen-1 expression, which has been observed in vitro with gemcitabine (Liu 2010);
4. CCI
5. CCI Inhibition of TGF-β impairs $T_{regulatory}$ cell activation (Eriksson 2016);
6. CCI
7. CCI

8. Altered immune tumor microenvironment may increase the $T_{effector}$ population and/or decrease the $T_{regulatory}$ population. For example, in an orthotopic model of pancreatic ductal adenocarcinoma, local, low-dose gemcitabine therapy resulted in a decrease of the immunosuppressive CD4+/FoxP3+ $T_{regulatory}$ cells and improved survival in mice (Shevchenko 2013). Additionally, in a small cohort of participants with pancreatic cancer receiving gemcitabine, the ratio of $T_{effector}$:$T_{regulatory}$ was increased, myeloid-derived suppressor cells were decreased, TGFβ-1 levels were reduced, and the proliferative ability of T cells was unaffected (Eriksson 2016)

2.2.3.1. TAR-200 + IV Cetrelimab Combination

In addition to this study, TAR-200 + IV cetrelimab is currently being evaluated in 3 ongoing studies: 17000139BLC2001 (NCT04640623) in patients with Bacillus Calmette-Guérin (BCG) unresponsive high risk-NMIBC who are ineligible for or refusing RC, 17000139BLC3002 (NCT05714202) in participants with BCG-naïve, high-risk NMIBC, and 17000139BLC3001 (NCT04658862) in patients with MIBC who are not receiving RC. The Independent Data Monitoring Committees (IDMCs) conducted per charter to date for ongoing studies have recommended to continue studies unmodified. No safety concerns were identified (refer to the TAR-200 IB for safety data at the last data cut).

2.3. Benefit-Risk Assessment

The standard of care in MIBC includes RC with urinary diversion and is considered the preferred treatment option for patients who are considered surgical candidates. Systemic neoadjuvant chemotherapy for these patients is associated with increased OS. Specifically, pathologic partial and complete responses, as well as negative lymph node status, correlate with meaningful disease-free and OS benefits (Sonpavde 2009). However, systemic chemotherapy is associated with significant toxicity, and up to 80% of patients may refuse or be ineligible for neoadjuvant and/or adjuvant regimens (Haseebuddin 2015). There is a significant unmet need for efficacious and more tolerable neoadjuvant treatments, specifically for patients who are ineligible for cisplatin-based chemotherapy. A clinical benefit has been demonstrated in this platinum-ineligible patient population utilizing checkpoint inhibitor monotherapy (anti-PD-1/PDL-1) and provides rationale for potential efficacy of single-agent cetrelimab. (Necchi 2019; Powles 2019). In addition, it is postulated that the sustained antineoplastic local therapy of TAR-200, in combination with an efficacious anti-PD1 immunotherapy, could potentially provide comparable CR rates to neoadjuvant chemotherapy, without an overlapping toxicity profile.

Intravesical gemcitabine has consistently exhibited activity and a good toxicity profile in bladder cancer, albeit in the setting of non-muscle invasive disease (Shelley 2012). Ongoing clinical studies in MIBC and NMIBC have demonstrated good tolerability of intravesical dosing. Prior clinical trials evaluating the safety of TAR-200 itself have noted an excellent tolerability ad safety profile.

For safety details of intravesical gemcitabine and the TAR-200 drug-device combination product, refer to the most recent version of the IB.

Overall, the safety profile of cetrelimab monotherapy is well-tolerated and generally consistent across completed and ongoing clinical trials. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to cetrelimab dose level.

For the recognized pattern of immune-related adverse events that are defined, management algorithms have been developed. Treatment plans for diarrhea/colitis, renal insufficiency, pneumonitis, transaminitis, asymptomatic thyroid stimulating hormone elevation, symptomatic endocrinopathy, retinopathy, suspicion of adrenal crisis, rash, and neurological toxicity are provided in Section 10.9, Appendix 9, Guidelines for Management of Immune-Related Adverse Events and Adverse Events of Clinical Interest. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of cetrelimab, including results from other clinical studies, are also available in the cetrelimab IB.

Overall, for participants who are ineligible for cisplatin-based treatment, the treatment of TAR-200 in combination with IV cetrelimab or IV cetrelimab alone, has the potential to increase disease-free and survival periods relative to patients who are unable to receive neoadjuvant chemotherapy. CCI

Accounting for the measures taken to minimize adverse events in participants of this study, the identified potential risks of TAR-200 in combination with IV cetrelimab are justified by the anticipated benefits that may be afforded to participants with MIBC who are scheduled for radical cystectomy and ineligible for platinum chemotherapy.

From a risk-based alternative treatment perspective, chemoradiotherapy has been proposed as an alternative to RC. Several organizations, including the AUA and the EAU, have updated their guidelines to support chemoradiotherapy as an alternative to RC in patients with muscle-invasive disease. However, chemoradiotherapy has been associated with both acute and latent toxicity, including local and systemic symptoms. Such acute toxicities include anemia, fatigue, colitis, and cystitis, while latent longer-term toxicities and side effects may include bladder contracture, hemorrhagic cystitis, secondary malignancy, and urethral or rectal stricture. Therefore, while participants in this clinical study should be counseled on all treatment options, radical cystectomy remains a standard of care.

More detailed information about the known and expected benefits and risks of TAR-200 and cetrelimab may be found in the respective IBs for these study drugs.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the anti-tumor effects of TAR-200 + IV cetrelimab (Cohort 1) and IV cetrelimab alone (Cohort 2)	• pCR rate at RC is defined as the proportion of participants with a pathologic complete response (pCR) or ypT0N0 on RC specimen. pCR will be derived from analysis of the RC bladder specimen.
Secondary	
• To evaluate the safety and tolerability of up to 4 dosing cycles of TAR-200 + IV cetrelimab (Cohort 1) and IV cetrelimab (Cohort 2) alone prior to RC	• Frequency and grade of AEs (according to CTCAE version 5) • Laboratory abnormalities: CTCAE grades comparing baseline to the worst post-baseline value.
• To determine the recurrence-free survival (RFS) in participants receiving TAR-200 + IV cetrelimab (Cohort 1), and IV cetrelimab alone (Cohort 2)	• RFS - time from first dose of any study treatment to first radiologic (as assessed by RECIST 1.1 criteria) or histologic evidence of nodal or metastatic disease or death due to any cause.
Exploratory	
• To assess the participant's cancer-related Quality of Life (QoL) using the FACT-Bl (Functional Assessment of Cancer Therapy – Bladder)	• Change in sub-scale and total scores from baseline through Week 12 of study drug treatment.
• To evaluate changes in gene or protein expression in the tumor, blood and urine with the correlation of other endpoints	• Analysis of pretreatment and on-study tissue. blood and urine samples via assessment of circulating tumor DNA, DNA seq and/or and RNA seq, or alternative methods.
• To determine whether the baseline immune status, molecular subtype or mutational status influences treatment response	• Expression of PD-L1, and other immune markers by immunohistochemistry (IHC) or alternate methods. • Molecular subtyping and expression of immune signatures by RNA-sequencing (RNA-seq) and mutational status by DNA sequencing.
• To determine the OS in participants receiving TAR-200 + IV cetrelimab (Cohort 1), and IV cetrelimab alone (Cohort 2)	• Time from first dose of any study treatment to death.
• To determine the pathologic overall response (pOR) rate at RC in TAR-200 + IV cetrelimab (Cohort 1), and IV cetrelimab alone (Cohort 2)	• pOR rate at RC is defined as the proportion of participants with a pOR, which is determined by composite evaluation of local disease in the bladder and evaluation of radiographic and surgical nodal as well as metastatic disease as defined in protocol. • pOR rate is defined as the proportion of participants with either ypCR or ypPR. The

Objectives	Endpoints
	response assessments are presented for participants who are N0 at the start of the study in Table 10.
• To determine time to symptomatic progression (TSP) in participants receiving TAR-200 + IV cetrelimab (Cohort 1), and IV cetrelimab alone (Cohort 2)	Time from first dose of any study treatment to documentation of any of the following (whichever occurred earlier): • Progression of pain or worsening of disease-related symptoms requiring initiation of a new systemic anticancer therapy. • Development of clinically significant symptoms due to locoregional tumor progression requiring surgical intervention or radiation therapy. • Development of symptomatic deterioration on the basis of global deterioration of health status.
• To explore the relationships between PK, pharmacodynamic, adverse event profile, and antitumor activity	• Quantitative relationship between PK parameters, pharmacodynamic parameters, and safety/efficacy parameters.
• To evaluate the PK of gemcitabine (TAR-200) and major metabolite dFdU in urine and plasma following administration of TAR-200 in combination with IV cetrelimab (Cohort 1)	Gemcitabine and dFdU concentrations in urine and plasma.
• To evaluate the PK and immunogenicity of cetrelimab in serum following administration of TAR-200 in combination with IV cetrelimab (Cohort 1), and IV cetrelimab alone (Cohort 2)	• Serum concentration of cetrelimab and incidence of anti-cetrelimab antibodies.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis is that the treatment with TAR-200 + IV cetrelimab and IV cetrelimab alone will produce a pCR rate >20%. The statistical evaluation of the hypothesis will use a Bayesian approach to assess the likelihood of whether a true pCR rate ≤20% can be ruled out.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, open-label, multicenter, Phase 2 clinical study of intravesical gemcitabine delivered via TAR-200 in combination with neoadjuvant IV cetrelimab and neoadjuvant IV cetrelimab alone in participants with muscle-invasive urothelial carcinoma of the bladder (clinically referred to as MIBC) who are scheduled for RC and are ineligible for or refusing platinum based neoadjuvant chemotherapy. The initial, diagnostic TURBT confirming a pathologic diagnosis of cT2-T4a MIBC must have been completed within 120 days of randomization. All participants who have confirmed MIBC with absence of nodal or metastatic

disease at screening and have met all eligibility criteria will be randomly assigned (5:3) to receive intravesical TAR-200 in combination with IV cetrelimab (Cohort 1, Table 1) or IV cetrelimab alone (Cohort 2, Table 2). Two stratification factors for analysis will be completeness of TURBT (visibly complete vs incomplete and ≤3 cm) and tumor stage (cT2 vs. cT3-4a) at initial diagnosis. Participants must have tumor volume ≤3 cm prior to randomization.

A target of 160 participants will be enrolled and be randomly assigned in a 5:3 ratio in this study with 100 participants planned to be randomized into Cohort 1 and 60 participants into Cohort 2.

Potential participants with newly diagnosed, histologically confirmed, muscle-invasive urothelial carcinoma of the bladder will be screened following documented informed consent. Participants who underwent the diagnostic TURBT at an outside, referring institution from the study site, will undergo a screening assessment cystoscopy within the [redacted]-day screening window. Residual tumors >3 cm at this screening cystoscopy will undergo repeat completion re-TURBT prior to randomization. Formal evaluation of the diagnostic TURBT pathologic specimens will initially be performed by the study site and confirmed by central pathologic review. Staging imaging will be performed during the screening period to ensure the absence of N+ or M+ disease (as assessed by RECIST 1.1). This imaging will undergo central radiology review. Participants who meet eligibility criteria will be randomly assigned (5:3) to receive intravesical TAR-200 in combination with IV cetrelimab (Cohort 1) or IV cetrelimab alone (Cohort 2) neoadjuvant to scheduled radical cystectomy and urinary diversion. For Cohort 1, at the initial treatment visit, TAR-200 will be placed intravesically via the UPC and cetrelimab will be dosed intravenously (360 mg via a 60 [+/-10] minute initial IV infusion). For Cohort 1 and Cohort 2, IV cetrelimab will be dosed approximately every 21 days for 4 consecutive cycles, with cycles starting at Week 0, Day 1. Subsequent doses will be administered at [redacted] Cetrelimab is not required to be administered on the same day as placement of TAR-200, but treatments should occur within [redacted] and no more than [redacted] of each other. On days in which both TAR-200 and IV cetrelimab are administered on the same day, TAR-200 placement should be separated by a minimum of [redacted] from the start of IV cetrelimab infusion to allow for discrete evaluation of potential adverse events of each treatment.

For Cohort 1, the initial TAR-200 will be removed via flexible and rigid cystoscopy at [redacted] and then the second TAR-200 will be placed via a UPC. This removal/replacement procedure will be repeated for [redacted] The fourth TAR-200 will be removed at [redacted]). A cystoscopy is not required at these visits if TAR-200 removal is not needed.

For all cohorts, cetrelimab will be dosed approximately every 21 days for 4 consecutive cycles, with cycles starting at Week 0, Day 1. Subsequent doses will be administered at Weeks [redacted]

For all cohorts, Week 0, Day 1 will be defined as the day of the first dose of the first treatment administered. The RC should occur no later than [redacted] weeks following the Week [redacted] visit. During Week [redacted] participants in all cohorts will undergo an imaging assessment via computed tomography/magnetic resonance imaging (CT/MRI). If metastatic progression is noted on the local

report and confirmed by central radiology review, the participant will be discontinued from the efficacy (imaging) follow-up and continued to be followed for survival status, subsequent anti-cancer therapies, and other malignancies. If local progression is suspected or clinical symptoms warrant, the participant will proceed with immediate RC and urinary diversion, at local Investigator's discretion. If the RC is delayed, from the Week C visit, the date of the RC surgery will become the protocol-specified 'RC visit' (per Schedule of Activities, Section 1.3).

Following the RC and urinary diversion, all participants will have a safety follow-up visit 4 weeks following the RC surgery. Additionally, participants will have follow-up study visits at Weeks 8, 12, 24, 36, 48, 60, 72, 84, 96, and 108 (End of Study) post RC. The post RC follow-up visits (eg, Weeks 4, 8, 12, 24, etc) are derived from the date of the RC surgery. No restrictions are placed on adjuvant therapy after RC.

An IDMC will be commissioned for this study. Refer to Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations for details.

Diversity and Inclusion

Cancer affects all population groups in the United States, but due to social, environmental, and economic disadvantages, certain groups bear a disproportionate burden of cancer compared with other groups. Although cancer incidence and mortality overall are declining in all population groups in the United States, certain groups continue to be at increased risk of developing or dying from particular cancers.

The 17000139BLC2002 study will aim to enroll a participant population that is geographically reflective of the overall incidence/prevalence of MIBC. Enrollment of study participants in a given country may continue beyond the global enrollment period defined to reach the overall planned sample size, in order to ensure adequate representation of this country in the study.

For further discussion of diversity metrics and goals, refer to the latest version of the Diversity Plan.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Radical cystectomy remains the standard of care in the management of MIBC, and systemic neoadjuvant chemotherapy is associated with increased overall survival. Specifically, pathologic partial and complete responses, as well as negative lymph node status at RC, correlate with meaningful disease-free and overall survival benefits (Sonpavde 2009). This Phase 2 study design is congruent with previous studies such as PURE-01 (pembrolizumab) and ABACUS (atezolizumab) neoadjuvant studies, which were designed to assess the efficacy of neoadjuvant anti-PD-1 antibody administration in patients with MIBC who are scheduled for Radical Cystectomy. In addition, the primary and secondary outcome measurements are also in alignment with previously conducted trials.

While this clinical study is similar in study design and outcome measurements as previously conducted neoadjuvant MIBC studies, it also has differentiating factors which include additional dosing of an anti-PD-1 antibody (cetrelimab), and inclusion of intravesical treatment (TAR-200). Given the prior data from NCT02722538, this study will be stratified by complete vs. incomplete resection status, as well as tumor stage (cT2 vs cT3-4a).

Moreover, this Phase 2 clinical study within our bladder portfolio of trials, will provide supportive data demonstrating the impact the individual components of TAR-200 and cetrelimab in participants with MIBC.

Given the proven benefit of neoadjuvant therapy, prior studies, and potential synergies between local and systemic treatment, we postulate the pCR rates and RFS will meet or exceed prior studies.

Biomarker Collection

Biomarker samples will be collected from participants in all cohorts to evaluate the mechanism of action of TAR-200 + IV cetrelimab and IV cetrelimab alone or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to a study treatment.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Patient-Reported Outcomes Research

A patient-reported outcome (PRO) is any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy. PRO instruments are used to measure these patient reports. PROs provide a unique perspective on medical therapy, because some effects of a health condition and its therapy are known only to patients. Patient-reported outcome instruments capture meaningful change in patient-reported health status to assess health-related quality of life (HRQoL) for participants treated with TAR-200 and IV cetrelimab (Cohort 1) and IV cetrelimab alone (Cohort 2). The disease specific PRO captured in this clinical trial is the Functional Assessment of Cancer Therapy – Bladder (FACT-Bl). The Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC) will also be administered to participants within the study to provide anchor-based assessment. In approved countries, these PRO measures will be administered to test the hypothesis that treatment with TAR-200 and IV cetrelimab maintains a HRQoL as measured by time to symptom deterioration (TSP) of a prespecified meaningful change threshold. PRO data will be collected as outlined in the Schedule of Activities (Section 1.3).

Medical Resource Utilization Data Collection

Treatment of MIBC with TAR-200 in combination with systemic IV cetrelimab and systemic IV cetrelimab alone may result in lower utilization of medical resources. Exploratory analyses of Medical Resource Utilization (MRU) data collected for participants in both treatment groups will be performed.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

For the purposes of this study, all references to participants who have provided consent refers to the participants and the participant's legal guardian(s) or legally acceptable representative(s) who have provided consent.

The total blood volume that will be collected is considered within the normal range allowed for this participant population over this time frame. For adult participants, the amount of blood collected is less than the American Red Cross (ARC) standard blood donation of 500 mL over 60 days (ARC 2020) and is aligned with World Health Organization (WHO) blood donation guidelines (WHO 2020).

4.3. Justification for Dose

4.3.1. TAR-200 Dose Selection

TAR-200 is available in one dose only (containing 225 mg free base equivalents of gemcitabine); the TAR-200 which will remain indwelling for up to 21 days (3 weeks) per each dosing cycle. For Cohort 1, the first TAR-200 will be removed via flexible or rigid cystoscopy at CCI [redacted] and then the second TAR-200 will be placed via the UPC. This removal/replacement procedure will be repeated for a CCI [redacted] respectively. The fourth TAR-200 will be removed at CCI CCI [redacted]

Each TAR-200 releases gemcitabine into the bladder during the indwelling period, with the majority being delivered within the first 7 days. TAR-200 maintains therapeutic gemcitabine urine concentrations, exceeding the EC90 of many bladder tumor cell lines, in the bladder urine over the first 5 to 10 days (Jeon 2011). Studies have demonstrated that prolonged gemcitabine exposure increases intracellular concentrations of the active di- and tri- phosphorylated metabolites enhancing overall drug potency compared to short duration dosing (Cattel 2006).

The first dosing regimen (TAR-200-101) evaluated in human studies comprised two 7-day dosing cycles with a 14-day recovery period in between dosing cycles. This regimen was found to be well tolerated in the initial study participants. CCI [redacted]

concentration of gemcitabine remaining in the TAR-200 after 7 days is low, and the rate of release of additional gemcitabine at Day 7 is minimal. The safety of 21-day (3 week) dosing cycles has been evaluated in 2 completed Phase 1b clinical studies (NCT02720367, NCT03518320) and has been generally well tolerated to date based on preliminary data of these studies. A third study, TAR-200-103/NCT03404791 is currently ongoing.

As there is only one dose option for TAR-200 there will be no dose modifications of TAR-200. Information regarding the management of missed cycles and stopping rules are outlined in Section 6.5.1.

4.3.2. IV Cetrelimab Dose Selection

For this study, Cohort 1 and Cohort 2 will receive IV cetrelimab dosed at 360 mg Q3W for four doses, neoadjuvant to RC, which aligns with the dosing frequency of TAR-200. The 360 mg Q3W IV regimen was selected based on population PK modeling and simulation of cetrelimab, which predicted that the steady state predose concentration at steady-state (C_{trough}) and maximum serum concentration (C_{max}) of cetrelimab CCI [redacted]

The recommended monotherapy dose for cetrelimab is based on clinical activity in the ongoing Phase 1 Study 63723283LUC1001. CCI [redacted]

4.4. End of Study Definition

End of Study Definition

The end of study is considered as approximately 2 years after the last participant receives RC. The study can be prematurely ended per Sponsor decision, as outlined in Section 7 and Section 10.3.14. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

Participant Completion of Study Definition

A participant will be considered to have completed the study if they have completed the treatment and follow-up phases or died before the end of the treatment or follow-up phases. 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 in the Follow-Up Phase. However, if a participant develops metastatic disease progression, they should be discontinued from the efficacy (imaging) follow up portion of the study and continued to be followed for survival status, subsequent anti-cancer therapies, and other malignancies per Section 1.3. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her 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

This study will randomize approximately 160 participants with MIBC. The TURBT resulting in pathologic evidence of an initial diagnosis of cT2-T4a MIBC must be within 120 days of randomization. The participant must also undergo screening CT/MRI imaging to confirm N0, M0 disease status (assessed per RECIST 1.1). The screening period for the study will be [redacted] days (refer to Schedule of Activities, Section 1.3). Refer to Section 5.4, Screen Failures, for conditions under which the repeating 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 9.2, Sample Size Determination.

5.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristic

2. Criterion modified per Amendment 2

   2.1 Histologically proven, cT2-T4a N0, M0 infiltrating urothelial carcinoma (AJCC 2017) of the bladder. Initial diagnosis must have been within 120 days of

randomization date. Participants with variant histologic subtypes are allowed if tumor(s) demonstrate urothelial predominance. However, the presence of small cell or neuroendocrine variants will make a participant ineligible.

3. Criterion modified per Amendment 2

3.1 Participants with no residual tumor, or intravesical tumor size of ≤3 cm following TURBT are eligible; debulking TURBT for any residual disease is encouraged but not mandated. Participants with persistent tumors >3 cm at screening must undergo a second debulking, re-staging TURBT. Participants will be ineligible if any individual tumor is >3 cm after debulking TURBT.

4. Criterion modified per Amendment 1

4.1 Deemed eligible for and willing to undergo RC by the attending urologist. Investigators should refer to Section 10.15, Appendix 15 for guidance on assessing cardiac risk via the Adapted Cardiac Risk Index for Pre-Operative Risk (RCRI).

5 Eastern Cooperative Oncology Group (ECOG) performance status Grade 0 or 1 (Section 10.12, Appendix 12, ECOG Performance Status Scale).

6. Criterion modified per Amendment 1

6.1 Criterion modified per Amendment 2

6.2 Thyroid function tests within normal range or stable on hormone supplementation per Investigator assessment. Note: If thyroid stimulating hormone (TSH) is not within normal limits, the subject may still be eligible if T3 (either total or free) and free T4 are within normal limits. Investigators may consult an endocrinologist for participant eligibility assessment in the case of equivocal or marginal tests results.

7. Criterion modified per Amendment 1

7.1 Criterion modified per Amendment 2:

7.2 Adequate bone marrow, liver, and renal function:

a. Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks):
   i. Absolute neutrophil count (ANC) ≥1,500/mm^3
   ii. Platelet count ≥80,000/mm^3
   iii. Hemoglobin ≥9.0 g/dL

b. Liver function:
   i. Total bilirubin ≤1.5xULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5xULN (except participants with Gilbert's Syndrome, who must have a total bilirubin <3.0 mg/dL),
   ii. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5x institutional ULN

c. Renal function:

i. Creatinine clearance ≥30 mL/min calculated using the Cockcroft-Gault formula (see Section 10.17, Appendix 17)

8. Criterion modified per Amendment 2:

8.1 Participants must refuse cisplatin-based combination chemotherapy (and understand the risk and benefits of doing so) or be deemed ineligible for cisplatin-based chemotherapy by meeting at least one of the following criteria:

- GFR <60 mL/min/1.73 m^2 (assessed using the CKD-EPI equation) (see Section 10.18, Appendix 18)
- Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Grade ≥2 audiometric hearing loss
- CTCAE version 5.0 Grade ≥2 peripheral neuropathy

9. Prior systemic chemotherapy for indications other than urothelial cell carcinoma of the bladder is permitted, but interval between this treatment and study enrollment must exceed 24 months. All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI-CTCAE version 5.0) or baseline before administration of study treatment. Participants with toxicities attributed to prior anticancer therapy which are not expected to resolve and result in long lasting sequelae, such as peripheral neuropathy after platinum-based therapy or audiometric hearing loss, are ineligible.

10. All adverse events associated with any prior surgery must have resolved to CTCAE version 5.0 Grade <2 prior to randomization.

Sex and Contraceptive/Barrier Requirements

11. Criterion modified per Amendment 1

11.1 Criterion modified per Amendment 2

11.2 Contraceptive use by participants should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies (See Section 10.5, Appendix 5: Contraceptive and Barrier Guidance). Investigators will advise participants on the options for banking of sperm and ova for reproductive conservation. A female participants must agree not to be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study treatment.

a. A female participant must be either of the following (as defined in Section 10.5, Appendix 5: Contraception and Barrier Guidance):

i. Not of childbearing potential

ii. Of childbearing potential and

- practicing true abstinence, or

- have a sole partner who is vasectomized, or
- practicing at least 1 highly effective user independent method of contraception (see Section 10.5, Appendix 5: Contraception and Barrier Guidance).

Participant must agree to continue the above throughout the study and for 6 months after the last dose of study treatment.

Note: If a participant becomes of childbearing potential after start of the study, the participant must comply with point (ii), as described above.

A female participant must also:

- agrees to not donate eggs (ova, oocytes, or freeze for future use) for the purposes of assisted reproduction during the study and for at least 6 months after the last dose of study treatment.
- not be breastfeeding (including temporarily withholding breastfeeding in order to participate in the study) and not planning to become pregnant during the study and for at least 6 months after the last dose of study treatment. Female participants should consider preservation of eggs prior to study treatment as anti-cancer treatments may impair fertility. Investigators will advise female participants on the options for banking of ova for reproductive conservation.

b. A male participant must wear a condom (with or without spermicidal foam/gel/film/cream/suppository) when engaging in any activity that allows for passage of ejaculate to another person during the study and for a minimum of 6 months after receiving the last dose of study treatment. His female partner, if of childbearing potential, must also be practicing a highly effective method of contraception (see Section 10.5, Appendix 5: Contraception and Barrier Guidance).

If the male participant is vasectomized, he still must wear a condom (with or without spermicidal foam/gel/film/cream/suppository), but his female partner is not required to use contraception.

A male participant must also:

- agree to not donate sperm for the purpose of reproduction during the study and for a minimum of 6 months after the last dose of study treatment
- not plan to father a child while enrolled in this study or within 6 months after the last dose of study treatment. Male participants should consider preservation of sperm prior to study treatment as anti-cancer treatments may impair fertility. Investigators will advise male participants on the options for banking of sperm for reproductive conservation.

12. Criterion modified per Amendment 1

12.1 A female participant of childbearing potential must have a highly sensitive negative serum (β-human chorionic gonadotropin [β-hCG]) or urine test at

screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study, that may exceed those listed in the Schedule of Activities (Section 1.3).

Informed Consent

13. 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 agree to store samples when applicable.

5.2. Exclusion Criteria

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

Medical Conditions

1. Criterion modified per Amendment 1:
   1.1 Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:
      a. skin cancer (non-melanoma or melanoma) that is considered completely cured.
      b. non-invasive cervical cancer that is considered completely cured.
      c. Localized prostate cancer (N0M0):
         - with a Gleason score of 6, treated may include surgery, radiation, or ablation) within the last 24 months or untreated and under active surveillance,
         - with a Gleason score of 3+4 that has been treated (may include surgery, radiation, or ablation) more than 6 months prior to full study screening and considered to have a very low risk of recurrence,
         - or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
      d. Breast cancer:
         - adequately treated lobular carcinoma in situ or ductal carcinoma in situ,
         - or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
      e. Malignancy that is considered cured with minimal risk of recurrence

2. Criterion modified per Amendment 1

   2.1 Must not have received prior systemic chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to starting study treatment (treatment exceptions not precluding participants from enrollment are noted in the active malignancies exclusion criterion).

3. Must not have had urothelial carcinoma or histological variant at any site outside of the urinary bladder. Ta/T1/CIS of the upper urinary tract (including renal pelvis and ureter) is allowable if treated with complete nephroureterectomy more than 24 months prior to randomization.

4. Criterion modified per Amendment 2:

   4.1 Participants must not have evidence of cT4b, or N1-3, or M1 disease based on central radiology staging (chest, abdomen, and pelvis must be performed using CT or MRI) within 42 days prior to randomization.

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.

6. Uncontrolled adrenal insufficiency.

7. A history of clinically significant polyuria with recorded 24-hour urine volumes greater than 4,000 mL.

8. Criterion modified per Amendment 2

   8.1 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.

9. Must not have active tuberculosis.

10. Criterion deleted per Amendment 1

11. Pyeloureteral tube externalized to the skin is exclusionary. Unilateral nephrostomy tube or ureteral stent is permitted as long as it does not interfere with placement or retention of TAR-200 in the bladder. Bilateral ureteral stents are exclusionary.

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

13. Criterion modified per Amendment 2:

    13.1 Participants with an active, autoimmune disease that has required systemic treatment in the past 2 years are excluded. Participants with autoimmune disorders not requiring systemic treatment or conditions requiring hormonal replacement therapies such as type 1 diabetes mellitus or hypothyroidism are permitted to enroll.

14. Participants must not have clinically significant liver disease that precludes participant treatment regimens prescribed on the study (including, but not limited to active viral, alcoholic, or other autoimmune hepatitis, cirrhosis, or inherited liver disease).

15. Criterion modified per Amendment 1:

    15.1 Human immunodeficiency virus (HIV) infection, unless the participant has been on a stable anti-retroviral therapy regimen for the last 6 months or more and has had no opportunistic infections and a CD4 count of >350 in the last 6 months.

16. Criterion modified per Amendment 2:

    16.1 Evidence of active or chronic hepatitis B or C infection (however, participants with history of hepatitis C infection but normal hepatitis C virus polymerase chain reaction test and participants with hepatitis B with positive HBsAg antibody are allowed).

17. Criterion modified per Amendment 2:

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

18. Criterion deleted per Amendment 2

19. Evidence of interstitial lung disease or active non-infectious pneumonitis.

20. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.

21. Criterion modified per Amendment 2:

    17.1 Participants with current acute diverticulitis, intra-abdominal abscess, gastrointestinal obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation, and participants who have a history immune-mediated colitis.

22. Criterion deleted per Amendment 2

Prior/Concomitant Therapy

23. Not recovered from adverse events due to a previously administered agent.

24. Prior systemic chemotherapy for urothelial cell carcinoma of the bladder at any time.

25. Pelvic radiotherapy administered less than 6 months prior to screening. Participants who received radiotherapy ≥6 months prior to screening must demonstrate no cystoscopic evidence or symptoms of radiation cystitis.

26. Criterion modified per Amendment 1:

    26.1 Criterion modified per Amendment 2

    26.2 Received a live virus vaccine within 30 days of initiation of study treatment. Inactivated (non-live or non-replicated) vaccines approved or authorized for emergency use (eg, Coronavirus Disease 2019 [COVID-19]) are allowed (see Section 6.8). (Note: Specifically, for COVID-19 vaccines, please refer to Section 10.11, Appendix 11, Study Conduct During a Natural Disaster)

27. Criterion deleted per Amendment 2

28. Criterion modified per Amendment 1:

    28.1 Active infection requiring systemic intravenous therapy within 14 days prior to randomization. See exclusion criterion 17 for information regarding UTI.

29. Criterion modified per Amendment 1:

    29.1 Received intervening intravesical chemotherapy or immunotherapy from the time of most recent cystoscopy/TURBT to starting study treatment. Immediate post-TURBT single-dose peri-operative intravesical chemotherapy is allowed per institutional guidelines in the screening phase.

30. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

31. Participants with a history of Grade ≥3 toxic effects when using anti-TNF or anti-IL-6 agents are excluded.

32. Participants still recovering from toxicity of prior anticancer therapy which was received more than 24 months prior to enrollment (except toxicities which are not clinically significant such as alopecia, skin discoloration).

33. Participants who require immunosuppressive medications including but not limited to systemic corticosteroid at doses >10 mg/day of prednisone or its equivalence, methotrexate, cyclosporine, azathioprine, and TNF α blockers. Use of immunosuppressive medications for the management of immune related adverse

events, infusion related reactions, or in participants with contrast allergies is acceptable. Use of inhaled, topical, and intranasal corticosteroids are permitted.

34. Participants with a history of allergy to protein-based therapies and participants with a history of any significant drug allergy (such as anaphylaxis, hepatotoxicity, or immune-mediated thrombocytopenia or anemia) are excluded.

35. Known hypersensitivity to any study component including:

    a. Gemcitabine (or other drug excipients) or chemically-related drugs,

    b. TAR-200 device constituent materials,

    c. TAR-200 Urinary Placement Catheter materials,

    d. Cetrelimab excipients or chemically-related drugs

    Refer to the TAR-200 IB and cetrelimab IB for complete information on excipients.

Prior/Concurrent Clinical Study Experience

36. Currently participating or has participated in a study of an investigational agent and received study therapy or investigational device within 4 weeks prior to enrollment.

Diagnostic Assessments

37. Participants with evidence of bladder perforation during diagnostic cystoscopy. Participant is eligible if perforation has resolved prior to dosing.

38. Bladder post-void residual (PVR) volume >350mL at screening after second voided urine.

39. Criterion modified per Amendment 2:

    39.1 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).

Other Exclusions

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

41. The participant is unable to comply with the requirements of this protocol, including any factors that are likely to affect the participant's return for scheduled visits and follow-up.

NOTE: Investigators should 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 should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.3.1. Meals and Dietary Restrictions

There are no restrictions in meals or diet required for this study. However, participants in all cohorts will be recommended to consume at least [redacted] during the study treatment period to allow for adequate urine production.

5.3.2. Caffeine, Alcohol, and Tobacco

There are no restrictions regarding caffeine, alcohol, or tobacco intake while participating in this study.

5.3.3. Activity

There are no restrictions regarding activity or exercise while participating in this 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. When available, the Investigator may generate screening and enrollment logs directly from IWRS.

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 signed informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial signed informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. A participant who is a screen failure may be re-screened no more than one time, if in the opinion of the Investigator, the participant would likely meet eligibility if available care is provided (eg, blood product provided for low hemoglobin or platelet count) and is deemed an appropriate candidate for study participation. Rescreened participants should be assigned the same participant number as for the initial screening. A participant who is re-screened is not required to sign another ICF if the re-screening occurs within 42 days from the previous ICF signature date. If re-screened outside the CCI -day screening window, a new participant number must be assigned.

5.5. Criteria for Temporarily Delaying Administration of Study Treatment

TAR-200

Dose modifications with TAR-200 can only be achieved by early removal of TAR-200. See the TAR-200 Dosing Delay/Discontinuation Criteria in Section 6.5.1 for the conditions under which TAR-200 will either not be inserted (delayed) or will be removed and for the conditions under which participants will be permanently discontinued from TAR-200 study dosing. If the TAR-200 is removed, in consultation with the Sponsor, it may be replaced immediately in accordance with the protocol CCI Beyond CCI this will be considered a skipped dose and the next dose may occur no sooner than at the next treatment period.

Cetrelimab

Dose delay/interruption is the primary method for managing cetrelimab-related toxicities. Toxicities requiring dose delay as well as procedures for delay are outlined in Section 6.5.2.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

Study treatment administration must be captured in the source documents and the electronic case report form (eCRF).

TAR-200 and IV cetrelimab will be manufactured and provided under the responsibility of the Sponsor. Refer to current version of the TAR-200 and cetrelimab IBs for a list of excipients in each product. The designation of the study treatments administered are provided in the table below.

Designation	Product
Investigational Medicinal Product	TAR-200
Investigational Medicinal Product	Cetrelimab

For a definition of study treatment overdose, refer to Section 6.7, Treatment of Overdose.

Table 8: Description of Treatments

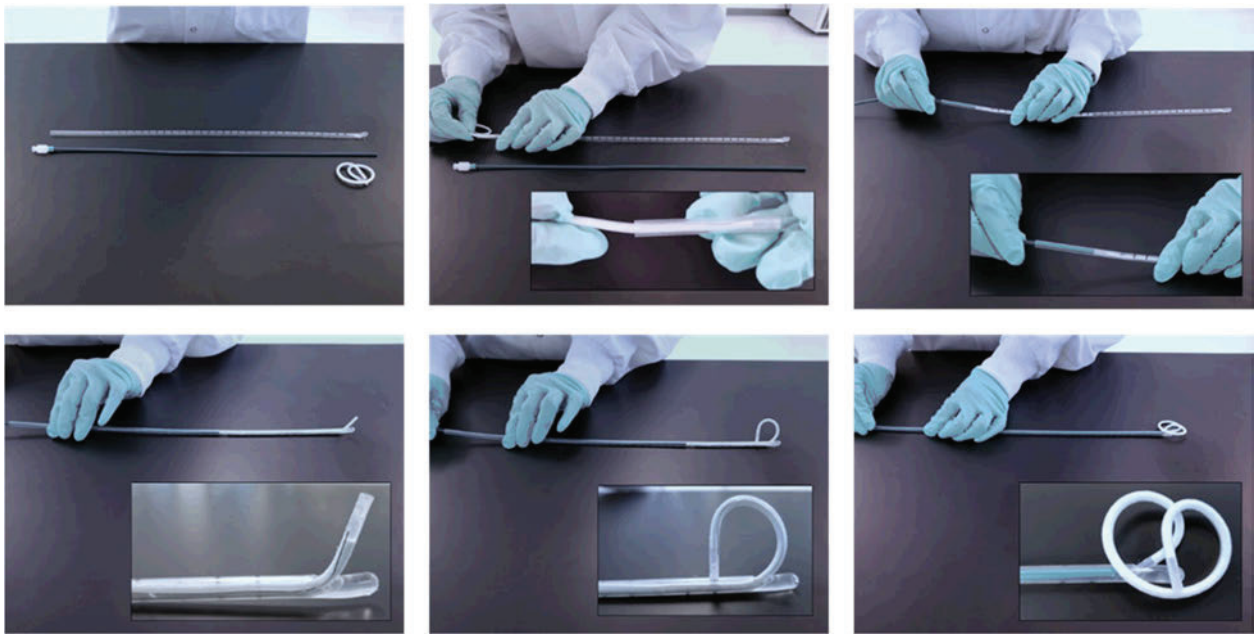
Group/Cohort Name	Cohort 1	Cohort 1 and Cohort 2
Study Treatment Name	**TAR-200**	**IV Cetrelimab**
Generic Name	JNJ-17000139	JNJ-63723283
Type	Integral drug-device combination product	Drug
Formulation (s)	Intravesical drug delivery system	Lyophilized or liquid product
Unit Dose Strength(s)	225 mg gemcitabine per TAR-200	30 mg/ml (for lyophilized product upon reconstitution and for liquid formulation)
Dosage Level(s)	1 TAR-200 (225 mg of gemcitabine) per 3-week dosing cycle	360 mg of cetrelimab given via IV infusion per 3-week dosing cycle.
Dosing Instructions	Intravesical system; inserted transurethrally into the bladder using the UPC and removed from the bladder using endoscopic non-cutting grasping forceps and a standard flexible or rigid cystoscope (flexible is preferred for the removal process)	The reconstituted (lyophilized) product solution is further diluted with 0.9% sodium chloride injection to make 100 mL IV solution and given via IV infusion.
Route of Administration	Intravesical	Intravenous
Use	Experimental	Experimental
Investigational Medicinal Product (IMP)	Yes	Yes
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No	No
Sourcing	Provided by the Sponsor	Provided by Sponsor
IP Packaging and Labeling	Study Treatment will be provided in individual participant treatment packages. Each treatment package will contain the TAR-200 and the UPC. All study treatment will not be dispensed in child-resistant packaging. Each individual treatment package will contain information and be labeled as required per country/territory regulatory requirements. Labels must remain affixed to the individual treatment packages	Study Treatment will be provided in individual participant treatment packages. Each treatment package will consist of 1 vial of lyophilized product. All study treatment will not be dispensed in child-resistant packaging. Each individual treatment package will contain information and be labeled as required per country/territory regulatory requirements. Labels must remain affixed to the individual treatment packages.

6.1.1. TAR-200 Insertion (Cohort 1)

The UPC shaft is placed via the urethra into the bladder with position confirmed by urine return. Note: The bladder should not be completely empty of urine when TAR-200 is inserted. TAR-200 is loaded into the UPC shaft. The green stylet is inserted into the clear shaft to advance the

TAR-200 through the UPC. The stylet manually advances the device through the UPC. The TAR-200 emerges at the exit port as it is being deployed into the bladder lumen. The TAR-200 is deployed into the bladder and returns to its original bi-oval form. Figure 3 below portrays a benchtop illustration of the TAR-200 insertion procedure.

Figure 3: Loading and Deployment (Insertion) of TAR-200 using the UPC



Note: The above pictures represent a benchtop illustration of the TAR-200 insertion procedure. Please refer to the Instructions for Use (IFU).

A post-insertion cystoscopy is not protocol mandated but may be performed at the discretion of the Investigator and is suggested for those utilizing the TAR-200 and UPC for the first time. A performed post-insertion cystoscopy would provide a visual assessment of TAR-200 to safeguard that the intravesical drug-device combination product is in its bi-oval shape and fully contained within the bladder. When placing the UPC, confirm position within the bladder with urine return, then block the opening of the catheter to allow urine to remain in the bladder. This creates a space within the bladder that may facilitate deployment of TAR-200 within the bladder. Alternatively, flexible cystoscopy after insertion of TAR-200 can confirm that it is freely floating within the bladder. Consider administering anticholinergics, anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 insertion. TAR-200 should not be inserted into an empty bladder. After insertion of TAR-200, the participant should be consulted to consume adequate liquids as reduced fluid consumption may exacerbate urinary symptoms.

To mitigate the risk of UTI, participants must receive at least one dose of prophylactic periprocedural antibiotics with TAR-200 insertion and/or removal. Complete instructions for TAR-200 insertion are provided in the IFU.

Insertion of TAR-200 and administration of IV cetrelimab do not need to occur on the same day but should occur no more than CCI of each other. The TAR-200 should generally be placed

after all other assessments required at that visit. Note that on days in which both TAR-200 and IV cetrelimab will be administered, TAR-200 will be inserted at least CCI before the start of IV cetrelimab infusion or at least CCI the completion of IV cetrelimab infusion.

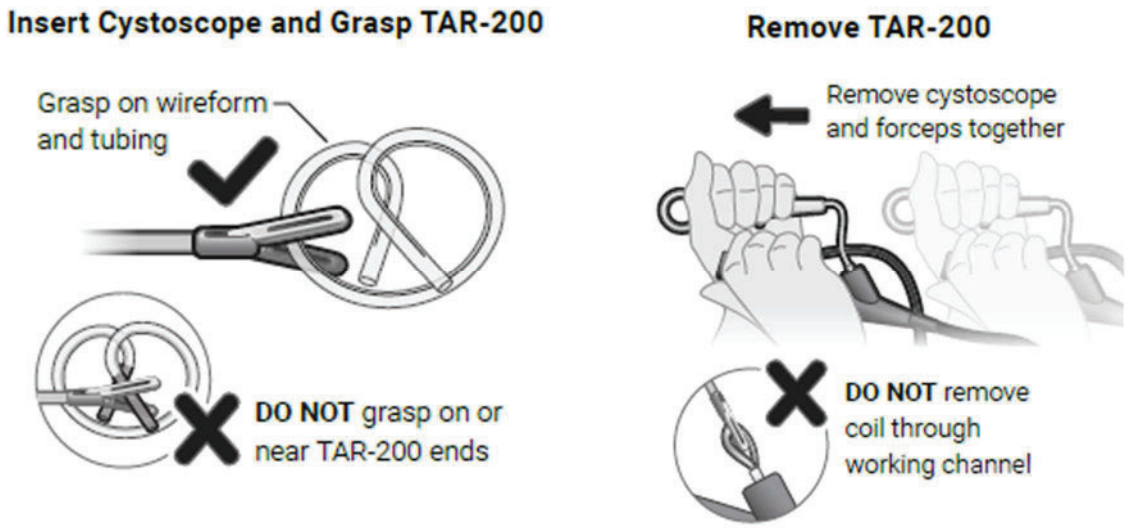
Complete instructions for TAR-200 insertion and removal are provided in the IFU.

TAR-200 should not be administered less than 14 days after any procedure resulting in traumatized urothelium during the biopsy (eg, gross hematuria).

6.1.2. TAR-200 Removal (Cohort 1)

When the TAR-200 is removed, it may be replaced immediately per protocol or CCI to allow for the resolution of any adverse event symptoms as assessed by the investigator and in consultation with the sponsor. The TAR-200 should generally be removed after all other assessments required at that visit and prior to the TAR-200 insertion, if a TAR-200 insertion is required at that visit. TAR-200 is to be removed by flexible (preferred) or rigid cystoscopy with the use of non-cutting grasping forceps. This must be performed by the Investigator or a trained healthcare professional. The TAR-200 should be grasped fully (wireform and tubing) and removed from the bladder under direct visualization, not through a cystoscope's working channel. Complete instructions for TAR-200 removal are provided in the IFU. A graphical representation of removal is presented in Figure 4.

Figure 4: TAR-200 Removal



If safe removal of the product through the urethra with the cystoscope and grasping forceps is not possible or not advised, this may require an operative procedure requiring local and/or general anesthesia.

Palliative radiation may only be administered after a 10-day gemcitabine washout period following removal of the TAR-200. Please refer to the TAR-200 IB for additional details.

6.1.3. Cetrelimab Administration

Cetrelimab (IV) will be dosed on a CCI schedule as outlined in the Schedule of Activities (Section 1.3): until CCI or until the participant has disease progression, intolerable toxicity, withdraws consent, there is a decision by the Investigator to discontinue study treatment, or the study is terminated, whichever occurs first. The dosing of IV cetrelimab may be delayed or skipped to allow for the resolution of any AE symptoms as assessed by the Investigator and subsequently conveyed to the Sponsor. See Section 6.5.2 for Dose Modifications.

For participant comfort, on days in which both TAR-200 and IV cetrelimab will be administered, cetrelimab infusion should be completed at least CCI before, or should be started at least CCI after, the insertion of the TAR-200. At the discretion of the Investigator, premedication with antihistamines or antipyretics/analgesics may be administered for subsequent infusions if an infusion reaction or injection site reaction is observed with IV cetrelimab.

For a definition of study treatment overdose, refer to Section 6.7.

6.2. Preparation/Handling/Storage/Accountability

TAR-200 (JNJ-17000139) Preparation/Handling/Storage

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all TAR-200 systems received and any discrepancies are reported to Sponsor immediately and resolved before use of TAR-200. TAR-200 must be stored at room temperature (15°C to 30°C) in a secure, environmentally controlled, and monitored (manual or automated) area with access limited to the Investigator and authorized site staff. Only participants enrolled in the study may receive TAR-200 and only documented trained and credentialed Investigators or designees may insert or remove TAR-200. A single-use, sterile UPC is co-packaged with TAR-200 and is used to insert TAR-200 into the bladder. Please refer to the IFU for information on TAR-200 insertion and removal. Refer to the IFU for TAR-200 and the UPC and the Site Investigational Product and Procedures Manual (SIPPM) for additional information and stepwise guidance on TAR-200 preparation, handling, and storage. The Investigator/institution is responsible for TAR-200 accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Cetrelimab (JNJ-63723283) Preparation/Handling/Storage

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all cetrelimab received and any discrepancies are reported to Sponsor immediately and resolved before use of cetrelimab. Cetrelimab must be stored at refrigerated temperatures ranging from 2°C to 8°C and protected from light in a secure, environmentally controlled, and monitored (manual or automated) area with access limited to the Investigator and authorized site staff. Protection from light is not required during administration. Only participants enrolled in the study may receive IV cetrelimab and only documented trained and credentialed Investigators or designees may prepare and dose the cetrelimab. Refer to the Investigational Product Preparation Instructions (IPPI) or the SIPPM for additional information and stepwise guidance on cetrelimab preparation, handling, and storage. The Investigator/institution is

responsible for cetrelimab accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Accountability of Study Treatment

The Investigator is responsible for ensuring that all study treatments received at the site are inventoried and accounted for throughout the study. The study treatment administered to the participant must be documented on the treatment administration form. All study treatment will be stored and disposed of according to the Sponsor's instructions. Study site personnel must not combine contents of the study treatment containers.

Study treatment must be handled in strict accordance with the protocol and the container label, IFU for TAR-200, IPPI for IV cetrelimab, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study treatment must be available for verification by the Sponsor's study site monitor during on-site monitoring visits or audits. When the study site is an authorized destruction unit and study treatment supplies are destroyed on-site, this must also be documented on the treatment return form.

Potentially hazardous materials containing hazardous liquids, such as used ampules, needles, syringes and vials, should be disposed of immediately in a safe manner and therefore will not be retained for study treatment accountability purposes.

Study treatment must be dispensed under the supervision of the Investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study treatment will be supplied only to participants participating in the study. Returned study treatment must not be dispensed again, even to the same participant. Study treatment may not be relabeled or reassigned for use by other participants. The Investigator agrees neither to dispense the study treatment from, nor store it at, any site other than the study sites agreed upon with the Sponsor. Further guidance and information for the final disposition of unused study treatment is provided in the IFU for TAR-200, and IPPI for IV cetrelimab.

6.3. Measures to Minimize Bias: Randomization and Blinding

Treatment Allocation

Central randomization will be implemented. Participants will be randomly assigned to 1 of 2 treatment groups in a 5:3 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the Sponsor. The randomization will be balanced in a 5:3 ratio by using randomly permuted blocks and will be stratified by two stratification factors:

- TURBT results: Visibly complete vs. Incomplete and ≤3 cm
- Tumor Stage: cT2 vs. cT3-4a (at initial diagnosis)

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment group assignment and matching study drug kits for the participant. The requestor must use his or her own user identification and personal identification number when

contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

As this is an open study, blinding procedures are not applicable.

6.4. Study Treatment Compliance

TAR-200

TAR-200 will be inserted and removed from the bladder by appropriately trained and credentialed Investigators or designees. The date of each insertion and each removal will be recorded in the source documents and recorded in the appropriate electronic electronic case report form (eCRF).

Cetrelimab

Cetrelimab will be administered in the controlled environment of a qualified medical research center, under the direct observation of qualified study site personnel. The details of each administration will be recorded in the eCRF (including date, start, and stop times of administration, and volume infused).

6.5. Management of Adverse Events and Dose Modification

Any dose/dosage adjustment should be overseen by medically qualified study site personnel (principal or sub-Investigator unless an immediate safety risk appears to be present).

6.5.1. TAR-200

6.5.1.1. Management of Adverse Events Related to TAR-200 and Procedures

As a prophylactic measure, participants should be instructed to ensure adequate fluid intake for improved tolerability. In addition, to mitigate the risk of UTI's, participants must receive at least 1 dose of periprocedural prophylactic antibiotics for any TAR-200 insertion and/or removal.

Any AEs related to TAR-200 or procedures should be treated in a timely manner for optimal outcome. Urinary symptoms should prompt evaluation Although a negative urine culture is not required for insertion of TAR-200, investigators should initiate treatment of symptomatic UTIs in a timely manner.

Symptoms including, but not limited to, hematuria, urinary retention, urinary urgency, bladder pain, may be treated with anticholinergics, NSAIDS, and bladder analgesics such as phenazopyridine. A short course of corticosteroids is also permitted. Although a negative urine culture is not required for insertion of TAR-200, investigators should initiate treatment of symptomatic UTIs in a timely manner.

TAR-200 Dose Modification (Cohort 1 only)

The Sponsor should be notified of any TAR-200 drug delays and directly consulted prior to discontinuation of TAR-200 at any time during the study. Given the relatively short treatment period, attempts to mitigate mild AEs related to urinary complaints should be performed to avoid future TAR-200 skipped doses.

There is only one dose option for this study, as TAR-200 is available in one dose only. Dose modifications are not permitted due to the nature of TAR-200, except for early removal, delayed placement or skipped dose (ie, a missed dosing cycle), or discontinuation of TAR-200.

A skipped dose is defined as a TAR-200 insertion that is not administered [redacted] as described in the Schedule of Activities (Section 1.3) and is not due to study treatment discontinuation.

Missed dosing cycles are not to be made up or rescheduled during the study. If a dosing cycle is missed, the participant would undergo placement of TAR-200 at the next scheduled insertion time, if the participant is eligible for continued administration of TAR-200 at that time. For example, if TAR-200 is removed early or not inserted due to AEs considered related to TAR-200 or the UPC (listed under 'Study Drug Delay or Removal' below), the participant could potentially resume the study schedule at the next scheduled protocol placement timepoint, assuming the participant no longer meets the participant stopping safety criteria at that time.

Participants with skipped TAR-200 dose due to AE which does not return to Grade 1 or baseline should be evaluated, **with Sponsor consultation**, for further delayed placement versus permanent TAR-200 discontinuation, based on the balance of clinical risk/benefit.

For participants in Cohort 1, at any point during a TAR-200 drug delay or permanent discontinuation, IV cetrelimab dosing alone may continue.

For participants in Cohort 1, an end-of-treatment visit should be conducted after both TAR-200 and IV cetrelimab treatments have been completed or permanently discontinued.

TAR-200 Participant Safety Stopping Criteria (Cohort 1 only)

If a participant discontinues TAR-200 before the end of the TAR-200 Treatment Phase, the participant must return for a clinic visit to have the TAR-200 removed.

TAR-200 should not be administered less than 14 days after any procedure resulting in traumatized urothelium/biopsy (due to the increased risk of systemic AEs) or until resolution of gross hematuria, whichever occurs later.

TAR-200 will either not be placed or will be removed early if the participant experiences any of the following (listed under 'Study Drug Delay or Removal' below) considered to be related to the TAR-200 or the UPC.

TAR-200 Delay or Removal (TAR-200 Treatment Interruption)

TAR-200 must be removed, and further TAR-200 dosing delayed if the following occur:

The following will require a dose delay of TAR-200:

- Grade ≥2 hematuria
- Grade ≥2 clinical and cystoscopic signs of aseptic cystitis,
- Urinary retention (inability to spontaneously pass urine) that the Investigator believes to be clinically significant or presumed to be caused by TAR-200.
- Signs of systemic gemcitabine toxicity (ie, hematological toxicity: ANC <1000/mm^3, platelet count <50,000/mm^3).
- Severe or medically significant, but not immediately life-threatening, opportunistic infections that require hospitalization or result in prolongation of hospitalization.
- Grade ≥2 active UTI that the Investigator believes to be clinically significant.

TAR-200 will be removed, or the insertion of an additional TAR-200 will be delayed for Grade ≥3 AEs not mentioned above, which are assessed as related to TAR-200 until such AEs return to Grade≤1 or baseline.

Exclusions to this criterion include Grade 3 nausea and Grade 3-4 emesis that resolve within 2 days on optimum treatment and Grade 3-4 laboratory abnormalities that do not result in hospitalization.

TAR-200 Discontinuation

TAR-200 must be removed, and the participant discontinued from TAR-200 treatment for the remainder of the study if the following occur:

- Grade ≥2 allergic reaction (shortness of breath, generalized edema, etc.) to the system device constituent materials ([CCI] drug (gemcitabine), excipients ([CCI]), urinary placement catheter (Inserter) materials ([CCI]).
- Grade 4 drug-related toxicities or AEs related to TAR-200
- Participants with drug delays related to TAR-200 that do not return to Grade 1 or baseline within 6 weeks, will be evaluated for TAR-200 discontinuation or further delayed placement of TAR-200 after Sponsor consultation. Consideration for a further delayed placement of TAR-200 may occur based on the balance of clinical risk/benefit after Sponsor's Medical Monitor and Investigator consultation.

Discontinuation of study treatment is described in Section 7.1.

6.5.2. Cetrelimab

6.5.2.1. Management of Adverse Events Related to Cetrelimab

Any AEs related to IV cetrelimab should be treated in a timely manner. Refer to Section 10.9, Appendix 9: Guidelines for Management of Immune-Related Adverse Events and Adverse Events of Clinical Interest for details about irAE management.

6.5.2.2. Cetrelimab Dose Modification

Dose modification of IV or cetrelimab is not permitted. Before each IV administration of cetrelimab, the participant will be evaluated for possible toxicities that may have occurred since the previous dose. Laboratory results and general physical status must be reviewed. If immune-related toxicity has occurred, the criteria outlined in Section 10.9, Appendix 9: Guidelines for Management of Immune-Related Adverse Events and Adverse Events of Clinical Interest must be followed for management. Treatment with IV cetrelimab may continue unless the criteria for discontinuation of study drug (Cetrelimab Discontinuation, see below) are met. The criteria for retreatment after improvement/resolution of AEs are outlined in Table 9.

Table 9: Retreatment Criteria for Cetrelimab

Adverse Event	Requirements Before Cetrelimab Administration
ANC	≥1.0 x 10^9/L with or without neutrophil growth factors
Platelet count	≥50.0 x 10^9/L without platelet transfusions, thrombopoietic cytokines, or both
Hemoglobin	≥7.5 g/dL with or without transfusion, erythropoietin, or both
Fasting glucose, if prompted by HbA1c[a]	≤250 mg/dL (13.9 mmol/L)
Hyperthyroidism Hypothyroidism	≤Grade 2
AST and ALT	≤3xULN
Total bilirubin	≤1.5xULN
Rash	≤Grade 2
	≤Grade 1 for bullous dermatoses
Other clinically significant toxicity	Recovery to Grade ≤1 or baseline.

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; HbA1c=hemoglobin A1c; ULN=upper limit of normal

[a] If fasting glucose results are available and meet the retreatment criteria, the HbA1c result does not need to be reviewed prior to dosing, but should still be collected.

Cetrelimab Dose Delay

A skipped dose is defined as an IV cetrelimab infusion that is not administered within the study window and is not due to study discontinuation. For IV cetrelimab only, a dose interruption is when the infusion is stopped before the entire dose has been administered.

Dose delay is the primary method for managing cetrelimab-related toxicities. In the event of a toxicity that meets the criteria below or is otherwise considered to be clinically significant by the Investigator, treatment of IV cetrelimab will be held and supportive therapy administered as clinically indicated. If clinically significant drug-related toxicity is present, treatment should be delayed until the toxicity resolves (with or without supportive therapy) to baseline or ≤Grade 1 except for fatigue, alopecia, hyperthyroidism, hypothyroidism, and rash (other than bullous dermatoses), which require resolution to ≤Grade 2 for subsequent treatment. Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline. If dose delay of IV cetrelimab is beyond the CCI [redacted], the dose should be delayed until the next protocol-specified CCI [redacted] then the dose will be considered a missed dose. If the toxicity does not resolve to Grade≤1 or baseline (or Grade ≤2 for those mentioned above)

within 6 weeks of identification of toxicity, (or prior to subsequent IV cetrelimab administration) discontinuation of IV cetrelimab is recommended unless agreement to continue dosing is reached by the Sponsor's Medical Monitor or designee and the Investigator. For participants in Cohort 1, TAR-200 dosing alone may continue if the Investigator and Sponsor's Medical Monitor agree.

The following drug related irAEs will require dose delays:

- Grade 2 pneumonitis (recurrent Grade 2 pneumonitis, study treatment must be permanently discontinued, see Cetrelimab Discontinuation below)
- Grade 2 or 3 diarrhea or colitis
- Grade 2 or 3 creatinine elevation
- Grade ≥2 AST, ALT or total bilirubin increased
- Symptomatic endocrinopathies (hypophysitis, adrenal insufficiency, and diabetes; excluding hypothyroidism and hyperthyroidism)
- Grade 3 or 4 hyperthyroidism or hypothyroidism
- Grade 2 uveitis
- Grade 3 rash or Grade 2 bullous dermatoses
- Grade 3 of other immune-mediated adverse reactions

The Investigator believes that for treatment-emergent toxicity it is in the best interest of the participant to discontinue study treatment.

Cetrelimab Discontinuation

A participant must discontinue study treatment for any of the following drug-related irAEs:

- irAEs that persist despite treatment modifications or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 6 weeks
- A treatment-related AE does not resolve to Grade ≤1 within 6 weeks of the last dose of study drug unless otherwise agreed to by the Sponsor's Medical Monitor and the Investigator based on evidence of clinical benefit
- Grade 4 toxicities (ie, Grade 4 diarrhea or colitis, Grade 4 creatinine elevation, Grade 4 rash) except for:
  - Endocrinopathies that are controlled with replacement hormones
  - Grade 4 hematologic toxicities that resolve in less than 7 days may not result in study treatment discontinuation at the discretion of the treating physician
- Any non-hematologic study treatment-related event occurs a second time at Grade ≥3 severity
- Grade ≥3 (or recurrent Grade 2) pneumonitis/interstitial lung disease
- Grade ≥3 elevation of AST or ALT or total bilirubin that does not resolve to Grade ≤1 within 7 days or is symptomatic
- Grade ≥3 local infusion or injection site reactions

- Grade ≥3 infusion-related reactions (IRRs) due to IV cetrelimab
- Grade ≥3 uveitis
- Immune-mediated encephalitis
- Recurrence of Grade 3 of other immune-mediated adverse reactions
- The Investigator believes that for treatment-emergent toxicity it is in the best interest of the participant to discontinue IV cetrelimab treatment. Participants may continue TAR-200 for those in Cohort 1.

If a participant's study treatment is discontinued, this will not result in automatic withdrawal of the participant from the study. Following treatment discontinuation, the participant should proceed to the RC Visit if clinically appropriate. Once a participant discontinues treatment with IV cetrelimab, the participant may not be retreated with the study drug. For those participants in Cohort 1, if IV cetrelimab is permanently discontinued, then treatment with TAR-200 dosing alone may continue if the Investigator and Sponsor's Medical Monitor agree.

Discontinuation of study treatment is described in Section 7.1

6.6. Continued Access to Study Treatment After the End of the Study

Given that radical cystectomy will preclude future TAR-200 placement, continued access to either study drug is not applicable.

6.7. Treatment of Overdose

In the event of an overdose, the Investigator should:

- Contact the Sponsor's Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Sponsor's Medical Monitor, whether study treatment must be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/serious AE (SAE) and laboratory abnormalities until resolution.
- Obtain a serum sample for PK analysis after last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Discussions of overdose for each study treatment are discussed in following subsections below.

TAR-200

Due to the nature of TAR-200 administration, overdoses are not considered to be a potential risk for TAR-200 in this study.

Urothelial carcinoma, specifically transitional cell carcinoma of the upper and lower genitourinary tract, has demonstrated meaningful responsiveness to deoxycytidine analogues. Gemcitabine, delivered systemically or locally, is an effective treatment of metastatic and local transitional cell

carcinoma of the upper and lower genitourinary tract, respectively. There has been broad human experience with high dose (>2 g/100-mL normal saline) intravesical gemcitabine instillations in the management of participants with NMIBC. Minimal systemic absorption occurs through the bladder and safety has been documented in both once- and twice-weekly dosing regimens, in addition to long-term maintenance regimens.

Intravesical instillations of chemotherapeutic agents, including gemcitabine, are frequently used in the treatment of NMIBC. However, intravesical gemcitabine delivery is currently limited by: (1) the logistics of frequent dose delivery; (2) the short bladder dwell time; and (3) morbidity following a high-dose bladder administration (2 g over one to two hours).

TAR-200 continuously delivers gemcitabine at an average of CCI over the first seven days (with CCI expected to be released daily after Day 7) for a maximum of 225 mg, a dose that is significantly less than the doses used in standard gemcitabine instillations today. Given this low total payload dose within TAR-200, even in the event of a dose dumping, wherein the entire drug load is released into the participant urine at one time, this dose would be significantly less than the typical intravesical gemcitabine instillation doses traditionally employed. Finally, participant voiding of the bladder urine upon the subsequent voiding cycle would eliminate this gemcitabine volume from the participant's bladder, limiting the dwell time of this drug load.

Cetrelimab

There are no human or animal data regarding overdose of cetrelimab. Treatment of overdose of cetrelimab should consist of general supportive care. There is no known specific antidote for overdose with cetrelimab.

6.8. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, or herbal supplements), therapy (including palliative procedures), or vaccine that the participant is receiving at the time of signed initial informed consent or that the participant receives during the study must be recorded along with:

- Indication for use
- Dates of administration including start and end dates, if available
- Dosage information including route of administration, dose, and frequency

Prophylactic antibiotics should be administered at time of TAR-200 insertion and/or removal to reduce the risk of procedure related UTI. Additionally, the use of thromboprophylaxis is strongly recommended perioperatively for radical cystectomy per local guidelines. Details pertaining to the type of thromboprophylaxis and duration of use should be recorded in the eCRF.

Concomitant therapies, Relevant Procedures (including genitourinary events and procedures), and Healthcare encounters must be recorded throughout the study, beginning with signed initial informed consent and through the Week 108 Follow-up visit. Concomitant therapies should also be recorded in conjunction with new or worsening serious adverse events that meet the criteria

outlined in Serious Adverse Events in Section 8.9.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study treatment must be recorded in the eCRF.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Permitted Medications

Throughout the study, Investigators may prescribe concomitant medications or treatments (including nutritional support, correction of metabolic disorders, optimal symptom control, and pain management) deemed necessary to provide adequate supportive care. Participants may continue the use of bisphosphonates or denosumab for bone disease. Concurrent use of hormones for noncancer related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Concomitant medications (eg, acetaminophen/paracetamol or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylaxis and management of IRR are allowed.

In addition, the following medications may be administered during the study:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor [H2] antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease) as clinically indicated, according to institutional standards and as deemed necessary by the Investigator.
- Documented infectious complication should be treated with oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.
- Growth factor support for the management of treatment-emergent hematological toxicity as recommended according to National Comprehensive Cancer Network/European Organization for Research and Treatment of Cancer (NCCN/EORTC) guidelines.

Prohibited Medications

The following medications are prohibited during the study. The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

- Concurrent experimental or investigational therapy.
- Concurrent anti-neoplastic agents [eg, chemotherapy, anticancer immunotherapy other than cetrelimab or hormonal therapy (hormone replacement therapy is acceptable)]; however, supportive care agents, including denosumab, bisphosphonates, and hormonal agents are

allowed. Also, Androgen Deprivation Therapy (ADT) for prostate cancer or antihormonal therapy for breast cancer (see Section 5.2) are permitted to be continued.

- Other immunosuppressant agents, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg per day of prednisone or its equivalent, methotrexate, azathioprine, and tumor necrosis factor α (TNF-α) blockers, should not be given while the patient is on study treatment. Use of immunosuppressive medications for the management of immune-related AEs, IRRs, or in participants with contrast allergies is acceptable. In addition, use of inhaled, topical, local, and intranasal corticosteroids is permitted.
- Vaccinations with live vaccines within 30 days of the initiation of study treatment, during study treatment, and for 90 days following completion of study treatment (non-live or non-replicating vaccines such as annual inactivated influenza, COVID-19, or monkeypox vaccine are allowed). (Note: Specifically, for COVID-19 vaccines, please refer to Section 10.11, Appendix 11, Study Conduct During a Natural Disaster)
- Medications, treatments, or procedures that are exclusionary for entry in the study should not be introduced during treatment. Please see Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria for those therapies which would preclude study participation

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Possible Drug-Drug Interactions

No drug-drug interaction studies have been conducted by Sponsor to date. No drug-drug interactions studies are discussed in the prescribing information for gemcitabine (Gemzar US Prescribing Information 2019; Gemzar Summary of Product Characteristics 2019). A case was reported of increased international normalized ratio (INR) values and hematomas subsequent to the concomitant administration of warfarin and intravesical gemcitabine in a 90-year-old man with BCG-unresponsive bladder cancer (Kurtzhalts 2016). The participant had started warfarin one month prior to starting intravesical gemcitabine (2 g, administered once weekly). During the first five cycles of gemcitabine, critically elevated INRs resulting in hospitalization were reported. Warfarin was discontinued, and enoxaparin was initiated after the hematomas resolved and hemoglobin stabilized (Refer to the TAR-200 IB).

Gemcitabine may potentiate the effects of antithrombotic medications (thrombolytics, anticoagulants, and anti-platelet agents); therefore, Investigators should monitor participants who are administered these medications closely for risks of increased bleeding.

No preclinical or clinical studies that examine the interaction between cetrelimab and other products have been conducted (Refer to the cetrelimab IB).

The main toxicities of cetrelimab and TAR-200 are non-overlapping.

6.8.1. Rescue Medication

There are no prespecified rescue medications in this study. All concomitant rescue medications, treatments, and procedures should be documented in the eCRF.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

A participant's study treatment must be discontinued if:

- The participant withdraws consent to receive study treatment
- Any clinical AE, laboratory abnormality or intercurrent illness which the Investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study treatment.
- The Investigator believes that for safety reasons or tolerability reasons (eg, due an AE, laboratory abnormality or intercurrent illness) it is in the best interest of the participant to discontinue study treatment.
- The participant becomes pregnant
- Noncompliance with study treatment or schedule.
- Participant develops clinical symptoms or disease progression that precludes RC surgery
- Participant develops metastatic disease (as assessed by RECIST 1.1 criteria)
- The Sponsor closes the study.
  - The Sponsor reserves the right to close the study or close the study site at any time for any reason at the sole discretion of the Sponsor (eg, in case of unacceptable risk, intolerable toxicity, or change in the risk/benefit profile); this might include recurrence of adverse events of which character, severity, or frequency is new in comparison to the existing risk profile. Also, data derived from other clinical or toxicology studies, which negatively influence the risk/benefit assessment, might cause discontinuation or termination of the study.

Participants that develop the following should continue within the efficacy (imaging) Follow-up Phase of the study:

- Clinical symptoms or pelvic nodal disease that precludes RC surgery
- Evidence of pelvic nodal disease following RC surgery

Participants that develop metastatic disease progression should be discontinued from further efficacy (imaging) follow-up and continue to be followed for survival status, subsequent anti-cancer therapies, and other malignancies.

If a participant permanently discontinues study treatment for any reason before the end of the Treatment Phase, the participant must commit to a clinic visit to have the TAR-200 removed. All efforts will be made to continue to follow participants in the Follow-up Phase of the study until the participant meets discontinuation criteria in Section 7.2. The primary reason for study treatment discontinuation will be clearly documented in the participant’s medical record and recorded in the eCRF. Study drug assigned to the participant who discontinued study drug may not be assigned to another participant. Additional participants will not be entered to account for those participants who discontinue study treatment.

- The Investigator must document whether the participant is withdrawing from taking the study drug only or withdrawing from taking the study drug, attending future visits, and participating in future assessments.
- Efforts will be made to continue follow-up of participants who withdraw prematurely, especially with respect to disease progression and survival through Week 108 post RC as described in the Schedule of Activities (Section 1.3).
- Efforts will be made to undergo protocol-specified follow-up of any ongoing AEs and SAEs.

7.2. Discontinuation from Efficacy (Imaging) Follow-up

A participant should be discontinued from efficacy (CT/MRI) imaging follow-up if:

- Participant develops metastatic disease (as assessed by RECIST 1.1 criteria)
  - Note that participants should continue to be followed for survival status through End of Study Visit.

7.3. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

If a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion) as local regulations permit.

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons as described above. This is expected to be uncommon occurrence for this study.

- If a participant in Cohort 1 withdraws from the study, he/she must return to the site for TAR-200 removal (if applicable).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study record.

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Prior to a participant withdrawing consent for follow-up, the investigator must offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described below.

Circumstances for Reduced Follow-up

In the situation where a participant may be at risk for withdrawal of consent and is unable to return for scheduled visits at the protocol-defined frequency, the investigator may consider options for reduced follow-up. These may include (as local regulations permit):

- Less frequent clinical visits
- Telephone, email, letter, social media, fax, or other contact with:
  - participant
  - relatives of the participant
  - participant's physicians (general or specialist)
- Review of any available medical records

Details regarding these contacts must be properly documented in source records including responses by participants.

7.3.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.4. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, text-message, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Should a study site close, eg, for operational, financial, or other reasons, and the Investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

7.5. Death

If it is determined that the participant has died, the site will use permissible local methods to determine the date and cause of death. Any information regarding the participant's death, including cause and date of death, will be entered into the applicable eCRF.

8. STUDY ASSESSMENTS AND PROCEDURES

Please refer to Section 1.3, Schedule of Activities.

Overview

The Schedule of Activities summarizes the frequency and timing of assessments applicable to this protocol. If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PROs, electrocardiograms (ECGs), vital signs, and any type of blood draw last. Blood collections for pharmacokinetic and immunogenicity assessments should be kept as close to the specified time as possible. Assessments and procedures should be completed on the day indicated (± window indicated). At the Week 6 visit, imaging should be performed prior to dosing.

In Cohort 1, placement of TAR-200 and administration of IV cetrelimab, respectively, do not need to occur on the same day but should occur within CCI and no more than CCI of each other. At times when both TAR-200 and IV cetrelimab are administered on the same day, TAR-200 should be provided at least CCI before the start of IV cetrelimab infusion or cetrelimab injection or CCI fter the IV or cetrelimab administration is completed. If one treatment is held, the other may still be administered in consultation with the Sponsor. Actual dates

and times of assessments will be recorded in the source documentation and eCRF. All PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses. Refer to the PRO completion guidelines for instructions on the administration of electronic patient-reported outcome(s) (ePROs). MRU data will also be collected. Refer to Section 8.14, Healthcare Resource Utilization for details.

Home Health Care and Telehealth Visits

Home health care and telehealth visits may be implemented by or with approval from the Sponsor and per the clinical judgment of the Investigator, for certain circumstances when warranted where feasible and permissible by local policy, regulations (as applicable) and for participants for whom there is no safety concern.

Study procedures such as participant reconsent; ECOG assessment; AE and concomitant medication reporting; review of body systems; and collection of information on the participant's current health status may be performed with home health care and telehealth visits. Protocol-specified laboratory assessments for efficacy and safety may be collected during home health care visits. All assessments should be followed with in-person examination, as applicable.

For samples analyzed at local laboratories, it is important to ensure appropriate documentation of laboratory reference ranges. Source documentation and, if applicable, the appropriate case report forms should be completed and should detail how each assessment was collected (eg, remote versus on-site, central versus local laboratory [if applicable], and vital signs taken at home by delegated in-home nursing) may be performed with home health care and telehealth visits. Protocol-specified laboratory assessments for efficacy and safety may be collected during home health care visits.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure. See Section 5.4 for information on screen failures.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) or sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to the Schedule of Activities (Section 1.3) for the timing and frequency of all sample collections.

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

Study-Specific Materials

The Investigator will be provided with the following supplies:

- Study Protocol
- Investigator's Brochure for cetrelimab and TAR-200
- TAR-200 IFU
- Cetrelimab IPPI
- Pharmacy manual/study SIPPM
- Combination Products Instructions for Use Manual
- Laboratory manual
- CTCAE Version 5.0
- PRO questionnaire and ePRO completion guidelines
- Tablet for onsite ePRO completion
- ePRO Completion Guidelines
- Electronic clinical outcome assessment Manual
- RECIST guidelines Version 1.1
- IVRS/IWRS Manual
- eDC Manual
- Participant Wallet cards

8.1. Screening

During the Screening Phase, all participants who have qualified for enrollment will consent to the study by signing the ICF. For Cohort 1 and Cohort 2, the Screening Phase includes the interval between signing the ICF and the day the participant is randomly assigned to either cohort. The full Screening Phase should not exceed 42 days. Assessments that are required to demonstrate eligibility may be performed over the course of multiple days during the screening process.

Screening imaging and cystoscopy should be completed as soon as possible following the participant's signing of the informed consent. The participant should be screen failed if, upon imaging central read, the participant is confirmed to have nodal or metastatic disease.

A screening cystoscopy is required within CC days prior to randomization if participant is referred from outside institution. This is performed to assess the bladder burden of disease, to ensure that

no underlying anatomical abnormality is found that could prevent safe placement, indwelling use, or removal of TAR-200, to assess for abnormal urothelium that would preclude participation, and to determine the presence of any residual tumors >3 cm. The diagnostic TURBT may be sufficient for screening cystoscopy assessment if performed within 42 days of randomization, performed by study Investigator, and tumor size is documented as ≤3 cm. Eligible participants may have either completely or partially resected tumors (≤3 cm) if the treating urologist attempted maximal resection. If tumor is >3 cm on the assessment cystoscopy, a debulking re-TURBT must be performed prior to randomization. Tumors larger than 3 cm in greatest diameter following debulking TURBT during screening will result in the participant's screen failure. Randomization is to occur once the initial diagnostic TURBT histopathology and imaging confirms cT2-T4a N0, M0 urothelial carcinoma by local pathology and central radiographic evaluation. Local pathology interpretations will be confirmed centrally. Participants should receive initial dosing of study treatment within 7 days following randomization.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, disease assessment, and cystoscopy) and obtained before signing the ICF may be used for screening purposes provided the procedure meets the protocol-defined criteria and has been performed within the time frame of the study (see Section 1.3). All information associated with eligibility requirements must be entered onto the appropriate eCRF. Requirements for biopsy specimens for histologic assessment for diagnosis are provided in Section 8.7.1. The participant's previous anticancer therapies and TURBT details, the dose and timing of administrations, and the participant's responses to each therapy will be collected and recorded in source documents and the eCRF. Tests with results that fail eligibility requirements may be repeated once during screening if the Investigator believes that these results are in error. For screening assessments that are repeated, the most recent available results before initiation of study drug will be used to determine participant eligibility.

The PVR will be measured at the Screening Visit per the study site's standard of care method (ie, bladder scan, catheterization). At the Screening Visit, participants with a bladder PVR >350 mL after an attempted second voiding will be excluded from the study.

Results from the screening evaluations will be reviewed to confirm participant eligibility before randomization.

Please refer to Schedule of Activities (Section 1.3) for all screening procedures and activities.

8.2. Treatment

The Treatment Phase for Cohorts 1 and 2 will begin following a 5:3 random assignment into the study. Treatment may continue until the participant experiences discontinuation events noted in Section 7.1. During study visits, all ePRO assessments should be conducted and completed before any other tests, procedures, or consultations to prevent influencing participant perceptions.

All scheduled non-dosing assessments should be completed prior to dosing of any therapy. Assessments and procedures should be completed on the day indicated (± window indicated); if

this is not possible because of a weekend, holiday, or emergency, the assessment or procedure should be completed within 72 hours of the scheduled day.

Cohort 1: Administration of IV cetrelimab and the placement of TAR-200 do not need to occur on the same day; however, should occur within CCI and no more than CCI of each other. At times when both TAR-200 and IV cetrelimab are administered on the same day, TAR-200 should be provided at least CCI before the start of cetrelimab IV infusion **OR** at least CCI after the infusion is completed. If one treatment is held, the other may still be administered in consultation with the Sponsor.

Cetrelimab administration will take place every three weeks for four consecutive cycles on study per the Schedule of Activities (Section 1.3).

Cohort 1 and Cohort 2: The first infusion of IV cetrelimab should be administered over 60 (±10) minutes. In the absence of infusion-related reactions, subsequent infusions may be administered intravenously over 30 minutes (but not less than 25 minutes). Study drug is to be administered under the supervision of qualified site staff. For the first infusion, vital signs should be monitored before the start of the infusion, during infusion, at the end of infusion (+10 minutes), and 2 hours (±15 min) after the completion of infusion. After the completion of the first infusion, the participant may be discharged if considered clinically stable and all other study procedures have been completed. During subsequent infusions of cetrelimab, vital signs should be monitored before the start of the infusion.

Cohort 1 and Cohort 2: Dose modification of cetrelimab is not permitted. Dose delay is the primary method for managing cetrelimab-related toxicities (see Section 6.5 Dose Modifications). CCI), then the dose will be considered a missed dose. Administration may resume at the next planned dosing date if participant meets requirements to resume treatment.

Cohort 1: TAR-200 insertion will take place Q3W four times on the study (Week 0, Day 1 and then at Weeks 3, 6, and 9). The TAR-200 kit includes the TAR-200 device and UPC (Inserter). Participants will undergo insertion of TAR-200 into the bladder using the provided UPC in accordance with the IFU. All Investigators or healthcare professional designees must have training completed and documented in accordance with TAR-200 training guidelines and be trained prior to performing their first TAR-200 insertion. Only one TAR-200 may be contained in the bladder at any given time.

Cohort 2: Cetrelimab alone will be dosed approximately every 21 days for four consecutive cycles, with cycles starting at Week 0, Day 1. Subsequent doses will be administered at Weeks 3, 6, and 9.

Cohort 1 and Cohort 2- Early Disease Progression: The Investigator will assess response to treatment at the Week CCI Visit using radiographic imaging (CT/MRI), which will be reviewed locally and centrally. For participants who are determined by Investigator to have metastatic progression (M1a or b), or who do not undergo RC, further study treatment will be discontinued.

If a participant develops imaging consistent with pelvic nodal disease, further treatment (inclusive of radical cystectomy) and/or percutaneous biopsy should proceed at Investigator's discretion. In cases of discordance or equivocal findings, additional imaging may be obtained at Investigator's discretion to adjudicate; these cases must be discussed with Sponsor.

Cohort 1 and Cohort 2 - Radical Cystectomy: Participants should proceed to RC at Week [redacted] (or up to 3 weeks [21 days] after the Week [redacted] visit, if clinically indicated), regardless of any dosing delays or missed doses that may occur during the study. All participants should undergo pre-operative cardiac and risk stratification prior to RC per institutional guidelines. Please refer to detailed instructions for the collection, processing, storage, and shipment of samples as provided in the Central Laboratory Manual. Radical cystectomy outside of the protocol-specified timeframes is at the Investigator's discretion.

For participants in Cohort 1, TAR-200 will be removed at [redacted]). RC may be performed on the same day or within 3 weeks (21 days) after the Week [redacted] visit.

Any pre-operative assessments specifically for the preparation of the RC procedure, intra-operative care, and post-operative hospitalization and recovery care should be according to institutional standard of care.

Follow-up Visits: No restrictions are placed on adjuvant therapy after RC. Following the RC, all participants will have a safety follow-up visit 4 weeks (one month) following the RC surgery. Additionally, participants will have follow-up study visits at Weeks 8, 12, and then every 12 weeks through Week 108 post RC (eg, Weeks 24, 36, 48, 60, 72, 84, 96, 108 [End of Study]).

Unscheduled visits may occur throughout the study at the discretion of the Investigator and for clinical necessity.

8.3. Follow-up Phase

For participants who complete the Treatment Phase of the study, including radical cystectomy surgery, the participant will proceed to the follow up phase of the trial. This Follow-up Phase includes the Week 4, 8, and 12 post RC visits with subsequent disease status visits assessed every 12 weeks through Week 108 post RC. For participants with metastatic progression following study treatment, other malignancies, and subsequent anti-cancer therapies will be collected in the eCRF, and these participants will continue to be followed for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Participants with locoregional pelvic recurrence should continue efficacy evaluations (imaging) per the Schedule of Activities (Section 1.3). All drug-related serious adverse events beyond 100 days after last dose of study drug should be collected while participants are in study follow-up phase.

8.4. Overall Survival

Overall Survival status will also be determined and collected in the eCRF until death, withdrawal of consent, or the end of the study, whichever occurs first. This may be obtained via telephone

with the participant or the participant's family or friends, if approved by the participant in the ICF, or by any means applicable by local laws and regulations.

8.5. End of Study Visit

For each participant, the study is considered completed after the participant completes the Week 108 post RC (End of Study Visit). Additionally, they will be considered completed if they have died before the end of the study, have not been lost to follow-up, or have not withdrawn consent for study participation before the end of the study as defined above.

8.6. Unscheduled Visits

Clinic visits not described in the schedule of assessments may be performed at any time as clinically indicated. Results of assessments performed at these visits will be entered as "unscheduled" visits in the eCRF.

8.7. Efficacy Assessments

8.7.1. Disease Assessments

8.7.1.1. TURBT Biopsies, Cystoscopy, and Radical Cystectomy Pathology

- Initial diagnostic TURBT specimens will be sent for central pathologic review.
- A screening cystoscopy is required within the [redacted]-day screening period to determine the presence of any residual tumor >3 cm. The diagnostic TURBT may be sufficient for screening cystoscopy assessment if all three criteria are met: 1) performed within 42 days of randomization, 2) performed by study Investigator, and 3) the residual tumor size at that time is documented as ≤3 cm. For participants referred from outside the institution, a repeat screening cystoscopy is required.
- Procedures conducted as part of the participant's routine clinical management (eg, cystoscopy) and obtained before signing the ICF may be used for screening purposes provided the procedure meets the protocol-defined criteria and has been performed within the time frame of the study (see Section 1.3).
- All efforts should be made to resect multifocal tumors to visual completion. If screening cystoscopy demonstrates any residual mucosal disease, debulking TURBT is encouraged to attain complete resection, but not mandated if all individual residual tumors are <3 cm.
- If the total size of an individual, residual tumor exceeds 3 cm, it must undergo re-resection (re-TURBT) for entry into the study.
- All screening assessments should be performed within the screening period of [redacted] days prior to randomization.
- All initial, diagnostic TURBT specimens will be collected and shipped to the central laboratory for a central histopathologic review per the Pathology Charter.
- All debulking, completion TURBT specimens will be evaluated by local site pathology.
- Participants that develop metastatic disease (as assessed per RECIST 1.1) prior to RC, will be taken off protocol treatment and discontinued from the efficacy (imaging) follow-up.

- If a participant develops imaging consistent with pelvic nodal disease, radical cystectomy and/or percutaneous biopsy should proceed at Investigator's discretion.
- The radical cystectomy specimen will be processed and reviewed by local site pathology. Pathology material will then be collected and shipped to the central laboratory for central histopathologic review per the Laboratory Manual and will form the basis of primary outcome measure of complete response (CR).

Refer to the Laboratory Manual for instruction on sample handling.

8.7.1.2. Computed Tomography/Magnetic Resonance Imaging (CT/MRI)

The CT/MRI with contrast to include the chest, abdomen, and pelvis:

- A CT/MRI should be performed at screening, Week [redacted] on treatment, Week [redacted] post RC, and then every [redacted] weeks thereafter up to Week 108 (End of Study). Please also refer to Section 1.3 for time points that CT/MRI should be performed. In the case of abdominopelvic imaging with MR, chest imaging should be obtained, per Investigator discretion, and further clarified below. The same scanning parameters will be used throughout the study and should be in accordance with the Imaging Manual. All per-protocol imaging (CT/MRI) must be read/confirmed centrally. Additionally, the time window for all on-study CT/MRI imaging throughout the study is +/- 7 days. Eligibility is determined by central read of CT/MRI at screening. All on-study treatment decisions should be based on the Investigator's assessment of the CT/MRI images and not on the central review. In cases of discordance between local and central review of CT/MRI images, the Investigator should consult with Sponsor for support.
- The participant's hydration should be handled per local institutional policy.

Incidental Findings: The Investigator is responsible for following up on the participant per their institutional standard of care for incidental findings on CT. The responsibilities of the imaging core laboratory, if any, with respect to incidental findings will be defined in the Imaging Charter.

Off-study CTs: Off-study imaging is defined as imaging that is not performed for the purpose of evaluation of disease progression or response for this study and/or consists of a modality and/or anatomy that is not study specific.

Alternative Imaging: The preferred imaging modality is the contrast-enhanced CT of the chest abdomen, and pelvis (ie, the full body CT) and this modality should be used consistently throughout the study if there are no contraindications. However, in participants who are unable to undergo contrast-enhanced CT, alternative imaging may be used. If contrast-enhanced CT of the chest, abdomen, and pelvis is not possible, the following alternative methods, may be used, in order of preference:

1) Non-contrast CT of chest with contrast-enhanced MRI of abdomen and pelvis
2) Non-contrast CT of chest with non-contrast MRI of abdomen and pelvis
3) Non-contrast CT of chest, abdomen, and pelvis

Additional information will be provided in the Imaging Manual.

Magnetic Resonance Imaging Conditional Compatibility (Applicable Only for Participants on Treatment with TAR-200 [Within Cohort 1])

TAR-200 is Magnetic Resonance conditional. A participant with TAR-200 can be scanned safely in a Magnetic Resonance system under the following conditions:

- Static magnetic field of 1.5-Tesla and 3-Tesla, only.
- Maximum spatial gradient magnetic field of 3000 Gauss/cm or less.
- Maximum magnetic resonance system reported, whole body averaged specific absorption rate of 2-W/kg for 15 minutes of scanning in the Normal Operating Mode of operation for the magnetic resonance system.
- Under the scan conditions defined, TAR-200 is expected to produce a maximum temperature rise of 2.0° C after 15 minutes of continuous scanning.

Additional information will be provided in the Imaging Manual. PET/CT may be utilized only in the screening phase, with the non-contrast CT phase serving as the baseline CT scan for future CT imaging comparisons. PET/CT is not permitted as an imaging modality on-study, during the treatment and follow-up phases, in order to maintain imaging fidelity and consistency throughout the study.

8.7.2. Response Assessments

8.7.2.1. TURBT Biopsies, Cystoscopy, and Radical Cystectomy Pathology

TURBT/Biopsy: Participants will have undergone an initial diagnostic TURBT resulting in pathologic diagnosis of cT2-T4a MIBC to initiate study enrollment. Pathology will be based upon the American Joint Committee on Cancer (AJCC) Bladder Cancer Staging nomenclature (AJCC 2017). The initial TURBT must be completed within 120 days of randomization. The biopsy specimen (accompanied by a pathology report) will be sent to a central pathology vendor for review and confirmation of tumor stage. A debulking re-TURBT must be completed if individual residual tumor volume exceeds 3 cm. A debulking re-TURBT is encouraged if there is residual mucosal disease ≤3 cm.

All debulking, re-TURBT specimens will be evaluated by local site pathology and are not required to be sent to the central pathology vendor.

Cystoscopy: A cystoscopy is required during screening to determine the presence of any residual tumor >3 cm within the [redacted]-day screening period. The diagnostic TURBT may be sufficient for screening cystoscopy assessment if performed within 42 days of randomization it is performed by study Investigator, and the residual post-TURBT tumor size is documented as ≤3 cm.

For participants in Cohort 1: Visual assessment of the bladder urothelium and known tumor site(s) will be performed at each placement/removal of TAR-200.

For participants in Cohort 2: There are no additional protocol-specified cystoscopic assessments beyond screening, however, cystoscopy may be performed at Week [redacted] if clinically indicated.

Radical Cystectomy: The primary outcome assessment will be the rate of pCR within the bladder as well as analysis of residual tumor stage, ypTa, ypTis, ypT1-ypT4 will be performed as an outcome assessment for Cohort 1 and Cohort 2. The extent of nodal disease involvement after RC will be based upon the AJCC Bladder Cancer Staging nomenclature (AJCC 2017). Adjuvant or subsequent anti-cancer treatments will be documented within the eCRF and participants will continue per protocol study follow up visits. Participants with pelvic nodal disease at RC will be followed for efficacy assessments. Participants with metastatic disease noted at the time of RC, or at any time point, will be discontinued from the efficacy (imaging) follow-up. Participants should be followed for survival status.

8.7.2.2. Imaging

Classification of Disease Progression via Nodal or Metastatic Disease

The presence of radiographic nodal and metastatic disease involvement will be assessed at participant screening, Week [redacted] and during post RC follow up visits (every [redacted] weeks) through Week 108 (End of Study Visit). Additionally, radiographic response to treatment will be determined during on-study timepoints and will be based upon the AJCC Bladder Cancer Staging nomenclature (AJCC 2017).

- All imaging will be performed for assessment of response and read/confirmed with central radiology review.
- At Week [redacted], if a participant develops imaging consistent with pelvic nodal disease, radical cystectomy and/or percutaneous biopsy should proceed at Investigator's discretion.
- If participants develop metastatic disease (as assessed per RECIST 1.1) prior to RC, they should be taken off protocol study treatment and discontinued from the efficacy (imaging) follow-up.
- If local progression is suspected from cystoscopy or based on clinical signs, participant should proceed with immediate RC if clinically indicated.
- At post RC follow-up imaging assessment timepoints, if distant metastatic progression is confirmed, the participant should be discontinued from further imaging assessments and continued to be followed for survival status, subsequent anti-cancer therapies, and other malignancies. Participants with locoregional pelvic recurrence should continue efficacy evaluations (imaging) per the Schedule of Activities (Section 1.3).

8.7.3. Overall Response Assessment

Overall response will be determined by findings radical cystectomy. The response assessments are presented for participants in Table 10.

Table 10: Overall Response Assessments after Radical Cystectomy

Bladder Disease	Lymph Node Disease	Overall Response
No evidence of intravesical disease pathologically (ypT0)	No evidence of pathologic nodal involvement	pCR
No evidence of intravesical disease pathologically (ypT0)	Evidence of new pathologic nodal disease	PD
Downstaged intravesical disease (<ypT2)	No evidence of pathologic nodal involvement	pPR
Downstaged intravesical disease (<ypT2)	Evidence of new pathologic nodal disease	PD
Increased burden of intravesical disease pathologically relative to clinical stage	No evidence of pathologic nodal involvement	PD
Increased burden of intravesical disease pathologically relative to clinical stage	Evidence of new pathologic nodal disease	PD
No change in intravesical disease	No evidence of pathologic nodal involvement	Stable disease
No change in intravesical disease	Evidence of new pathologic nodal disease	Stable disease

Abbreviations: pCR=pathologic complete response; PD=progressive disease; pPR=pathologic.

8.7.4. Patient-Reported Outcomes

Patient-Reported Outcomes Assessments

Patient-reported outcomes measures will be collected at the times specified in the Schedule of Activities (Section 1.3). All PROs should be administered prior to other assessments.

The disease specific PRO captured in this clinical trial is the FACT-Bl (Section 10.6, Appendix 6, PRO Questionnaires [FACT-Bl]). PGIS (Section 10.7, Appendix 7, PRO Questionnaires [PGIS]) and PGIC (10.8, Appendix 8, PRO Questionnaires [PGIC]) are single-item questionnaires that provide an anchor-based comparison for the FACT-Bl.

The PGIS and PGIC should be administered prior to other PRO assessments. The PGIC will not be administered at the first visit because it captures change. The PRO instrument will be provided in the local language in accordance with local guidelines.

8.8. Safety Assessments

8.8.1. Specification of Safety Parameters

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, 12-lead ECG, physical examinations, clinical laboratory tests, cystoscopic examination, ADA assessments, concomitant treatments/procedures, and other safety evaluations at specified time points as described in the Schedule of Activities (Section 1.3). All AEs will be reported from the time of the informed consent form signature to the end of the 100-day safety follow-up visit. All drug-related SAEs beyond 100 days after last dose of study treatment must be reported for participants during the Follow-up Phase. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

In the event that a participant complains of unexpected fever, shortness of breath/dyspnea, or dry cough, a thorough evaluation for interstitial pneumonitis is recommended per institution standard of care.

Details regarding the internal Data Review Committee are provided in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the Investigator as specified in Section 8.9, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities or toxicities persisting at the end of the study/early withdrawal will be followed by the Investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.8.2. Immune-Mediated Adverse Events

Every AE must be assessed by the Investigator regarding whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's eCRF. Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology, which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's eCRF.

8.8.3. Physical Examinations

A complete physical examination including head, ears, eyes, nose, throat and neck, cardiovascular, abdomen, musculoskeletal, skin, and genitourinary systems will be performed at the Screening Visit. Height is assessed at the Screening Visit only. A targeted physical examination must be conducted at every disease assessment visit, and as clinically indicated throughout the study. Weight will be assessed at each study visit. The Investigator must review physical examination results and record any clinically relevant changes occurring during the study in the medical history or adverse event section of the eCRF.

8.8.4. Vital Signs

Vital signs will be assessed per the Schedule of Activities (Section 1.3). Blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature will be assessed. The Investigator must review vital signs results and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

8.8.5. Electrocardiograms

12-lead electrocardiograms will be performed as specified in the Schedule of Activities (Section 1.3). Additional ECGs may be performed as clinically indicated. The participant should rest in a supine position for at least 5 minutes before ECG recording and should refrain from talking or moving the arms or legs. The 12-lead ECG recorder device used should have been recently serviced and calibrated. The Investigator will comment on the clinical relevance and document this in the eCRF (along with details of clinically significant findings).

8.8.6. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. More frequent clinical laboratory tests may be performed, as indicated by the overall clinical condition of the participant and for abnormalities that warrant more frequent monitoring. The Investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

Prior to dosing, laboratory tests are to be completed per the protocol schedule of activities (Section 1.3). The laboratory tests will be performed by the local laboratory. The Investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

Laboratory certificates or accreditation and normal ranges of the laboratory facility at the site must be submitted to the Sponsor before the screening of any participant at the site. If the participant has the laboratory assessments conducted at a laboratory facility other than the one associated with the investigational site, the Investigator must submit to the Sponsor laboratory certificates or accreditation and normal ranges for that facility as well. The laboratory reports must be filed with the source documents. Required laboratory evaluations are detailed in Section 10.2, Appendix 2, Clinical Laboratory Tests.

8.8.7. Pregnancy Testing

Pre-dose urine or serum samples will be obtained for β-hCG pregnancy testing in participants of childbearing potential at time points indicated in the Schedule of Activities (Section 1.3) and as required per local regulations. Participants who are not of documented childbearing potential do not require a pregnancy test (Section 10.5). Potential childbearing status will be confirmed and documented pre- and if appropriate, post RC. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

Pregnancy tests will be performed to establish the absence of pregnancy at any time during the participant's participation in the study. If a urine pregnancy test is positive, it will be repeated with serum pregnancy test. The study treatment will be provided only upon confirmation of negative pregnancy test.

8.8.8. ECOG Performance Status

The ECOG performance status grade will be determined as part of screening evaluations, during disease assessment visits, and as clinically indicated throughout the study. The scoring information is provided in Section 10.12, Appendix 12, ECOG Performance Status Scale.

8.9. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, Product Quality Complaints (PQCs), and Device Deficiencies from clinical studies are crucial for the protection of participants, Investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures. Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, and PQC can be found in Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Further details on Device Deficiencies (related to the UPC) can be found in Section 10.10, Appendix 10 (Adverse Events, Adverse Device Effects, Serious Adverse Events, Serious Adverse Device Effects, Unanticipated Serious Adverse Device Effects, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies).

8.9.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated study ICF is obtained until 100 days after the participant's last dose of study treatment or before the start of subsequent anticancer therapy. If a participant begins a new systemic anti-cancer therapy, the AE reporting period for non-SAEs ends at the time the new treatment is started. All drug-related SAEs beyond 100 days after last dose of study treatment should be reported for all cohorts while participants are in the study Follow-up Phase. The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

For this study, all device-related safety reporting will be done according to local legislation.

Serious Adverse Events, PQCs, and Device Deficiencies

All SAEs, as well as PQCs and Device Deficiencies, occurring during the study must be reported to the appropriate Sponsor contact person by study site personnel immediately, without undue delay but no later than 24 hours of their knowledge of the event as required by local regulations.

Serious adverse events, including those spontaneously reported to the Investigator within 100 days after the last dose of study treatment, must be reported using the Serious Adverse Event Form. Any SAE occurring after the end of the study period must be promptly reported if a causal relationship to the investigational drug is suspected. The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the Sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site and transmitted to the Sponsor immediately without undue delay or within 24 hours of the event as required by local regulations. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first. Device Deficiencies of the UPC and PQCs associated with TAR-200 will be reported on the PQC form.

8.9.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

8.9.3. Follow-up of Adverse Events and Serious Adverse Events, PQCs, and Device Deficiencies

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, PQC or Device Deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events and the special reporting situation of pregnancy, will be followed by the Investigator as specified in Section 10.4, Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.9.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The Sponsor will also report to the Investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The Investigator (or Sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. Please refer to Anticipated Events (US only), Section 10.16, Appendix 16 for a list of anticipated events. Please note that the list of anticipated events is pertinent for SUSAR reporting to the US FDA, US-based IECs/IRBs and Investigators only (refer to Section 10.16, Appendix 16 for further background and details). All SAEs reported from study sites will be reviewed and assessed case by case by the Sponsor.

8.9.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the Sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drugs on sperm is unknown, pregnancies in partners of male participants included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be requested.

8.9.6. Adverse Events of Special Interest

There are no AEs of special interest for TAR-200 or cetrelimab for this protocol.

8.9.7. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

Expected progression of disease, which is part of the natural course of the disease under study, should not be considered or reported as an adverse event (or serious adverse event).

However, if determined by the investigator to be more likely related to the study treatment, protocol design, or protocol procedures than being expected from the underlying disease, the treatment-invoked progression (ie the treatment-invoked signs/symptoms of such progression)

should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Death that is attributed by the investigator explicitly to progression of disease should not be considered nor reported as an adverse event (or serious adverse event). Progression of disease and death due to disease progression should be documented on the appropriate eCRF forms (eg, the Disease Progression form and the Death form).

Signs or symptoms of disease progression that are of clinical significance, such as spinal cord compression, bony metastasis, vena cava superior syndrome, major vessel rupture, renal obstruction or organ failure, should be documented on the appropriate eCRF forms (eg, the Symptomatic Progression Form).

8.9.8. Product Quality Complaints and Medical Device Deficiencies

All PQC related to IV cetrelimab and TAR-200 as well as Device Deficiencies related to the UPC (including malfunction, use errors, or inadequacy in information supplied by the manufacturer) shall be documented and reported by the Investigator on the PQC reporting form (see Sections 10.4 [for TAR-200 and IV cetrelimab] and 10.10 [for the UPC]) and will be reviewed by the Investigator and Sponsor and reported in accordance with local legislation (see Section 10.10). If a PQC or Device Deficiency is reported, the TAR-200, cetrelimab, or UPC (for Device Deficiencies), respectively, must be retained under the correct storage conditions until a shipment request is received from the Sponsor. Please refer to the IFU for additional instructions.

NOTE: If an AE/SAE is reported as a consequence of Device Deficiency, follow the processes outlined in Section 8.9, Adverse Events, Serious Adverse Events, and Other Safety Reporting and Section 10.10, Appendix 10: Adverse Events, Adverse Device Effects, Serious Adverse Events, Serious Adverse Device Effects, Unanticipated Serious Adverse Device Effects, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device) of the protocol.

8.10. Pharmacokinetics

Samples collected will be used to evaluate the PK of cetrelimab and TAR-200. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.10.1. Evaluations

Sparse Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 Only)

One single collection of urine samples will be collected from participants within 24 hours pre-dose at Week 0 Visit. One pooled 24-hr cumulative urine collection will be collected from participants anytime between Days 2 to 7 following TAR-200 insertion on either Week CCI and the urine

output of this 24-hr pooled urine collection will also be recorded. The 2 to 7 days sampling window is selected based on prior PK information from gemcitabine release from TAR-200, in which there is an approximate 1-day delay in drug release. Limited drug release occurs after the 7th indwelling day of TAR-200.

Detailed instructions for the collection, processing, storage, and shipment of samples are provided in the Laboratory Manual. The exact collection date and time of sampling must be recorded in the laboratory requisition form/source documentation and/or eCRF.

The final post placement sample collection days will be determined at the study participant and Investigator's discretion. These sparse samples will be collected for assessment of gemcitabine and dFdU concentrations in urine (also see Table 3). The 20 participants in Cohort 1 in the serial urine sampling are not required to complete the Week 0 and CCI sparse timepoints as the serial urine sampling will meet these requirements.

Serial Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 Only)

- Serial urine samples for gemcitabine and dFdU levels will also be collected according to the following schedule (also see Table 4) in up to 20 participants in Cohort 1. If participants have a documented sufficient rationale for not participating in this serial urine sampling, it will not preclude them from screening for the study.
- Within 24 hours pre-dose at Week 0 (one single collection).
- Beginning at Week 0, on all days from Day 1 through Day 5 and Day 8 through Day 12 (one pooled 24-hr cumulative urine collection per day).
- Beginning at Week CCI on all days from Day 1 through Day 5 and Day 8 through Day 12 (one pooled 24-hr cumulative urine collection per day).

Daily urine output over this sampling period in these approximately 20 participants will also be collected to demonstrate any correlation between a participant's gemcitabine urine concentrations and daily urine output.

Detailed instructions for the collection, processing, storage and shipment of samples are provided in the Laboratory Manual. The exact collection date and time of sampling must be recorded in the laboratory requisition form/source documentation and/or eCRF.

Plasma PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 Only)

Blood samples will be collected from participants at the following 2 time points (which coincide with sparse urine PK time points) as presented in Table 5:

- Within 24 hours pre-dose at Week 0 Visit (required)
- Anytime between Days 2 to 7, following TAR-200 insertion on either WeekCCI

The exact collection date and time of sampling must be recorded in the laboratory requisition form/source documentation and/or eCRF.

Serum PK Samples for IV Cetrelimab (Cohort 1 only)

- Blood for the assessment of cetrelimab serum PK, including minimum concentration (C_{min}) (pre-infusion) and C_{max} (End -of -Infusion [EOI]) will be collected at the time points specified in Table 6 (Serum Pharmacokinetics for Cetrelimab). All pre-infusion trough samples should be drawn within 30 minutes and before cetrelimab infusion. Blood samples should be obtained from the arm contralateral to the arm where cetrelimab is infused. The exact dates and times of dosing and blood samples must be recorded accurately. Additional details are provided in the Laboratory Manual.

The exact collection date and time of blood sampling must be recorded in the laboratory requisition form/source documentation and/or eCRF.

8.10.2. Analytical Procedures

Venous blood samples will be collected for measurement of serum concentrations of cetrelimab and the generation of antibodies to cetrelimab using validated immunoassay methods.

Plasma and urine samples will be analyzed to determine concentrations of gemcitabine and dFdU using validated liquid chromatography/tandem mass spectrometry (LC/MS) methods by or under the supervision of the Sponsor.

If required, some plasma, serum, and urine samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma, serum, and urine PK samples may be stored for future analysis of the metabolite profile.

Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

8.11. Genetics and Pharmacogenomics

Genetics and pharmacogenomics are not evaluated in this study.

8.12. Biomarkers

Biomarker samples will be collected to evaluate the mechanism of action of TAR-200 in combination with cetrelimab in participants with muscle-invasive urothelial carcinoma. Samples may help to identify population subgroups that respond differently to TAR-200 in combination with cetrelimab.

Tissue for Immune Biomarkers and Molecular Subtyping and Mutational Profiling

Tissue collected on study will be used to assess the immune marker status and identify the molecular subtype of participants' tumors, as well as identify changes in the tumor in response to treatment with TAR-200 in combination with IV cetrelimab. If participants demonstrate progression, a tissue sample should be collected for biomarker analysis.

The following analyses may be performed:

- IHC analysis of immune markers (PD-L1, other expression) on the TURBT samples.

- RNA sequencing on tumor specimens to conduct molecular subtyping and to evaluate changes after treatment. Whole exome sequencing may also be performed on the TURBT specimen.
- DNA mutation profiling to explore molecular markers of response and resistance.

Circulating Biomarkers

Blood samples for circulating tumor DNA (ctDNA)should be collected pre-dose and at timepoints specified in the Schedule of Activities (Section 1.3).

Circulating Tumor DNA

Blood and urine for analysis of ctDNA will be collected at multiple time points on study. Analysis of ctDNA offers the potential of a non-invasive method to track response to treatment by monitoring changes in target ctDNA levels over time and assess correlation with clinical responses. As such, measuring ctDNA levels will be assessed as a non-invasive disease surveillance approach and evaluated as a pharmacodynamic marker of response. Additionally, collection of blood or urine samples may be used to identify the emergence of potential markers of resistance.

Additional cancer relevant biomarkers may also be obtained from assessing DNA, RNA, protein, and serum soluble factors in blood, urine and tissue samples collected on the study to better understand the disease and mechanisms of response or resistance to TAR-200 in combination with cetrelimab.

The timing of biomarker collections may be modified during the study based on emerging data, however the number or volume of biomarker sampling will not increase.

Residual samples of blood or tissue for biomarker analysis may be stored for up to 15 years for additional research.

Detailed instructions for the collection, processing, storage, and shipment of samples are provided in the Study Reference Manual.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded tumor sample for the successful completion of the protocol-specified analyses, the Sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the Sponsor may request additional material

from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study treatment(s) or diseases being investigated.

8.13. Immunogenicity Assessments

Serum Immunogenicity Samples for Cetrelimab (Cohort 1 and Cohort 2)

- Blood samples will be collected, and serum will be analyzed for antibodies to cetrelimab, using a validated immunoassay for ADA analysis at the timepoints specified in Table 7. The incidence of anti-cetrelimab antibodies will be summarized for all participants who receive at least 1 dose of IV cetrelimab and have appropriate samples for detection of antibodies to IV cetrelimab (ie, participants with at least 1 sample obtained after their first dose of cetrelimab).
- All pre-infusion samples should be drawn within 30 minutes before infusion of IV cetrelimab. If drug was administered via a central venous catheter, sample collection for PK should be from a different site. Blood samples will be processed to obtain serum for measurement of cetrelimab concentration by a validated analytical method by the Sponsor. Additional details are provided in the Laboratory Manual. The exact date and time of sample collections must be recorded on the appropriate eCRF.

The exact collection date and time of blood sampling must be recorded in the laboratory requisition form/source documentation and/or eCRF.

8.14. Medical Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the eCRF by the Investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

The statistical hypothesis is that the combination of TAR-200 + IV cetrelimab (Cohort 1) will lead to a pCR rate CCI or greater (against a hurdle rate of CCI), and the IV cetrelimab alone (Cohort 2)

will lead to a pCR rate CCI or greater (against a hurdle rate of CCI). There is no formal statistical hypothesis testing for the comparison between the 2 cohorts.

9.2. Sample Size Determination

This study will randomize approximately 160 participants in a 5:3 randomization ratio to receive TAR-200 + IV cetrelimab (n=100) or IV cetrelimab alone (n=60).

This sample size determination utilizes a Bayesian approach with Beta(0.5,0.5) as the prior distribution and Beta(0.5+m, 0.5+n-m) as the posterior distribution for the pCR rate, where m is the observed number of participants with pCR and n is the total number of participants. Assuming a pCR rate of CCI for TAR-200 + IV cetrelimab (Cohort 1), 100 participants will provide over 90% probability to have the lower limit of the 80% credible interval exceeding CCI pCR rate (or about 80% probability of exceeding CCI pCR rate). Assuming a pCR rate of CCI for the IV cetrelimab alone (Cohort 2), 60 participants will provide about 65% probability to have the lower limit of the 80% credible interval exceeding CCI pCR rate.

9.3. Participant for Analysis Sets

For purposes of analysis, the following populations are defined:

Analysis Sets	Description
Enrolled	All participants who signed Informed Consent Form (ICF)
Randomized	All participants who were randomized in the study
Treated	All participants who receive at least 1 dose of any study treatment
Evaluable	All participants who receive at least 1 dose of any study treatment, undergo RC and have adequate disease assessment at the RC

9.4. Statistical Analyses

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

This study is being performed to assess safety, efficacy, and tolerability of 4 consecutive dosing cycles of TAR-200 + IV cetrelimab, and IV cetrelimab alone (monotherapy) neoadjuvant to radical cystectomy. A side-by-side descriptive summary of efficacy will be provided to illustrate the contribution of TAR-200 to the efficacy of the combination therapy.

9.4.2. Primary Endpoint

Primary Estimand

- Population: participants with muscle-invasive urothelial carcinoma of the bladder who are scheduled for radical cystectomy and are ineligible for or refusing platinum-based neoadjuvant chemotherapy
- Variable: pCR or ypT0N0, at the radical cystectomy

- Study Treatment: TAR-200 + IV cetrelimab, or IV cetrelimab alone
- Intercurrent event: subsequent therapy. Hypothetical Strategy: Response after this intercurrent event will not be considered as a response
- Summary: pCR rate at the radical cystectomy

The primary endpoint, pCR rate, is defined as the proportion of participants with a pCR which will be derived from analysis of a RC bladder specimen.

The point estimate of pCR rate and the corresponding 2-sided 80% credible interval (CrI) will be calculated for each cohort. The 80% CrI will be symmetric (ie, 10% for each tail) and be calculated utilizing a Bayesian approach with Beta(0.5, 0.5) as prior distribution and Beta(0.5+m, 0.5+n-m) as the posterior distribution for the pCR rate, where m is the observed number of participants with pCR and n is the total number of participants. Additionally, 95% exact confidence interval will also be calculated for each cohort based on binomial distribution.

Dynamic borrowing external data from similar PD-1/PD-L1 treatments in the similar disease population may be explored to support the primary analysis.

9.4.3. Secondary Endpoint(s)

Recurrence-free survival (RFS) will be determined in participants receiving TAR-200 + IV cetrelimab (Cohort 1) and IV cetrelimab alone (Cohort 2). Recurrence-free survival is defined as the time from first dose of any study treatment to first radiologic (as assessed by RECIST 1.1 criteria) or histologic evidence of nodal or metastatic disease or death due to any cause. For participants who are free from RFS event, data will be censored at the last study disease assessment.

The distribution of RFS will be estimated for each cohort using Kaplan-Meier method.

9.4.4. Exploratory Endpoint(s)

Overall survival (OS) will be determined in participants receiving TAR-200 + IV cetrelimab (Cohort 1), and IV cetrelimab alone (Cohort 2) OS is defined as the time from first dose of any study treatment to death. The distribution of OS will be estimated for each cohort using Kaplan-Meier method.

Pathologic overall response (pOR) will be determined in participants receiving TAR-200 + IV cetrelimab (Cohort 1), and IV cetrelimab alone (Cohort 2). Pathologic overall response (pOR) will be determined by composite evaluation of local disease in the bladder and evaluation of nodal and metastatic disease as defined above. pOR rate is defined as the proportion of participants with either pCR or pPR. The response assessments are presented for participants who are N0 at the start of the study in Table 10. The pOR rate will be tabulated together with its 95% exact confidence interval. In addition, the number and percentage of participants in each response category will be tabulated.

The TSP will be determined in participants receiving TAR-200 + IV cetrelimab and IV cetrelimab alone. The TSP defined as the time from first dose of any study treatment to documentation of any of the following (whichever occurred earlier):

- Progression of pain or worsening of disease-related symptoms requiring initiation of a new systemic anticancer therapy
- Development of clinically significant symptoms due to locoregional tumor progression requiring surgical treatment or radiation therapy.
- Development of symptomatic deterioration on the basis of global deterioration of health status.

The distribution of TSP will be estimated for each cohort using Kaplan-Meier method.

9.4.5. Safety Analyses

All safety analyses are to be performed on data from the All Treated Analysis Set. The baseline value for safety assessment is defined as the value collected at the time closest to, but prior to, the start of either TAR-200 or IV cetrelimab. Safety evaluations include the incidence, severity, and type of adverse events, clinically significant changes in the participant's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to investigational product and reasons for discontinuation of study treatment will be tabulated. Adverse events will be summarized by system organ class, preferred term, and worst grade experienced by the participant.

Adverse Events

The verbatim terms used in the eCRF by Investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study treatment through the day of last dose plus 100 days or that is a consequence of a pre-existing condition that has worsened since baseline is considered to be treatment-emergent. All reported treatment-emergent AEs which occur within 100 days after last dose of study treatment will be included in the analysis. Serious Adverse Events, if considered related to study treatment, occurring more than 100 days after the last dose of study treatment should also be reported. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue treatment due to an AE, or who experience a severe or a SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for laboratory analytes at baseline and at each scheduled timepoint. Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst grade experienced by the participant during the study will be provided as shift tables.

Electrocardiogram

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT corrected according to Fridericia's formula (QTcF).

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

Vital Signs

Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized descriptively.

9.4.6. Other Analyses

Pharmacokinetic Analyses

TAR-200:

Urine and plasma concentration of gemcitabine and dFdU, and urine amount of gemcitabine and dFdU will be listed (for both sparse and serial urine PK and plasma PK) and summarized (for serial urine PK only) at each timepoint using descriptive statistics (arithmetic mean, standard deviation [SD], coefficient of variation [CV], geometric mean, geometric CV, median, minimum, and maximum). All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration and amount data presentation. For serial urine PK, PK parameters will be listed and summarized using descriptive statistics. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics and for the calculation of PK parameters. All participants and samples excluded from the analysis will be clearly documented in the study report. Details of the analyses will be described in the Clinical Pharmacology Analysis Plan.

If feasible, population PK analysis of urine and plasma concentration-time data of TAR-200 may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Cetrelimab:

Cetrelimab concentrations will be summarized by cohort and at each timepoint using descriptive statistics (arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum) and figures. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics and for the calculation of PK parameters. All participants and samples excluded from the analysis will be clearly documented in the study report.

If feasible, population PK analysis of serum concentration-time data of cetrelimab may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Biomarkers Analyses

Associations between baseline levels and changes from baseline in select markers and clinical response will be explored.

Results of exploratory biomarker analyses may be presented in a separate report. Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information.

Immunogenicity Analyses

The incidence of anti-cetrelimab antibodies will be summarized for all participants who receive at least 1 dose of cetrelimab and have appropriate samples for detection of antibodies to cetrelimab (ie, participants with at least 1 sample obtained after their first dose of cetrelimab). A listing of participants who are positive for antibodies to cetrelimab will be provided. The maximum titers of antibodies to cetrelimab will be summarized for participants who are positive for antibodies to cetrelimab by cohort. Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Pharmacokinetic/pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic models may be explored to understand and characterize the exposure-response relationship for key efficacy, safety, and pharmacodynamic/biomarker data parameters, to detect the influence of covariates, and to identify inter-individual variability in response. The details will be provided in a separate analysis plan and the results of the analyses will be summarized in a separate report.

Patient-Reported Outcomes Assessments

Results for FACT-Bl data will be summarized descriptively for participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline measurement by treatment

group and study visit. Each multi-item scale and individual item will be summarized using count and percent.

The change of FACT-Bl from baseline will also be assessed. The meaningful clinical important difference will be assessed with an anchor-based method utilizing the PGIC and PGIS. A supplemental PRO Statistical Analysis Plan may be provided to describe analyses.

Time to worsening in FACT-Bl total score and individual scales will be analyzed using a Kaplan-Meier method and stratified Cox proportional hazard model. Additional analysis may be done, if appropriate. Analysis details will be included in the Statistical Analysis Plan.

The PRO and AE data will not be reconciled with one another. Only PRO data will be used to conduct these analyses.

Healthcare Resource Utilization and Health Economics Analyses

Healthcare resource utilization and health economics will be descriptively summarized by cohort.

9.5. Interim Analysis (Cohort 1 and Cohort 2)

Two interim analyses are planned. The first interim analysis (IA1) will be conducted after [redacted] participants in total (ie, approximately [redacted] in Cohort 1 and approximately [redacted] in Cohort 2) complete the RC and have the disease assessment of pCR at RC. The second interim analysis (IA2) will be after approximately [redacted] participants in total (ie, approximately [redacted] Cohort 1 and approximately [redacted] in Cohort 2) complete the RC and have the disease assessment of pCR at RC. The analyses will utilize the Bayesian approach described in Section 9.4.2

At IA1, the cetrelimab cohort may be stopped for futility if the posterior probability of pCR rate [redacted] is greater than 80%, ie, the number of participants with pCR is [redacted]. The criteria ensure at least 60% probability of early termination for futility if the true pCR rate for the cetrelimab cohort is less than [redacted]

At IA2, the cetrelimab cohort may be stopped for futility if the posterior probability of pCR rate [redacted] is greater than 80%, ie, the number of participants with pCR is [redacted] Similarly, an early success may be declared for the TAR-200 and cetrelimab cohort if the posterior probability of pCR rate [redacted] is greater than 80%, ie, the number of participants with pCR is [redacted] The criteria ensure at least 71% probability of early termination for futility if the true pCR rate for the cetrelimab cohort is less than [redacted], or 71% probability of early success for the combination if the true pCR rate for the combination cohort is greater than [redacted]

IDMC will be established to review interim data. Specific details will be outlined in the IDMC Charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

ADA	anti-drug antibody
AE	adverse events
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUA	American Urological Association
AUC_{tau}	area under the curve for 1 dosing interval
β-hCG	β-human chorionic gonadotropin
C_{avg}	observed mean maximum serum concentration
CFU	colony forming units
C_{max}	maximum serum concentration
CR	complete response
CRC	colorectal cancer
CrI	credible interval
CT	computed tomography
C_{trough}	predose concentration at steady-state
dFdU	2′,2′-difluorodeoxyuridine
EAU	European Association of Urology
ECG	Electrocardiogram
eCRF	electronic case report form(s)
eDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
ECOG	Eastern Cooperative Oncology Group
FACT-Bl	Functional Assessment of Cancer Therapy – Bladder
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HCV	hepatitis C
HIV	human immunodeficiency virus
HNT	human nucleoside transporter
HRQoL	health-related quality of life
MRU	Medical resource utilization
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFU	instructions for use
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	international normalized ratio
IPPI	Investigational Product Preparation Instructions
irAE	immune-related adverse event
IRB	Institutional Review Board
IRR	infusion-related reactions
IWRS	interactive web response system
IV	Intravenous
mAb	monoclonal antibody

MedDRA	Medical Dictionary for Regulatory Activities
MIBC	Muscle Invasive Bladder Cancer
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NMIBC	Non-muscle Invasive Bladder Cancer
NSAIDs	anticholinergics, nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
pCR	pathologic complete response
PD-1	programmed-cell death protein 1
PD-L1	programmed-cell death ligand 1
PD-L2	programmed-cell death ligand 2
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
POCBP	Participants of Childbearing Potential
pOR	pathologic overall response
pPR	pathologic partial response
PQC	Product Quality Complaint
PRO (ePRO)	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PVR	Post-Void Residual
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Q4W	once every 4 weeks
QoL	Quality of Life
RBC	red blood cell
RC	radical cystectomy
RCRI	Revised Cardiac Risk Index
RFS	recurrence-free Survival
RP2Ds	recommended Phase 2 dose(s)
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SIPPM	Site Investigational Product and Procedures Manual
SUSAR	suspected unexpected serious adverse reaction
TGF-β	transforming growth factor beta
TSP	time to symptom deterioration
TURBT	transurethral resection of bladder tumor
ULN	upper limit of normal
UPC	Urinary Placement Catheter
UTI	urinary tract infection
WBC	white blood cell
WHO	World Health Organization

Definitions of Terms

Electronic Source System	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in an eCRF as determined by the protocol. Data in this system may be considered source documentation.
PRO	Reports directly from the participant without interpretation by clinician or anyone else

10.2. Appendix 2: Clinical Laboratory Tests

Blood samples for serum chemistry, hematology, serology, and coagulation will be collected as shown in the Schedule of Activities (Section 1.3). More frequent clinical laboratory tests may be performed if indicated by the participant's overall clinical condition. Screening laboratory results must be available to the Investigator for evaluation before the first dose of study treatment and prior to each study treatment administration. The Investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed according to the Schedule of Activities by the local laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count Hemoglobin	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes
Clinical Chemistry	Sodium Potassium Phosphate Calcium Albumin Creatinine Glucose (Fasting) at screening* Total Protein Thyroid Stimulating Hormone (TSH) Triiodothyronine (T3) Free Thyroxine (T4) HbA1c (to be tested at Screening through Week C[redacted] post RC only)*	Alkaline Phosphatase (ALP) Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic Lactic acid dehydrogenase (LDH) Total bilirubin Uric Acid C-Reactive Protein (CRP) Gamma-Glutamyl Transferase (GGT) Lipase Amylase C-peptide (Unscheduled visit only)
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Urine Culture (at Screening and if clinically indicated per Investigator discretion) Nitrites Ketones (Unscheduled visit only)	Sediment (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria

Laboratory Assessments	Parameters
Other Tests	• Serum Pregnancy Testing for participants of childbearing potential only • Serology (at Screening only if applicable) HIV antibody: if positive, further testing of CD4 count and HIV viral load should be carried out. Hepatitis B virus surface antigen (HBsAg) and core (HBc) antibody: if positive, further testing of quantitative levels to rule out active infection is required Hepatitis C virus (HCV) antibody: if positive, further testing quantitative levels to rule out active infection is required • Coagulation Panel (Tested through Week [redacted] post RC only) o Prothrombin Time (PT) o Activated Partial Thromboplastin Time (APTT) o International Normalized Ratio (INR)

* HbA1c results can replace the requirement for fasting blood glucose prior to each dose; however, if fasting glucose results are available, the HBA1c result does not need to be reviewed prior to dosing, but should still be collected.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The Investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country- or territory-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the Investigator nor the Sponsor will modify this protocol without a formal amendment by the Sponsor. All protocol amendments must be issued by the Sponsor, and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the Investigator and IEC/IRB must be provided to the Sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the Investigator or other physician in attendance will contact the appropriate Sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Sponsor must be made as soon as possible

to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study treatment to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal Investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an Investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of Investigator (eg, Form FDA 1572), if applicable
- Documentation of Investigator qualifications (eg, curriculum vitae)
- Completed Investigator financial disclosure form from the principal Investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the Sponsor before enrollment of the first participant:

- Completed Investigator financial disclosure forms from all sub-Investigators
- Documentation of sub-Investigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the Investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the Investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study treatment

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the Investigator's care
- Notification if a new Investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the Investigator (or Sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.3.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Pre-study Documentation (above) and contracts for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the participant can read

and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the Investigator or an authorized member of the study site personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the Investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant (or legally acceptable representative) will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the participant's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 42 days from the previous ICF signature date.

If the participant or legally acceptable representative is unable to read or write, an impartial witness must be present for the entire informed consent process (which includes reading and explaining all written information) and must personally date and sign the ICF after the oral consent of the participant or legally acceptable representative is obtained.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place.

Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the Investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the Investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the Sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or Investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand cetrelimab and TAR-200, to understand urothelial cancer, to understand differential drug responders, and to develop tests/assays related to cetrelimab, TAR-200, and urothelial cancer. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.3.1, Withdrawal From the Use of Research Samples).

10.3.6. Committees Structure

Independent Data Monitoring Committee (IDMC)

An IDMC of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician will be established to monitor data on an ongoing basis to ensure the safety of the participants enrolled in this study. The committee membership responsibilities, authorities, and procedures will be documented in the IDMC Charter. The safety review will focus on deaths, study drug discontinuations, SAEs, Grade ≥3 events, and emerging safety data. Based on the results from these scheduled safety review meetings, the IDMC chair may request more frequent monitoring. Until the first IDMC review, all deaths, study drug discontinuations and SAEs will be reviewed by the Sponsor's medical monitor on an ongoing basis to identify safety concerns, and the IDMC will be informed of any new potential signals. The committee will meet periodically to review

interim data. After the review, the IDMC will make recommendations regarding the continuation of the study.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the Investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The Investigator agrees to maintain this information in confidence and use this information only to accomplish goals of this study and will not use it for other purposes without the Sponsor's prior written consent.

The Investigator understands that the information developed in the study will be used by the Sponsor in connection with the continued development of TAR-200 and cetrelimab, and thus may be disclosed as required to other clinical Investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating Investigator for the study. Results of biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the Investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the Sponsor shall have the right to publish such primary (multicenter) data and information without approval from the Investigator. The Investigator has the right to publish study site-specific data after the primary data are published. If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the Investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. If issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the Investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, Investigators will recognize the integrity of a multicenter study by not submitting for publication data derived

from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The Sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and study site personnel before the study, periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study.

The Sponsor will review the eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the Sponsor for each participant in electronic format. All data relating to the study must be recorded in the CRF. All eCRF entries, corrections, and alterations must be made by the Investigator or authorized study site personnel. The Investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the Sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) system. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC system at their own initiative or as a response to an auto query (generated by the eDC system).
- Sponsor or Sponsor delegate can generate a query for resolution by the Investigator and study site personnel.

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; treatment receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that patient-reported outcomes (PROs) are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by trial participants into source records cannot be overridden by site staff or Investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the Investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum
- Blood pressure and pulse/heart rate
- Height and weight

- Details of physical examination
- Investigator-completed scales and assessments, PRO, Health Economics data

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the Sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.3.11. Monitoring

The Sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the Sponsor and study site personnel and are accessible for verification by the Sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The Sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the Sponsor as requiring central review.

10.3.12. On-Site Audits

Representatives of the Sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The Investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the Investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator/institution must permit access to such reports.

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study treatment development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The Sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.9.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions. For combination products with a device constituent, AEs include those resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. It includes any AE resulting from use error or from intentional misuse of the investigational device.

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

Note: Events that do not qualify as an AE cannot be reported as a SAE, even if the conditions for seriousness are met. In particular, this is the case for events due to disease progression leading to death, hospitalization, etc.

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unexpected if the nature or severity is not consistent with the applicable product reference safety information. For TAR-200 and cetrelimab, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity grade will be made by the Investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 5.0).

Any adverse events or serious adverse events not listed in the NCI-CTCAE Version 5.0 should be evaluated for severity/intensity by using the standard grades as follows:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Activities of Daily Living (ADL)

- *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The Investigator must use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

Safety events of interest on a Sponsor study drug in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study treatment
- Suspected abuse/misuse of a Sponsor study treatment
- Accidental or occupational exposure to a Sponsor study treatment
- Any failure of expected pharmacologic action (ie, lack of effect if used according to the local label) of a Sponsor study treatment (to be reported as a PQC for marketed products)
- Unexpected therapeutic or clinical benefit from use of a Sponsor study treatment
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a Sponsor study treatment from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

Anticipated events will be recorded and reported as described in Anticipated Events (US only), Section 10.16, Appendix 16.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the Investigator may choose to hospitalize the participant for the duration of the treatment period.

Expected progression of disease, which is part of the natural course of the disease under study, should not be considered an AE (or SAE). However, if determined by the Investigator to be more likely related to the study treatment, protocol design, or protocol procedures, than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study intervention is enhancing disease progression, should be reported per the usual reporting requirements. In this latter case, these will be reported if they fulfill the SAE definition (refer to Adverse Event Definitions and Classifications in Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Information regarding SAEs will be transmitted to the Sponsor using an SAE reporting form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the Sponsor personnel immediately, without undue delay or within 24 hours after being made aware of the event, as required by local regulations. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage of the product or the drug delivery system. This definition includes any PQC related to a device constituent in a drug-device combination product, including those used in the administration of the study intervention or the comparator. All PQCs related to TAR-200 and IV cetrelimab shall be documented and reported by the Investigator on the PQC reporting form (see Section 10.10) and will be reviewed by the Investigator and Sponsor and reported in accordance with local legislation (see Section 10.10).

For additional information regarding Device Deficiencies related to the UPC, please see Section 10.10.

Procedures

All initial PQCs must be reported to the Sponsor using the PQC form by the study site personnel immediately, without undue delay or within 24 hours after being made aware of the event, as required by local regulations.

A sample of the suspected product should be maintained under the correct storage conditions, per institutional guidelines, until a shipment request is received from the Sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQCs, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.9.5, and Pregnancy, and Section 10.4, Appendix 4 (Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Definitions

Participants of Childbearing Potential

A participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Participants Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in female participants not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  If there is a question about menopausal status in female participants on HRT, the female participant will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  - Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
  - Has congenital abnormalities resulting in sterility.

Note: If the childbearing potential changes after start of the study eg, a premenarchal female participant experiences menarche) or the risk of pregnancy changes (eg, a female participant who is not heterosexually active becomes active), a female participant must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by male or female participants must be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives[a]

1. HIGHLY EFFECTIVE METHODS *(Failure rate of <1% per year when used consistently and correctly.)*

1.1. USER INDEPENDENT - Highly Effective Methods.

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
- Azoospermic partner (*Vasectomized or due to medical cause*)

(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the female of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 74 days.)

1.2. USER DEPENDENT - Highly Effective Methods

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[b]
  - oral
  - injectable
- Sexual abstinence

(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

[a] **Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.**

Pregnancy During the Study

All initial reports of pregnancy in female participants or partners of male participants must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the study drugs on sperm is unknown, pregnancies in partners of male participants included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. Follow-up information may continue to be collected up to 12 months after the birth of a baby, if a congenital anomaly or significant medical condition is diagnosed at birth.

10.6. Appendix 6: PRO Questionnaires (FACT-BI)

FACT-BI (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GP 1	I have a lack of energy	0	1	2	3	4
GP 2	I have nausea	0	1	2	3	4
GP 3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP 4	I have pain	0	1	2	3	4
GP 5	I am bothered by side effects of treatment	0	1	2	3	4
GP 6	I feel ill	0	1	2	3	4
GP 7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GS 1	I feel close to my friends	0	1	2	3	4
GS 2	I get emotional support from my family	0	1	2	3	4
GS 3	I get support from my friends	0	1	2	3	4
GS 4	My family has accepted my illness	0	1	2	3	4
GS 5	I am satisfied with family communication about my illness	0	1	2	3	4
GS 6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS 7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE 1	I feel sad	0	1	2	3	4
GE 2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE 3	I am losing hope in the fight against my illness	0	1	2	3	4
GE 4	I feel nervous	0	1	2	3	4
GE 5	I worry about dying	0	1	2	3	4
GE 6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BL1	I have trouble controlling my urine	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BL3	It burns when I urinate	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BL5	(For men only) I am able to have and maintain an erection	0	1	2	3	4
Q2	Do you have an ostomy appliance? No___ Yes___ If yes, answer the following two items: ↓					
C8	I am embarrassed by my ostomy appliance	0	1	2	3	4
C9	Caring for my ostomy appliance is difficult	0	1	2	3	4

10.7. Appendix 7: PRO Questionnaires (PGIS)

Patient Global Impression of Severity (PGIS) of Cancer

Considering all aspects of your bladder cancer symptoms right now, would you say your bladder cancer symptoms are: (Please select one response)

- ☐ 1. None
- ☐ 2. Mild
- ☐ 3. Moderate
- ☐ 4. Severe
- ☐ 5. Very Severe

10.8. Appendix 8: PRO Questionnaires (PGIC)

Patient Global Impression of Change (PGIC) of Cancer

Compared to when you received the first treatment in this study, how has your cancer changed? (Please select one response)

- ☐ 1. A lot better now
- ☐ 2. Moderately better now
- ☐ 3. A little better now
- ☐ 4. Neither better, nor worse (no change)
- ☐ 5. A little worse now
- ☐ 6. Moderately worse now
- ☐ 7. A lot worse now

10.9. Appendix 9: Guidelines for Management of Immune-Related Adverse Events and Adverse Events of Clinical Interest

Therapy with immuno-oncology agents such as cetrelimab can lead to specific irAEs that differ in nature, severity and duration as compared to AEs caused by agents with a different mode of action. Early recognition and management of these irAEs may mitigate more severe/subsequent toxicity. However, differential diagnoses including non-inflammatory etiologies as well as the impact of the underlying malignant disease and/or concomitant medication should be evaluated according to standard medical practice.

Management algorithms have been developed to assist Investigators in assessing and managing specific irAEs following administration of nivolumab (Nivolumab SmPC; Nivolumab USPI) and pembrolizumab (Pembrolizumab SmPC; Pembrolizumab USPI). These guidelines are presented below and should be followed for cetrelimab. In addition to the management algorithms provided in following sections, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (Ipilimumab USPI). These guidelines recommend the following:

1. Participants should be evaluated to identify any alternative etiology.
2. In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
3. Symptomatic and topical therapy should be considered for low-grade events.
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5. More potent immunosuppressives should be considered for events not responding to systemic corticosteroids (eg, anti-TNF agents or mycophenolate).

If delaying the dose is necessary to ameliorate a toxicity, follow the guidance in Section 6.5.

NCI-CTCAE (Version 5.0) guidelines for severity grading and management of cytokine release syndrome are provided in Section 10.13, Appendix 13. There is no expectation of immune related adverse events due to TAR-200 or the combination, based on prior Phase 1b data, as detailed in the IB.

10.9.1. Gastrointestinal Adverse Events

Diarrhea and colitis have been observed in participants receiving anti-PD-1 therapies. Early recognition and treatment of diarrhea and colitis are critical to their management. Participants should be advised to seek immediate medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. In participants with pre-existing diverticulosis and/or diverticulitis receiving concomitant medication with corticosteroids, NSAIDs, and opioid analgesics together with anti-PD-1 therapies, diverticular perforation has been observed. Management of immune-related gastrointestinal AEs is provided in Table 11.

Table 11: Management of Immune-Related Gastrointestinal Adverse Events

For guidelines for delaying a dose, refer to Section 6.5.	
Grade 1	Symptomatic treatment according to institutional standards Close monitoring; instruct participant to report worsening immediately and treat as Grade ≥2
Grade 2	**≤5 days:** Symptomatic treatment according to institutional standards **>5 days or recurrence:** 1.0 mg/kg/d prednisone or equivalent; consider prophylactic antibiotics; consider consultation with gastroenterology **Persistence or worsening despite steroids >3 days:** treat as Grade 3/4 **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections, resume study therapy per protocol
Grade 3-4	**Immediately:** 1.0–2.0 mg/kg/d methylprednisolone IV; consider prophylactic antibiotics and lower endoscopy **Persistence >3 days, high-risk endoscopic features (large deep ulceration, multiple ulcers, extensive colitis beyond left colon), or recurrence:** add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis) **Improvement to ≤Grade 2 within ≤3 days:** taper steroids over at least 4 weeks
General	The oral corticosteroid equivalent of the recommended IV dose may be considered for ambulatory participants; the lower bioavailability of oral corticosteroids needs to be considered. Clinical caution should be exercised, for participants receiving concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, monitor for signs and symptoms of potential perforation, especially in participants with known diverticular disease. Narcotics should be used with caution as pain medicines may mask the signs of colonic perforation.

Abbreviations: IV=intravenous; NSAID=non-steroidal anti-inflammatory drugs

10.9.2. Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug induced liver-injuries (DILI) have been observed following treatment with anti-PD-1 therapies. Early recognition and treatment of elevated LFTs and DILI are critical to their management. Participants should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each anti-PD-1 therapies. Participants who have a predominant cholestatic pattern of liver injury (dominant increase in ALP relative to ALT/AST) should be further evaluated to exclude a diagnosis of treatment emergent sclerosing cholangitis. An evaluation may include ultrasound of liver, cholangiography, and referral to gastroenterologist and/or hepatologist. Management of immune-related hepatic AEs is provided in Table 12.

Table 12: Management of Immune-related Hepatic Adverse Events

For guidelines for delaying a dose, refer to Section 6.5.	
Grade 1	Monitor LFTs as outlined in the protocol; **Worsening:** treat as Grade ≥2
Grade 2	Monitor every 3 days; **Returning to baseline:** resume per protocol monitoring **LFT elevation >5 days or worsening:** 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **LFT return to ≤Grade 1 or baseline:** taper steroids over at least 4 weeks; resume routine monitoring and resume study treatment per protocol
Grade 3-4	Monitor every ≤2 days; **Immediately:** 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; start prophylactic antibiotics; consult gastroenterologist **Persistence >3 days or recurrence:** add mycophenolate mofetil 1g bid if infectious cause is ruled out; if no response within ≤5 days consider other immunosuppressants per local guidelines **LFT return to Grade 2:** stop immunosuppressants **LFT return to ≤Grade 1:** taper steroids over at least 4 weeks

Abbreviations: IV=intravenous; LFT= liver function tests

10.9.3. Endocrinopathies

Endocrinopathies have been observed following treatment with anti-PD-1 therapies. The events have typically been identified through either routine periodic monitoring of specific laboratory tests (eg, TSH) or as part of a work-up for associated symptoms (eg, fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (eg, hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Participants should be advised to seek medical evaluation if they notice new onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens. Management of immune-related endocrinopathies is provided in Table 13.

Table 13: Management of Immune-Related Endocrinopathies	
For guidelines for delaying a dose, refer to Section 6.5.	
Asymptomatic TSH elevation	**TSH <0.5xLLN or TSH >2xULN or TSH >ULN in 2 subsequent measurements:** include free T4 assessment prior/after subsequent cycles of study treatment; consider endocrinology consultation
Symptomatic endocrinopathy	Assess endocrine function with appropriate laboratory testing; consider pituitary MRI scan **With abnormal lab and pituitary scan:** 1.0–2.0 mg/kg/d methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy; consider prophylactic antibiotics • In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy. • In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care. **Clinical and laboratory improvement:** taper steroids over at least 4 weeks; participants with adrenal insufficiency may need to continue steroids with mineralocorticoid component **Without abnormal lab and pituitary scan but symptoms persist:** repeat laboratory assessments in ≤3 weeks and MRI in 4 weeks
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Rule out sepsis **Immediately:** initiate/stress dose of IV steroids with mineralocorticoid activity; fluids IV; consult endocrinologist **Adrenal crisis ruled out:** treat as symptomatic endocrinopathy
Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)	For T1DM or Grade 3-4 Hyperglycemia: Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. Evaluate participants with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
General	Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered.

Abbreviations: DKA=diabetic ketoacidosis; IV=intravenous; LLN=lower limit of normal; MRI=magnetic resonance imaging; T1DM=type 1 diabetes mellitus; TSH=thyroid stimulating hormone; ULN=upper limit of normal

10.9.4. Rash

Rash and pruritus were the most common skin irAEs observed following treatment with anti--PD-1 therapies. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without treatment. Participants should be advised to seek medical evaluation if they notice new-onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash, or if there is any unusual appearance or clinical feature associated with it. A case of toxic epidermal necrolysis occurred in a participant receiving concomitant prophylaxis with trimethoprim /sulfamethoxazole, and it is possible that the initial rash was due to a sulfa-hypersensitivity reaction that was eventually augmented by anti-

PD-1 therapies. This case highlights the possible importance of discontinuing other suspected drugs in the management of rash. Management of rash is provided in Table 14.

Table 14: Management of Rash

For guidelines for delaying a dose, refer to Section 6.5.	
Grade 1-2	**Immediately:** Symptomatic therapy (eg, antihistamines, topical steroids) **Persistence ≤2 weeks or recurrence:** consider skin biopsy; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks **Worsening to >Grade 2:** treat as Grade 3-4
Grade 3-4	**Immediately:** consult dermatologist; consider skin biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤ Grade 1:** taper steroids over at least 4 weeks
General	Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

Abbreviations: IV=intravenous;

10.9.5. Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with anti-PD-1 therapies. Physicians should monitor creatinine regularly. Management of renal AEs is provided in Table 15.

Table 15: Management of Renal Adverse Events

For guidelines for delaying a dose, refer to Section 6.5.	
Grade 1	Monitor creatinine weekly **Creatinine returns to baseline:** continue monitoring per protocol **Creatinine increases:** treat as Grade ≥2
Grade 2-3	Monitor creatinine every ≤3 days **Immediately:** start 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics; consider renal biopsy **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks **Persistence >7 days or worsening:** treat as Grade 4
Grade 4	Monitor creatinine daily **Immediately:** consult nephrologist; consider renal biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks
General	Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

Abbreviations: IV=intravenous;

10.9.6. Neurological Adverse Events

Neurological AEs have been uncommonly observed following treatment with anti-PD-1 therapies. Neurological AEs can manifest as central abnormalities (eg, aseptic meningitis or encephalitis) or peripheral sensory/motor neuropathies (eg, Guillain-Barre Syndrome). The onset has been observed as early as after a single treatment. Early recognition and treatment of neurologic AEs is critical to their management. Participants should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes. Management of neurological AEs is provided in Table 16.

Table 16: Management of Neurological Adverse Events

For guidelines for delaying a dose, refer to Section 6.5.	
Grade 1	Monitor per protocol **Worsening:** treat as ≥Grade 2
Grade 2	**Immediately:** treat symptoms according to institutional standards; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent **Worsening:** treat as Grade 3-4
Grade 3-4	**Immediately:** consult neurologist; treat symptoms according to institutional standards; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; prophylactic antibiotics **Worsening or atypical presentation:** consider IV immunoglobulins (IVIG) or other immunosuppressive therapies according to institutional standards **Improvement to ≤ Grade 2:** taper steroids over at least 4 weeks
General	Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

Abbreviations: IV=intravenous; IVIG=immunoglobulins IV

10.9.7. Pulmonary Adverse Events

Pulmonary AEs including radiographic changes (eg, focal ground glass opacities and patchy infiltrates) indicative of drug-related pneumonitis have been observed in participants receiving anti-PD-1 therapies. These pulmonary AEs were either asymptomatic or associated with symptoms such as dyspnea, cough, or fever. The initial occurrence of pulmonary AEs may be as early as after a single dose of anti-PD-1 therapies or delayed after prolonged therapy. Early recognition and treatment of pneumonitis is critical to its management. Participants should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms. Management of pulmonary AEs is provided in Table 17.

Table 17: Management of Pulmonary Adverse Events

For guidelines for delaying a dose, refer to Section 6.5.	
Grade 1	Monitor for symptoms every 2-3 days; consider pulmonary and infectious-disease consult; re-image every 3 weeks **Worsening:** treat as ≥Grade 2
Grade 2	Monitor symptoms daily; re-image every 1-3 days; pulmonary and infectious-disease consultation; consider bronchoscopy and lung biopsy; consider hospitalization **Immediately:** start 1.0 mg/kg/d methylprednisolone IV or oral equivalent; prophylactic antibiotics **Persistence for 2 weeks or worsening:** treat as Grade 3-4 **Improvement to ≤ Grade 1 or baseline:** taper steroids over at least 4 weeks
Grade 3-4	Hospitalize; pulmonary and infectious-disease consult; consider bronchoscopy and lung biopsy **Immediately:** 1-2 mg/kg/d methylprednisolone or IV equivalent; add prophylactic antibiotics; **Persistence for 2 days or worsening:** add immunosuppression (eg, infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil) **Improvement to ≤ Grade 2:** taper steroids over at least 6 weeks
General	Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

Abbreviations: IV=intravenous; LFT= liver function tests

10.9.8. Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (eg, uveitis) is an uncommon, but clinically important, event. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause. Management of uveitis and visual complaints is provided in Table 18.

Table 18: Management of Uveitis and Visual Complaints

For guidelines for delaying a dose, refer to Section 6.5.	
Grade 1	Thorough eye examination Topical corticosteroids should be considered Persisting despite topical steroids, treat as Grade 3-4
Grade 2	
Grade 3-4	Thorough eye examination Systemic corticosteroids

10.9.9. Lipase/Amylase Elevations

Asymptomatic elevations in lipase and amylase have been reported in anti-PD-1 therapy studies in which systemic monitoring was used. Very few participants reported associated symptoms (eg, abdominal pain) or radiographic findings (eg, stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values. The recommended management of anti-PD-1 therapy-related elevated lipase/amylase values centers around close observation. Physicians should ensure that participants have no associated symptoms consistent with pancreatitis, such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low-grade levels over the course of weeks, whether or not participants receive corticosteroids. Asymptomatic elevations should be monitored approximately weekly.

10.9.10. Infection

Participants with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

10.9.11. Treatment of Anti-PD-1 Infusion-related Reactions

Since cetrelimab (JNJ-63723283) contains only human immunoglobulin protein sequences, it is less likely to induce a hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Management of IRRs is provided in Table 19.

All CTCAE Grade 3 or 4 IRRs should be reported immediately, without undue delay or within 24 hours after being made aware of the event, as required by local regulations.

Table 19: Management of Infusion-Related Reactions

Management and Follow-up of Infusion-Related Reactions. For guidelines for delaying a dose, refer to Section 6.5.	
Grade 1	No intervention indicated; remain at bedside and monitor participant until recovery from symptoms. Consider diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional study drug administration.
Grade 2	**Stop infusion**; start IV saline infusion; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol 325 to 1000 mg (acetaminophen); consider corticosteroids and bronchodilator therapy; remain at bedside and monitor participant until recovery from symptoms. **Restart infusion at 50% of initial rate:** if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate; monitor participant closely. **Symptoms recur** stop and discontinue further treatment at that visit; administer diphenhydramine 50 mg IV, and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF.
Grade 3-4	**Stop infusion**; start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
General	**Prophylactic medications (after initial event)**: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional study drug administrations; if necessary, corticosteroids (recommended dose: up to 80 mg of IV methylprednisolone or equivalent) may be used. Appropriate resuscitation equipment should be available in the room and a physician readily available during the infusion of study drug.

Abbreviations: IV=intravenous; SC= subcutaneous

10.9.12. Monitoring During and After Study Drug Administration

Participants should be carefully observed during study agent administration. Trained study staff at the clinic should be prepared to intervene in case of any IRRs or injection site reactions occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside. Attention to staffing should be considered when multiple participants will be dosed at the same time.

If an infusion-related reaction develops, then the infusion should be temporarily interrupted or slowed down. Guidelines outlined in Section 10.9.11, Appendix 9, must be followed to manage IRRs.

Participants should be monitored for at least 2 hours after the completion of the first study drug administration and may be discharged if considered clinically stable and all other study procedures have been completed. The Investigator will determine the duration of safety monitoring for subsequent administrations.

10.10. Appendix 10: Adverse Events, Adverse Device Effects, Serious Adverse Events, Serious Adverse Device Effects, Unanticipated Serious Adverse Device Effects, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device

- The safety reporting procedures described in this Appendix apply to the UPC used for the insertion of TAR-200 into the bladder (See Section 6.1.1, TAR-200 Insertion).
- The Investigator should distinguish whether the (S)AEs and **(**S**)**ADEs, as well as Device Deficiencies, are due to the procedure, ie, TAR-200 (gemcitabine) insertion and removal, or the UPC. An AE/ADE can be related both to the procedure and the investigational device.
- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the Investigator and the Sponsor will comply with all local and regional medical device reporting requirements.

10.10.1. Definitions (UPC Only)

Adverse Event (AE)	An AE is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including abnormal laboratory finding, in participants, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device. This definition includes events that are anticipated as well as unanticipated events. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.
Adverse Device Effect (ADE)	An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE)	Any AE that: • Led to death • Led to serious deterioration in the health of the participant, that resulted in any of the following: – Life-threatening illness or injury. The term ‘life-threatening' in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

	– Permanent impairment of a body structure or a body function, – Hospitalization or prolongation of patient hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. – Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, – Chronic disease (MDR 2017/745) • Led to fetal distress, fetal death or a congenital physical or mental impairment or birth defect
Serious Adverse Device Effect (SADE)	A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. Note: SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device should not be considered SADEs.
Unanticipated Serious Adverse Device Effect (USADE)	An USADE is defined as a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment. Procedures associated with the use of a device should be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are USADEs or not. Note: USADE is also identified as an unanticipated adverse device effect (UADE) in US Regulations 21 CFR 812.
Device Deficiency	A Device Deficiency is an inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device. Device Deficiencies include malfunctions, use errors, or inadequacy in information supplied by the manufacturer, including labeling.

10.10.2. Recording and Follow-up of Adverse Events and/or Serious Adverse Events, and Device Deficiencies (UPC Only)

Adverse Events, Serious Adverse Events, and Device Deficiency Recording
• When an AE/SAE/Device Deficiency occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE/Device Deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form.

- It is not acceptable for the Investigator to send photocopies of the participant's medical records to pharmacovigilance in lieu of completion of the AE/SAE/PQC (for Device Deficiencies) reporting form.
- There may be instances when copies of medical records for certain cases are requested by pharmacovigilance. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For Device Deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a Device Deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

See Section 10.4.3, Appendix 4, for details on severity grading.

An assessment of severity grade will be made by the Investigator according to the NCI-CTCAE Version 5.0.

Any AEs or SAEs not listed in the NCI-CTCAE Version 5.0 should be evaluated for severity/intensity by using the standard grades as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.

Grade 2 Moderate; minimal, local or noninvasive treatment indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4 Life-threatening consequences; urgent treatment indicated.

Grade 5 Death related to AE.

The Investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

Assessment of Causality

During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the IB, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable SAEs and the potential risks are listed and assessed there. The

presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each SAE will be classified according to four different levels of causality. The Sponsor and the Investigators will use the following definitions to assess the relationship of the SAE to the investigational device, the comparator or the investigational procedure.

- **Not related:** Relationship to the device, comparator or procedures can be excluded when:
  - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
  - the SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the SAE;
  - the event involves a body-site or an organ that cannot be affected by the device or procedure;
  - the SAE can be attributed to another cause (eg, an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
  - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

  In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.
- **Possible:** The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
- **Probable:** The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
- **Causal Relationship:** The SAE is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or procedures;
  - the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;

- the SAE follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the SAE (when clinically feasible);
- other possible causes (eg an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the participant is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

For each AE/SAE/Device Deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/Device Deficiency and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to pharmacovigilance. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events/Serious Adverse Events and Device -Deficiencies

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE/SAE or Device Deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide pharmacovigilance with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form(s).
- The Investigator must report the following information to the Sponsor immediately, without undue delay but no later than 24 hours after receipt of the information:
  - Any updated SAE information

– Any updated information regarding Device Deficiencies that result in a SAE or might have led to a SAE

Refer to Section 10.10.3 for further details regarding reporting requirements

10.10.3. Reporting Requirements (Investigator to Sponsor) (UPC only)

General guidelines on the data collections tools (eDC vs paper CRF) and reporting of safety information relating to medical devices is provided in the sections below. These guidelines are meant to ensure that this safety information is captured and reported appropriately.

10.10.3.1. Reporting of Serious Adverse Events and Serious Adverse Device Effects

All SAEs and SADEs must be reported to the sponsor by study site personnel immediately, without undue delay or within 24 hours of their knowledge of the event.

If the SAE/SADE is associated with a Device Deficiency, the device deficiency must also be reported as outlined in Section 10.10.3.2, Appendix 10.

The reporting procedures for SADEs are outlined below:

Serious Adverse Events Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE/SADE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) in order to report the event immediately, without undue delay, but no later than 24 hours. • The site will enter the SAE/SADE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE/SADE from a study participant or receives updated data on a previously reported SAE/SADE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next table) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the Contact Information page.

Serious Adverse Events Reporting via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Contact Information page.

10.10.3.2. Reporting of Device Deficiencies (UPC only)

Device Deficiencies related to the UPC (including malfunction, use errors, or inadequacy in information supplied by the manufacturer) shall be documented by the investigator and reported to the sponsor as 'Device Deficiencies' on the PQC reporting form.

Device Deficiency Reporting from Investigator to Sponsor

NOTE: There are additional reporting obligations for Device Deficiencies that might have led to an SAE (see next section).

- All Device Deficiencies must be reported to the Sponsor immediately, without undue delay but no later than 24 hours after the Investigator determines that the event meets the definition of a Device Deficiency via the PQC form.
- Contacts for Device Deficiency reporting can be found in the Contact Information page.
- The Investigator and Sponsor will review all Device Deficiencies and determine and document in writing whether they might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate. These Device Deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by regional and local legislation.

Reporting of Device Deficiencies that Led to a SAE or Might Have Led to a SAE

NOTE: There are additional reporting obligations for medical Device Deficiencies that are potentially related to an SAE that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

Important reporting obligations are bulleted below for 2 different situations:

1. Any Device Deficiency that is associated with an SAE, along with the SADE itself, must be reported to the Sponsor immediately, without undue delay but no later 24 hours after the Investigator determines that the event meets the definition of a Device Deficiency These SADEs should be reported via the eDC tool (as described in Section 10.10.3.1, Appendix 10) while the Device Deficiencies should be reported via paper PQC report form as 'Device Deficiency.'
2. Device Deficiency that may have led to a SAE: The Investigator and Sponsor will review all Device Deficiencies and determine and document in writing whether they might have

led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate. The primary collection will occur via the paper PQC form. Any Device Deficiency that might have led to an SAE should be reported via the paper PQC form to the sponsor immediately, without undue delay but no later than 24 hours after the investigator determines that the event meets the definition of a Device Deficiency.

These Device Deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by regional and local legislation regulations (Section 10.10.4, Appendix 10).

10.10.4. Sponsor Reporting Requirements (UPC only)

Reporting from the Sponsor to the National Competent Authorities in the EU (Article 80(2) of Regulation (EU) 2017/745):

The following events are considered reportable to national competent authorities:

- Any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible,
- Any Device Deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate,
- Any new findings in relation to any event referred to in the two points above.

The Sponsor must report to all NCAs where the clinical investigation is authorized to start:

- All reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/participants, users or other persons or a new finding to it: Immediately, but not later than 2 calendar days after awareness by the Sponsor of a new reportable event or of new information in relation to an already reported event.
- Any other reportable events or new finding/update to it: Immediately, but not later than 7 calendar days after awareness by the Sponsor of a new reportable event or of new information in relation to an already reported event.

10.11. Appendix 11: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the Sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the Investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study treatment will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study treatment, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, Investigator, and the Sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study treatments and withdrawal from the study should be documented with the prefix "COVID-19-related" in the electronic case report form (eCRF).

The Sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID 19, the Investigator should contact the Sponsor's responsible medical officer to discuss plans for study treatment and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

Guidance specific to this protocol:

- Regarding the COVID-19 vaccination, considering the risk-benefit for cancer patients the Sponsor will support the clinical decision of the Investigator for the individual participant based on Institutional Standard Guidelines. The Sponsor requests that all COVID-related participant interventions including COVID-19 vaccinations be appropriately captured in the clinical trial forms and documents.

- Missed assessments or change to protocol assessments will be documented in the source documentation and in the case report form. All study conduct performed outside of the protocol should be documented in the source documentation.
- If a site visit is not feasible, the Investigator may discuss with the Sponsor other mechanisms for the participant to receive study drug (eg, direct to participant shipment, obtain from another Investigative Site participating in the study). Any change in dispensing study drug must be documented in the source documentation and eCRF.
- Safety assessments may be conducted at a local facility after discussion with the Sponsor.
- Critical laboratory tests, imaging or other diagnostic tests may be done at an authorized/certified (as legally required nationally) local laboratory or clinical facility. A copy of the laboratory report must be reviewed by the Investigator and retained, along with the reference ranges, for the source documentation and provided with the eCRF.

10.12. Appendix 12: ECOG Performance Status Scale

Grade	ECOG Performance Status Grade
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;596:649-655.

10.13. Appendix 13: Cytokine Release Syndrome – Severity Grading and Management

Cytokine Release Syndrome Revised Grading System	
Grade	**Toxicity**
Grade 1	Fever, with or without constitutional symptoms
Grade 2	Hypotension responsive to fluids Hypoxia responding to <40% FiO_2
Grade 3	Hypotension managed with one pressor[a] Hypoxia requiring ≥40% FiO_2
Grade 4	Life-threatening consequences; urgent intervention needed
Grade 5	Death

[a] High-dose vasopressor doses are shown in table below

Source: NCI-CTCAE (Version 5.0)

High-dose Vasopressors[b]	
Pressor	**Dose**
Norephedrine monotherapy	≥20 µg/kg/min
Dopamine monotherapy	≥10 µg/kg/min
Phenylephrine monotherapy	≥200 µg/kg/min
Epinephrine monotherapy	≥10 µg/kg/min
If on vasopressin	Vasopressin + norephrine equivalent of ≥10 µg/kg/min[a]
If on combination vasopressors (not vasopressin)	Norephedrine equivalent of ≥20 µg/kg/min[a]

[a] VASST Trial vasopressor equivalent equation: norephedrine equivalent dose = [norephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [ephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10]

[b] All doses are required for ≥3 hours.

Source: Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-195.

10.14. Appendix 14: Hepatitis B Virus Screening

The following hepatitis B virus (HBV) screening guide is to be used to determine participant eligibility (see Section 5.2) for the study:

Active or chronic hepatitis B:

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti- HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA test is **negative**, the participant ***is eligible*** for this protocol. If the HBV DNA test is **positive**, the participant ***is NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this protocol.

Eligibility Based on Hepatitis B Virus Test Results

	Hepatitis B test result			
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	**Hepatitis B DNA**
Exclude	+	— *or* +	— *or* +	NA
	—	—	+	+
Include	—	—	—	NA
	—	+	+	NA
	—	+	—	NA
	—	—	+	—

Modified from source: https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf. Accessed 11 March 2020.

10.15. Appendix 15: Cardiovascular Risk Assessment Prior to Study Enrollment and Prior to Radical Cystectomy

The individual cardiovascular risk of each study participant must be assessed during the screening period prior to enrollment to the study. Participants undergoing radical cystectomy are at a high risk for cardiovascular and thromboembolic events. Participants can only be enrolled when the risk assessment has been performed and all subsequent steps for diagnostic procedures and medical clearance have been conducted as outlined below, which needs to be documented.

In addition, the cardiovascular risk of each study participant must be reassessed prior to radical cystectomy (RC) as outlined in the Schedule of Activities: ie, at approximately 1-3 weeks prior to the anticipated RC date. Diagnostic assessment and subsequent steps for diagnostic procedures and medical clearance prior to surgery must be conducted and documented. If a participant is assessed as not eligible for RC, surgery must be delayed until medical clearance is obtained. If medical clearance cannot be achieved, the participant should continue on study, but the Investigator might decide to adjust the treatment plan for a participant and consider alternative treatment options. In such cases, the Investigator should contact the Sponsor to agree on next steps.

To assess the cardiovascular risk of participants prior to enrollment in this study (17000139BLC2002) and the actual cardiac risk prior to RC, the formula outlined below adapted from the revised Cardiac Risk Index for Pre-Operative Risk (RCRI) should be used to calculate participants' point values reflecting the individual cardiovascular risk. The revised RCRI accurately stratifies participants based on their individualized risk prior to surgery.

Assessment of Individual Cardiovascular Risk

Risk Factor	Description	Points
History of ischemic heart disease	• History of myocardial infarction • Electrocardiogram with pathological Q waves • History of positive exercise test • Current chest pain considered due to myocardial ischemia/angina • Use of nitrate therapy • History of coronary artery disease • Prior percutaneous coronary intervention • Prior coronary artery bypass surgery	+1
History of congestive heart failure	• Pulmonary edema, bilateral rales or S3 gallop • Paroxysmal nocturnal dyspnea • Chest x-ray showing pulmonary vascular redistribution	+1
History of cerebrovascular disease	• Prior transient ischemic attack • Past stroke	+1
History of cardiac valvular disease	• Aortic stenosis	+1
Other risk factors[a]	• Peripheral arterial disease • Atrial fibrillation or other cardiac arrythmia	+1
Pre-operative treatment with insulin		+1
Pre-operative creatinine >2.0 mg/dL (176.8 µmol/L)		+1

[a] Only risk factors listed specifically on the RCRI form should be counted in risk assessment. Any other risk factors such as hypertension, hyperlipidemia, obesity, smoking, diabetes, etc, will not be included in the RCRI however, these factors should be taken under consideration for monitoring cardiac safety throughout the trial.

Interpretation of Risk Assessment and Next Steps for Assessment

Revised Cardiac Risk Index Score/Points*	Next steps during the study (17000139BLC2002) screening period	Next steps prior to RC
0	No additional diagnostic work-up	Standard pre-operative surgical and anesthesiology assessment; subsequent diagnostic procedures and clearance for cardiac risk factors prior to surgery depending on results of pre-operative assessment
≥1	Medical consultation prior to enrollment and assessment for eligibility for RC	Medical consultation prior to surgery; subsequent diagnostic procedures and medical clearance prior to surgery depending on results of pre-operative assessment.

* Any changes in risk factors between study entry and date of RC should prompt re-evaluation.

10.16. Appendix 16: Anticipated Events (US Only)

Purpose

This appendix only applies to the reporting of anticipated events by the Sponsor to the US FDA, and US-based Investigators and IECs/IRBs. The intent of this appendix is to minimize the submission of a multitude of uninformative IND safety reports to these recipients.

Background

The FDA acknowledges that certain AEs can be anticipated to occur commonly in the study population regardless of drug exposure. Anticipated events may occur as a consequence of (a) the underlying disease or condition under investigation, (b) characteristics of the study population (eg, age), or (c) the background treatment regimen. Although serious anticipated events may meet the definition of unexpected (ie, SUSARs), because they are deemed related and not listed in the IB, they do not warrant expedited reporting as individual cases, or even in aggregate if the incidence is consistent with the expected background rates in the study population. The anticipated events list is developed prior to the start of a study. A dedicated Anticipated Events Safety Monitoring Plan (ASMP) is developed to establish prespecified thresholds that would trigger a review of the aggregated unblinded anticipated event by the Sponsor's Safety Assessment Committee (SAC).

Sponsor's Safety Assessment Committee (SAC)

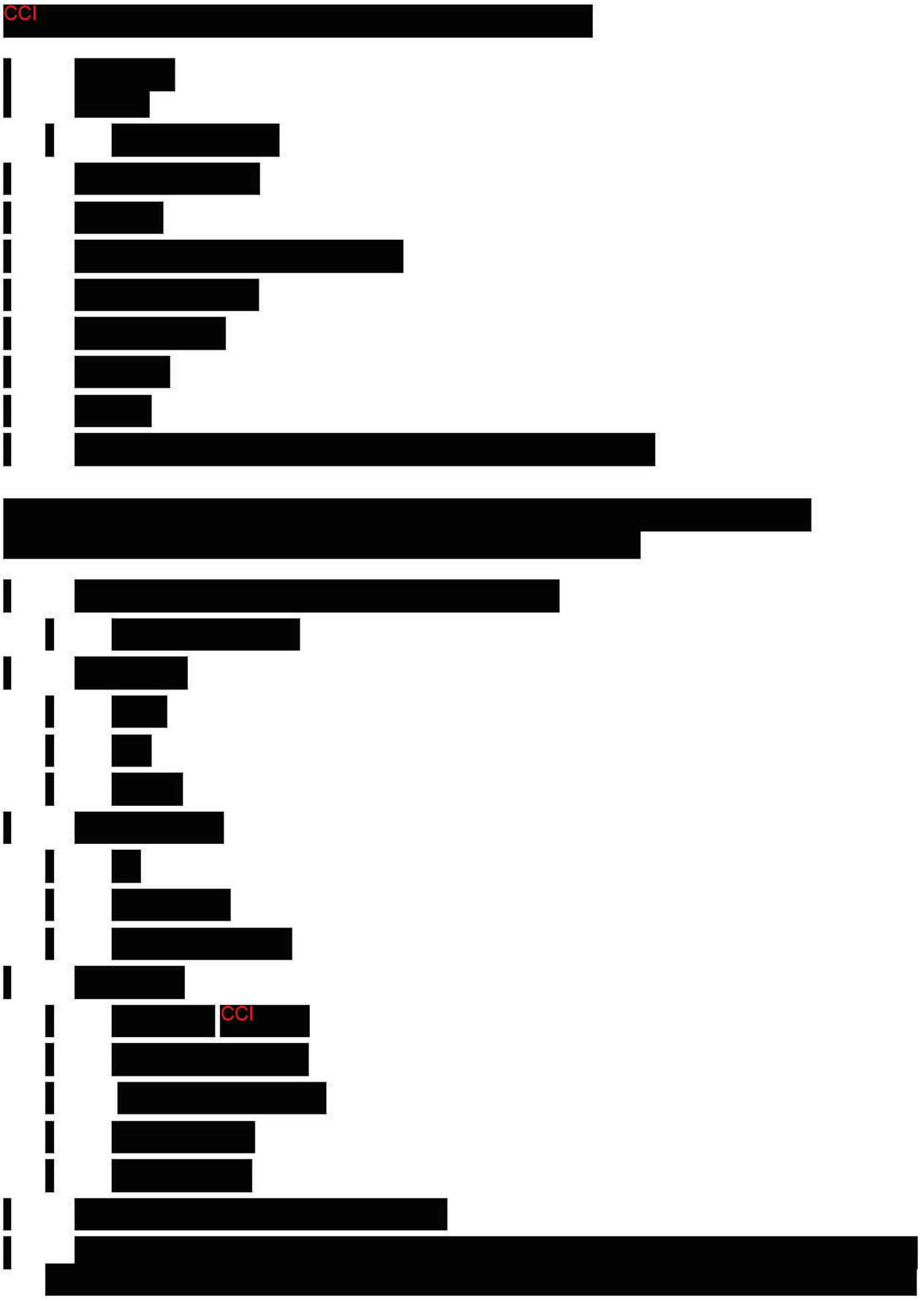
The Sponsor's SAC is an established safety committee, independent of the study team, that performs reviews of prespecified anticipated events that have met the prespecified threshold at an aggregate level. The SAC will meet to determine whether there is a reasonable possibility that an anticipated event is related to the study treatment. The SAC will consider in its analysis all relevant drug development data, in addition to the clinical study data. If an anticipated event is determined to occur more frequently in the experimental arm(s) of the study and there is a reasonable possibility that the anticipated event could be drug-related, the Sponsor will prepare an aggregate safety report for reporting of these events to FDA and US-based IRBs/ECs and Investigators.

SAE Reporting

This US-specific process does not impact the requirement for SAE reporting by investigators to the Sponsor. All AEs will be recorded by the investigator in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 8.9.

Anticipated Events for the Study

The below list includes adverse events that are commonly anticipated for the disease stage, study population and background treatment:


CCI
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CCI

10.17. Appendix 17: Cockcroft-Gault Formula – Calculated and Measured Creatinine Clearance

To calculate the subject's creatinine clearance (CrCl), use the following Cockcroft-Gault formula:

$$CrCl = \frac{(140 - \text{age [in years]}) \times \text{weight (kg)}}{(72 \times \text{serum creatinine [mg/dL]})} \quad (\times 0.85 \text{ for females})$$

If the serum creatinine is obtained using the International System of Units (SI) (ie, micromol/L), use the following formula to convert SI units to conventional (mg/dL) units (Manual of Laboratory and Diagnostic Tests, 2004):

- serum creatinine (micromol/L) divided by 88.4 = serum creatinine (mg/dL)

Source: Cockcroft and Gault 1976

10.18. Appendix 18: CKD-EPI Creatinine Equation (2021)

Formula

Expressed as a single equation:

eGFR =

142*

min(standardized S_{cr}/K, 1)$^{\alpha}$ *

max(standardized S_{cr}/K, 1)$^{-1.200}$ *

0.9938^{Age} *

1.012 [if female]

Abbreviations / Units

eGFR (estimated glomerular filtration rate) = mL/min/ 1.73 m^2

S_{cr} (serum creatinine) = mg/dL

K = 0.7 (females) or 0.9 (males)

α = -0.241 (females) or -0.302 (males)

min = indicates the minimum of S_{cr}/K or 1

max = indicates the maximum of S_{cr}/K or 1

Source: https://www.kidney.org/professionals/kdoqi/gfr_calculator/formula

10.19. Appendix 19: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (19 September 2022)

Overall Rationale for the Amendment: The primary focus of the protocol amendment was to clarify guidance on the clinical management of TAR-200 related adverse events, including drug delays and discontinuations. In addition, updates were made to harmonize shared protocol elements within the protocol and across SunRISe protocols for the TAR-200/cetrelimab program.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, Benefit-Risk Assessment	Added summary of benefit-risk assessment.	To provide a comprehensive synopsis and align with latest guidance and sponsor template.
1.1 Synopsis, Safety Evaluations	Added information regarding collection of adverse events throughout the study and description of safety oversight including IDMC.	To provide a comprehensive synopsis and align with latest guidance and sponsor template.
1.1 Synopsis 2 Introduction	Updated investigational product descriptions including the intravesical system and urinary placement catheter/inserter.	This change was made to align product language across study documentation.
1.1 Synopsis	Added descriptions for IV cetrelimab PK and immunogenicity.	To rectify an inadvertent omission.
1.2 Schema	Study Schema replaced with granular version indicating treatment visit follow-ups	Clarification.
1.3 Schedule of Activities, Table 1 and Table 2 3. Objectives	Added PROs at Week C in the Schedule of Activities. Modified the corresponding endpoint: "Change in sub-scale and total scores from baseline through Week CCI of study drug treatment."	To ensure PROs are assessed through the end of study treatment.
1.3 Schedule of Activities, Table 1 and Table 2 5.1 Inclusion Criteria 10.15 Appendix 15	Added a cardiac risk assessment at Screening and at approximately 1-2 weeks prior to the anticipated radical cystectomy (RC) date. Modified Criterion 4 (to Criterion 4.1) to indicate that: "Investigators should refer to Appendix 15 for guidance on assessing cardiac risk via the Adapted Cardiac Risk Index for Pre-Operative Risk (RCRI)." Added Section 10.15 Appendix 15 to provide guidance on assessing cardiac risk criteria.	To ensure proper screening of cardiac risk factors in order to determine study treatment eligibility and confirm cardiac clearance prior to the anticipated RC date.
1.3 Schedule of Activities, Table 1 and Table 2	Information on Relevant Procedures (including GU events and procedures) to be collected during Screening.	To ensure information on Relevant Procedures (including GU events and procedures) is collected from the time of initial signed informed consent as specified in Section 6.8.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, Table 1 and Table 2	Urine biomarker collections footnote clarified and collections marked at Screening and the RC visit: "Urine sample collection must occur immediately prior to TURBT or RC, as applicable." Biomarkers in blood collections clarified: removed "plasma ctDNA" and added collections at Screening and RC visit.	To ensure proper biomarker collections are performed.
1.1 Synopsis 1.3 Schedule of Activities, Table 3	Clarified that: "Participants in the serial urine PK sampling are not required to complete the Week 0 and Week CCI sparse timepoints"	Clarification.
1.3 Schedule of Activities, Table 1 and Table 2; 4.4 End of Study Definition	Added long-term follow-up activities: subsequent anti-cancer therapies & other malignancies, which are to be completed every C weeks beginning after a participant discontinues from treatment and/or disease assessment follow up visits until end of study.	To ensure comprehensive follow-up phase assessments are performed.
1.3 Schedule of Activities, Table 1 and Table 2 5.2 Exclusion Criteria Criterion 15	Added HIV, Hepatitis B (HBsAg), and Hepatitis C serology testing to screening. Removed the word "known" from exclusion criterion 15 (to 15.1) as testing for HIV will be required at screening.	This change was made to ensure participants who are eligible as prescribed in the protocol to enter the study with HIV or Hepatitis B or C.
1.3 Schedule of Activities, Table 1 and Table 2	Separated laboratory tests including coagulation, urinalysis, and urine culture and added appropriate notes from the respective sections of the protocol.	This change was made to clarify timing and requirements for each laboratory test.
1.3 Schedule of Activities, Table 1 and Table 2	Changed serum pregnancy to urine pregnancy to occur within 72 hours of first dosing.	Eliminated redundant testing.
1.3 Schedule of Activities, Table 1 and Table 2	Updated the window for screening labs from 14 days to 30 days of Week 0.	This change was made to reduce participant burden during screening process.
3. Objectives	Removed PK exploratory objective: "To explore gemcitabine and 2',2'-difluorodeoxyuridine (dFdU) concentrations in biopsied tissue."	PK assessments of gemcitabine and 2',2'-difluorodeoxyuridine (dFdU) concentrations in biopsied tissue will not be performed on this study.
3. Objectives	Modified definitions for RFS, OS, TSP to start from the "date of first dose of any study treatment"	Clarification.
3. Objectives	Clarified PK and/or immunogenicity exploratory objectives related to gemcitabine and cetrelimab as follows: • To evaluate the PK of gemcitabine (TAR-200) and major metabolite dFdU in urine and plasma **following administration of TAR-200 in combination with IV cetrelimab**	Clarification.

Section Number and Name	Description of Change	Brief Rationale
	(Cohort 1) ~~in combination with cetrelimab~~ • To evaluate the PK and immunogenicity of cetrelimab in serum **following administration of TAR-200 in combination with IV cetrelimab (Cohort 1) and IV cetrelimab alone (Cohort 2)**	
3. Objectives	Removed the following endpoint: ~~Cetrelimab and other derivative biproducts concentrations in plasma~~	Concentrations of derivative biproducts are not applicable for cetrelimab.
4.1 Overall Design	Added language to allow for enrollment in countries beyond the planned sample size.	To ensure adequate representation of the country in the study.
1.3 Schedule of Activities, Table 1 and Table 2 6.1.1 TAR-200 Insertion 8.9 Adverse Events, Serious Adverse Events, and Other Safety Reporting 8.9.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information 8.9.3 Follow-up of Adverse Events and Serious Adverse Events 8.9.8 Product Quality Complaints and Medical Device Deficiencies 9.4.5 Safety Analyses 10.4.6 Product Quality Complaint Handling 10.4.7 Contacting Sponsor Regarding Safety, Including Product Quality 10.10 Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, Serious Adverse Device Effects, Unanticipated Serious Adverse Device Effects, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device	Added further clarifications to the definition of PQC related to a device constituent in a combination product and device deficiencies, clarifying attribution definitions and device safety reporting requirements for TAR-200 versus the UPC. Added that SAEs should be reported without "undue delay" in addition to existing text. Incorporated medical device specific appendix to address adverse events and device deficiencies associated with the urinary placement catheter.	This change was made to address collection and reporting of device deficiencies related to the urinary placement catheter. This appendix was previously provided as a stand-alone document and has now been incorporated into the main protocol.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, Table 1 and Table 2	Added that overall survival may be obtained via telephone during the follow up phase.	This change was added to expand methods of obtaining survival status.
4.4 End of Study Definition	Relocated text from Section 7.3 to Section 4.4 describing that should a participant discontinue treatment prematurely for any reason, all efforts will be made to continue follow up procedures and assessments.	This change was made to clarify assessments for participants who discontinue treatment prematurely.
6.1 Study Treatment(s) Administered	Added description of study treatments and their associated designation.	This change was made to clarify the regulatory status of the study treatments and to align with the current Sponsor template.
6.5.1 TAR-200 Participant Stopping Safety Criterion	Required Sponsor notification and consultation for any TAR-200 drug delays and discontinuations. Provided specific details for management of TAR-200 drug delay due to an adverse event (AE) during the induction period (Week 0 to Week 12) as well as for participants who have achieved complete response (CR). Added information/term on skipped dose. Streamlined criteria for TAR-200 drug delay or removal.	To clarify guidance on the clinical management of TAR-200 related AEs, including drug delays and discontinuations.
6.5.1 TAR-200 Participant Stopping Safety Criterion	Removed Hy's law as a criterion for TAR-200 discontinuation: "ALT or AST >3xULN and Total bilirubin >2xULN without evidence of cholestasis (ALP>2xULN) and no other medical explanation. Note that this specific category of drug discontinuation criteria used ULN rather than CTCAE grade for definition"	To rectify an inadvertent inclusion of a discontinuation criterion applicable for cetrelimab only.
1.3 Schedule of Activities, Table 1 and Table 2 6.1.1 TAR-200 Insertion	Added statement/note: "To mitigate the risk of UTI's, participants must receive at least one dose of periprocedural prophylactic antibiotics for any intravesical study procedures"	This statement was added to ensure patient safety associated with study procedures.
2 Introduction 6.1.1 TAR-200 Insertion	Added clarifying statement that the TAR-200 is freely mobile/floating within the urine/bladder.	This statement was added to clarify the position of the TAR-200 while indwelling.
Introduction 2.2.3 Combination Therapy 4.3 Justification for Dose 6.7 Treatment of Overdose	Removed product details considered company confidential information.	This change was made to protect confidential information.
3 Objectives 9.4.4 Exploratory Endpoints	Added exploratory objective to determine time to symptomatic progression in participants receiving TAR-200 in combination with cetrelimab versus cetrelimab alone.	This change was made to enable evaluation of time to symptomatic progression between the treatment groups.

Section Number and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria, Criterion 6	Modified Criterion 6 (to 6.1) to indicate that an endocrinologist can be consulted in the case of unequivocal or marginal thyroid function tests.	This change was made to clarify eligibility of participants with unequivocal or marginal thyroid function tests.
5.1 Inclusion Criteria, Criterion 7	Modified Criterion 7 (to 7.1) to increase bone marrow and renal function requirements including absolute neutrophil count (from $\geq$1,000/mm^3 to $\geq$1,500/mm^3), platelet count (from $\geq$75,000/mm^3 to $\geq$80,000/mm^3, hemoglobin (from $\geq$8.0 g/dL to $\geq$9.0 g/dL) and creatine clearance (from $\geq$40 ml/min to $\geq$30 ml/min).	This change was made to enhance participant safety by ensuring adequate bone marrow and renal function at the time of enrollment.
5.1 Inclusion Criteria, Criteria 11 and 12 10.5 Contraceptive and Barrier Guidance	Updated Criterion 11 (to 11.1) and Criterion 12 (to 12.1) related to contraception and reproduction to align with the latest sponsor template including gender terminology. Updated contraception guidance replacing the term woman to female and removed duplicative information previously captured in inclusion criteria.	This change was made to align with latest guidance and sponsor template. This change was made to align to the latest Sponsor template.
5.2 Exclusion Criteria, Criterion 1	Updated Criterion 1 (to 1.1) to remove "treated within the last 24 months" from skin cancer and cervical cancer exceptions.	This change was made to provide clarity on exceptions to exclusion criterion.
5.2 Exclusion Criteria, Criterion 2	Updated Criterion 2 (to 2.1) to change window for past systemic chemotherapy from 2 years to 2 weeks prior to start of study treatment.	This was an error.
5.2 Exclusion Criteria, Criterion 10	Removed Criterion 10 regarding allogenic tissue/solid organ transplant.	This exclusion criterion is not necessary in this patient population and is redundant as participants on immunosuppressive therapy are excluded per exclusion criterion 33.
5.2 Exclusion Criteria, Criterion 26	Clarified that live virus vaccine within 30 days of "initiation" of study treatment is required	Clarification
5.2 Exclusion Criteria, Criterion 28	Updated Criterion 28 (to 28.1) to add cross reference to UTI exclusion criterion (criterion 17).	This change was made to provide clarification regarding UTI at the time of enrollment.
5.2 Exclusion Criteria, Criterion 29	Updated Criterion 29 (to 29.1) to allow from immediate post-TURBT single dose peri-operative intravesical chemotherapy in the screening phase.	This change was made to align with standard of care during the screening phase/prior to study enrollment.
6.1 Study Treatment(s) Administered	Added details on the 360 mg/vial liquid formulation product for IV cetrelimab expected fourth quarter (Q4) 2022.	To update IV cetrelimab description to include details on the liquid formulation product.
6.1.1 TAR-200 Insertion	Added subheading for TAR-200 Insertion	This section was updated to provide more information regarding the post-insertion cystoscopy procedure.

Section Number and Name	Description of Change	Brief Rationale
	Added guidance on performing a post-insertion cystoscopy following TAR-200 insertion.	
6.1.2 TAR-200 Removal	Added subheading for a TAR-200 Removal Added section/instructions regarding the TAR-200 removal procedure.	This section was added to provide complete information regarding all study procedures.
6.5.1 TAR-200, TAR-200 Missed Dosing Cycles (Cohort 1 only)	Added definition of skipped dose.	To provide clarity regarding a skipped dose.
6.6 Continued Access to Study Treatment After the End of the Study	Added rationale for lack of access to study drug after the end of the study (ie, due to RC).	To provide clarity on the rationale for not providing study drug after the end of the study.
6.8 Concomitant Therapy, Prohibited Medications	Added that participants should not receive a live vaccination while on study treatment and within 90 days of completion of study treatment.	This change was made to ensure participant safety.
7.1 Discontinuation of Study Treatment	Added clarifying statement that participants who permanently discontinue with TAR-200 indwelling must return for removal and EOT visit.	This change was made to ensure participant safety.
7.3 Participant Discontinuation/Withdrawal From the Study	Circumstances for Reduced Follow-up added.	To provide options for alternative follow-up mechanisms.
8.7.2.1 TURBT Biopsies, Cystoscopy, and Radical Cystectomy Pathology	Added that in Cohort 2 a cystoscopy may be performed at Week [redacted] if clinically indicated.	This change was to clarify this procedure in Cohort 2.
8.9.7 Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events	Added text and instruction related to disease-related events and outcomes that do not qualify as AEs or SAEs.	This change was made to provide clarity and align with the current Sponsor template.
8.12 Biomarkers	Applied CCI considerations to details of IHC analysis of immune markers.	To ensure compliance with CCI guidelines.
9.3 Participants for Analysis Sets 9.4.5 Safety Analyses	Added definition of the "Enrolled" patient population. Updated description of planned statistical analyses related to Clinical Laboratory Tests, Electrocardiogram, Vital Signs and Physical Examinations. Relocated information related to IDMC throughout the section.	This change was made to align with the SAP.
9.4.4 Exploratory Endpoints	Added statistical description and definition of Overall Survival.	Consistency.

Section Number and Name	Description of Change	Brief Rationale
9.4.6 Other Analyses	Clarified descriptives statistics for PK: Added gemcitabine and dFdU urine amount. Clarified that all PK results will be listed by study arm while summary statistics will be provided for serial urine PK only.	Summary statistics do not need to be performed for sparse PK sampling.
10.2 Appendix 2: Clinical Laboratory Tests	Added Nitrite as standard test for routine urinalysis. Added Ketones and C-Peptides as clinically indicated (unscheduled visit only).	This change was made to enhance patient safety and clarified required tests.
10.7 Appendix 7: PRO Questionnaires (PGIS)	Updated PGIS to bladder cancer specific questionnaire.	This change was made to correct an error.
10.9.2 Hepatic Adverse Events	Added information and instruction regarding participants with predominant cholestatic pattern of liver injury.	This change was made to provide guidance on management of participants with predominant cholestatic pattern of liver injury.
10.9.12 Injection Site Reaction	Deleted section 10.9.2 Injection Site Reaction.	This section is not applicable to this study due to the IV administration of the cetrelimab.
10.13 Appendix 13: Cytokine Release Syndrome – Severity Grading and Management 10.14 Appendix 14: Hepatitis B Virus Screening	Added appendices to provide guidance on management of cytokine release syndrome and screening for hepatitis B.	This change was made to enhance patient safety and align with the latest Sponsor template.
10.16 Appendix 16: Anticipated Events	Added an Anticipated Events Appendix (US only) to provide a list of anticipated events that commonly occurs in the study population independent of exposure to the drug under investigation.	To ensure compliance with US clinical trial legislation.
10.17 Appendix 17: Protocol Amendment History	Text revised to note that the Protocol Amendment Summary of Changes Table for this amendment is located directly before the Table of Contents (TOC).	Change for Protocol Amendment 1.
Throughout the protocol	Protocol template-driven updates were made where applicable. Minor clarifications including grammatical, formatting, or spelling changes were made, and links and cross-references corrected/updated. Abbreviations were added to tables and noted where applicable within the document.	To align with updates to the oncology protocol template. Minor errors were noted.

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INVESTIGATOR AGREEMENT

JNJ-17000139 (TAR-200) / JNJ-63723283 (Cetrelimab)
Clinical Protocol 17000139BLC2002 Amendment 2

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 20 April 2023