Janssen Research & Development *

Clinical Protocol

Protocol Title

Phase 2b Clinical Study Evaluating Efficacy and Safety of TAR-200 in Combination with Cetrelimab, TAR-200 Alone, or Cetrelimab Alone in Participants with High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Intravesical Bacillus Calmette-Guérin (BCG) who are Ineligible for or Elected Not to Undergo Radical Cystectomy

Short Title
SunRISe-1

Protocol 17000139BLC2001

Version: Amendment 5

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

*Janssen Research & Development is a global organization that operates through different legal entities in various countries/territories. Therefore, the legal entity acting as the Sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "Sponsor" is used throughout the protocol to represent these various legal entities; the Sponsor is identified on the Contact Information page that accompanies the protocol.
Studies conducted at sites in the United States (US) will be conducted under US Food & Drug Administration (FDA) Investigational New Drug (IND) regulations (21 CFR Part 312).
Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.

Regulatory Agency Identifier Number(s):
IND: CCI [redacted]
EudraCT NUMBER: CCI [redacted]
EU CTR NUMBER: CCI [redacted]
EUDAMED: CCI [redacted]

Status: Approved
Date: 02 July 2024
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 5	02 July 2024
Amendment 4	12 June 2023
Amendment 3	22 February 2023
Amendment 2	04 March 2022
Amendment 1	13 July 2021
Original Protocol	25 September 2020

Amendment 5 (02 July 2024)

Overall Rationale for the Amendment: The overall rationale for this amendment is to add a disease assessment visit at [CC] days after the onset of CR for participants in Cohort 2 for evaluation of duration of response, and to request redacted cystoscopy and pathology reports from investigational sites for review by the Sponsor and/or to address health authority requests.

The changes made to the clinical protocol 17000139BLC2001 as part of Protocol Amendment 5 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 10.15 Appendix 15: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities, Table 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 8.10.1.1 Cystoscopy 8.10.1.3 TURBT (Bladder Biopsies)	Added that redacted cystoscopy and pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.	To satisfy health authority requirements/To ensure availability of critical source documentation
1.3 Schedule of Activities, Table 4, Table 10	Removed requirement for PRO assessments at the 30 and 100 Day Safety Follow Up Visits for Cohort 1 and 3.	To reduce participant burden and align with Sponsor objectives.
1.3, Schedule of Activities, Table 6 8.10, Efficacy Assessments	Added the following statement: NOTE: Cohort 2 participants with a CR must have a [CCI] disease assessment visit at [CCI] from the date of onset of CR. The [CCI] disease assessment from onset of CR may occur in lieu of [CCI] disease assessment, if the two visits are within 6 weeks of each other. The [CCI] disease assessment post initial CR date will include assessment cystoscopy, urine cytology, TURBT bladder biopsy (if clinically indicated) and CT/MRI with contrast (if applicable).	To satisfy health authority requirements/to enable a more complete evaluation of duration of response.
9.4.2 Primary Endpoints	Added statement regarding analysis approximately 1 year from the time of onset of last CR in Cohort 2.	
2.2.3.1 Clinical Development in Muscle Invasive Bladder Cancer	Udpated planned enrollment in Study 17000139BLC3001 (SunRISe-2).	To align with the current protocol.
1.1 Synopsis 4.1 Overall Design	Removed "an increase of stage from Ta to T1" from the definition of disease progression.	To ensure consistency across all related clinical trials and avoid confusion.

Section Number and Name	Description of Change	Brief Rationale
	Progression will be defined as progression to MIBC, metastatic disease or death.	
9.3 Populations for Analysis Sets	Updated the definitions of the analysis sets to include enrolled, full, and safety.	To align to the study design (non-randomized) and company standards.
9.4.2 Primary Endpoints	Updated the description of analyses for Cohort 4 at 9 and 15 months.	To align with the Sponsor objectives.
9.4.5 Safety Analyses	Analyses of electrocardiograms was streamlined to include only ECG interpretations (clinically significant, not clinically significant) at baseline and end of treatment visits by cohort.	To align with the clinical impact of the drug product (ie, TAR-200 is not expected to impact ECG).
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

TABLE OF CONTENTS

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 2

TABLE OF CONTENTS 4

LIST OF IN-TEXT TABLES AND FIGURES 8

1. PROTOCOL SUMMARY 10
1.1. Synopsis 10
1.2. Schema 16
1.3. Schedule of Activities 19

2. INTRODUCTION 45
2.1. Study Rationale 46
2.2. Background 48
2.2.1. TAR-200 Nonclinical Studies 48
2.2.2. Cetrelimab Nonclinical Studies 49
2.2.3. TAR-200 Clinical Studies 50
2.2.3.1. Clinical Development Plan in Muscle Invasive Bladder Cancer 50
2.2.3.2. Clinical Development Plan in Non-Muscle Invasive Bladder Cancer 51
2.2.4. Cetrelimab Clinical Studies 51
2.2.5. Combination Therapy 53
2.3. Benefit-Risk Assessment 55

3. OBJECTIVES AND ENDPOINTS 57

4. STUDY DESIGN 58
4.1. Overall Design 58
4.2. Scientific Rationale for Study Design 63
4.2.1. Study-Specific Ethical Design Considerations 64
4.3. Justification for Dose 64
4.3.1. TAR-200 Dose Selection 64
4.3.2. Cetrelimab Dose Selection 65
4.4. End of Study Definition 65

5. STUDY POPULATION 66
5.1. Inclusion Criteria 67
5.2. Exclusion Criteria 70
5.3. Lifestyle Considerations 74
5.3.1. Meals and Dietary Restrictions 74
5.3.2. Caffeine, Alcohol, and Tobacco 75
5.3.3. Activity 75
5.4. Screen Failures 75
5.5. Criteria for Temporarily Delaying Administration of Study Treatment 75

6. STUDY TREATMENT AND CONCOMITANT THERAPY 76
6.1. TAR-200 and Cetrelimab Study Drug Dosing 77
6.1.1. TAR-200 Insertion 77
6.1.2. TAR-200 Removal 79
6.1.3. Cetrelimab Administration 79
6.1.4. Combination Products 80
6.2. Preparation/Handling/Storage/Accountability 80
6.3. Measures to Minimize Bias: Randomization and Blinding 81
6.4. Study Treatment Compliance 82
6.5. Management of Adverse Events and Dose Modification 82
6.5.1. TAR-200 82
6.5.1.1. Management of Adverse Events Related to TAR-200 and Procedures 82
6.5.1.2. TAR-200 Dose Modification and Missed Dosing Cycles 82

6.5.2. Cetrelimab ... 84
6.5.2.1. Management of Adverse Events Related to Cetrelimab ... 84
6.5.2.2. Cetrelimab Dose Modification ... 84
6.6. Continued Access to Study Treatment After the End of the Study ... 86
6.7. Treatment of Overdose ... 86
6.8. Concomitant Therapy ... 87
6.8.1. Permitted Medications ... 88
6.8.2. Prohibited Medications ... 88

7. DISCONTINUATION OF STUDY DRUG AND/OR STUDY ... 89
7.1. Discontinuation of Study Drug ... 89
7.2. Discontinuation of Study ... 90
7.3. Withdrawal of Consent ... 90
7.4. Withdrawal from the Future Use of Research Samples ... 91
7.5. Lost to Follow-up ... 91
7.6. Death ... 92

8. STUDY ASSESSMENTS AND PROCEDURES ... 92
8.1. Screening ... 94
8.1.1. Participant Referrals from an Outside Institution ... 95
8.1.2. Bladder Post-Void Residual ... 95
8.2. Treatment Phase ... 95
8.3. End of Treatment Visit ... 96
8.4. 30-Day Safety Follow-up Visit ... 97
8.5. 100-Day Safety Follow-up Visit ... 97
8.6. Follow-up Phase ... 97
8.7. Overall Survival ... 98
8.8. End of Study ... 98
8.9. Unscheduled Visits ... 98
8.10. Efficacy Assessments ... 98
8.10.1. Disease Assessments ... 98
8.10.1.1. Cystoscopy ... 98
8.10.1.2. Urine Cytology ... 99
8.10.1.3. TURBT (Bladder Biopsies) ... 99
8.10.1.4. CT/MRI Scan with Contrast ... 100
8.10.2. Patient-Reported Outcomes ... 101
8.10.2.1. EORTC-QLQ-C30 ... 101
8.10.2.2. EORTC-QLQ-NMIBC24 ... 102
8.11. Safety Assessments ... 102
8.11.1. Immune-Mediated Adverse Events ... 102
8.11.2. Physical Examinations ... 102
8.11.3. Vital Signs ... 103
8.11.4. Electrocardiograms ... 103
8.11.5. Clinical Safety Laboratory Assessments ... 103
8.11.6. Pregnancy Testing ... 104
8.11.7. ECOG Performance Status ... 104
8.11.8. Genitourinary and Non-Genitourinary Procedures ... 104
8.12. Adverse Events, Serious Adverse Events, and Other Safety Reporting ... 104
8.12.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information ... 105
8.12.2. Method of Detecting Adverse Events and Serious Adverse Events ... 105
8.12.3. Follow-up of Adverse Events and Serious Adverse Events, PQCs, and Device Deficiencies ... 106
8.12.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events ... 106
8.12.5. Pregnancy ... 106
8.12.6. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events ... 107

8.12.7. Adverse Events of Special Interest ... 107
8.12.8. Product Quality Complaints (PQCs) and Medical Device Deficiencies ... 107
8.13. Pharmacokinetics ... 107
8.13.1. Evaluations ... 108
8.13.1.1. Sparse Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1, Cohort 2, and Cohort 4) ... 108
8.13.1.2. Serial Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 and Cohort 2) ... 108
8.13.1.3. Plasma PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 and Cohort 2) ... 109
8.13.1.4. Serum PK/Immunogenicity Samples for Cetrelimab (Cohort 1 and Cohort 3) ... 109
8.14. Biomarkers ... 110
8.15. Medical Resource Utilization and Health Economics ... 112

9. STATISTICAL CONSIDERATIONS ... 112
9.1. Statistical Hypotheses ... 112
9.2. Sample Size Determination ... 112
9.3. Populations for Analysis Sets ... 113
9.4. Statistical Analyses ... 113
9.4.1. General Considerations ... 113
9.4.2. Primary Endpoints ... 113
9.4.3. Secondary Endpoints ... 114
9.4.4. Exploratory Endpoints ... 115
9.4.5. Safety Analyses ... 115
9.4.6. Other Analyses ... 116
9.5. Interim Analysis ... 118

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS ... 119
10.1. Appendix 1: Abbreviations and Definitions ... 119
10.2. Appendix 2: Clinical Laboratory Tests ... 121
10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations ... 123
10.3.1. Regulatory and Ethical Considerations ... 123
10.3.2. Financial Disclosure ... 126
10.3.3. Informed Consent Process ... 126
10.3.4. Data Protection ... 127
10.3.5. Long-term Retention of Samples for Additional Future Research ... 128
10.3.6. Committees Structure ... 128
10.3.7. Publication Policy/Dissemination of Clinical Study Data ... 129
10.3.8. Data Quality Assurance ... 130
10.3.9. Case Report Form Completion ... 130
10.3.10. Source Documents ... 131
10.3.11. Monitoring ... 132
10.3.12. On-Site Audits ... 133
10.3.13. Record Retention ... 133
10.3.14. Study and Site Start and Closure ... 134
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 for Medicinal Products ... 135
10.4.1. Adverse Event Definitions and Classifications ... 135
10.4.2. Attribution Definitions ... 136
10.4.3. Severity Criteria ... 137
10.4.4. Special Reporting Situations ... 137
10.4.5. Procedures ... 138
10.4.6. Product Quality Complaint Handling ... 139
10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality ... 140
10.5. Appendix 5: Contraceptive and Barrier Guidance ... 141
10.5.1. Definitions ... 141
10.5.2. Examples of Contraceptives ... 142

10.5.2.1. HIGHLY EFFECTIVE METHODS [a](Failure rate of <1% per year when used consistently and correctly.) 142
10.6. Appendix 6: PRO Questionnaires 143
10.7. Appendix 7: ECOG Performance Status Scale 147
10.8. Appendix 8: Study Conduct During a Natural Disaster 148
10.9. Appendix 9: Guidelines for Management of Immune-related Adverse Events and Adverse Events of Clinical Interest 150
10.9.1. Gastrointestinal Adverse Events 150
10.9.2. Hepatic Adverse Events 151
10.9.3. Endocrinopathies 152
10.9.4. Rash 153
10.9.5. Renal Adverse Events 154
10.9.6. Neurological Adverse Events 154
10.9.7. Pulmonary Adverse Events 155
10.9.8. Uveitis and Visual Complaints 155
10.9.9. Lipase/Amylase Elevations 156
10.9.10. Infection 156
10.9.11. Cardiovascular Events 156
10.9.12. Treatment of Anti-PD-1 Infusion-related Reactions 156
10.9.13. Monitoring During and After Study Drug Administration 157
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 158
10.10.1. Definitions (UPC only) 158
10.10.2. Recording and Follow-up of Adverse Events and/or Serious Adverse Events, and Device Deficiencies (UPC only) 159
10.10.3. Reporting Requirements (Investigator to Sponsor) (UPC only) 162
10.10.3.1. Reporting of Serious Adverse Events and Serious Adverse Device Effects 162
10.10.3.2. Reporting of Device Deficiencies (UPC only) 163
10.10.4. Sponsor Reporting Requirements (UPC Only) 163
10.11. Appendix 11: Cytokine Release Syndrome – Severity Grading and Management 165
10.12. Appendix 12: Hepatitis B Virus Screening 166
10.13. Appendix 13: Anticipated Events (US only) 167
10.14. Appendix 14: Cockcroft-Gault Formula and the CKD-EPI Creatinine Equation (2021) 169
10.15. Appendix 15: Protocol Amendment History 170

11. REFERENCES 195

INVESTIGATOR AGREEMENT 198

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

Table 1: Screening Activities (Cohorts 2 and 4 Only) 19
Table 2: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities -Treatment Phase -Week C through Week C (Year 1) 21
Table 3: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities -Treatment Phase -Week C through Week C (Year 2) 23
Table 4: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities - Follow-up Phase 26
Table 5: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities - Treatment Phase - Week C through Week C (Year 1) 28
Table 6: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities -Week C through Week C (Year 2) 30
Table 7: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities - Follow-up Phase 32
Table 8: Cohort 3 (C Cetrelimab Alone) Schedule of Activities -Treatment Phase -Week C through Week C (Year 1) 34
Table 9: Cohort 3 (Cetrelimab Alone) Schedule of Activities – Through End of Treatment Phase 37
Table 10: Cohort 3 (Cetrelimab Alone) Schedule of Activities: Follow-up Phase 39
Table 11: Sparse Urine Pharmacokinetics - (All Participants in Cohort 1, Cohort 2, and Cohort 4) See Section 8.13.1.1 42
Table 12: Serial Urine Pharmacokinetics – (approximately 40 Participants Across Cohort 1 and Cohort 2) See Section 8.13.1.2 42
Table 13: Plasma Pharmacokinetics - (All Participants in Cohorts 1 and Cohort 2) See Section 8.13.1.3 42
Table 14: Serum Pharmacokinetics for Cetrelimab- (Cohort 1 and Cohort 3) See Section 8.13.1.4 43
Table 15: Serum Immunogenicity for Cetrelimab- (Cohort 1 and Cohort 3) See Section 8.13.1.4 43
Table 16: Biomarker Tissue Collection – Treatment Phase - (Cohort 1, Cohort 2, and Cohort 3 Only) See Section 8.14 43
Table 17: Biomarker Blood Collection – Treatment Phase - (Cohort 1, Cohort 2, and Cohort 3 Only) See Section 8.14 43
Table 18: Biomarker Urine Collection – Treatment Phase - (Cohort 1, Cohort 2, and Cohort 3 Only) See Section 8.14 44
Table 19: Biomarker Collection – Follow-up Phase - (Cohort 1, Cohort 2, and Cohort 3 Only) See Section 8.14 44
Table 20: Description of Study Drugs 76
Table 21: Point Estimate and the 95% Exact Confidence Interval based on 80 Participants 113
Table 22: Management of Immune-related Gastrointestinal Adverse Events 151
Table 23: Management of Immune-related Hepatic Adverse Events 152
Table 24: Management of Immune-related Endocrinopathies 152
Table 25: Management of Rash 153
Table 26: Management of Renal Adverse Events 154
Table 27: Management of Neurological Adverse Events 154
Table 28: Management of Pulmonary Adverse Events 155
Table 29: Management of Uveitis and Visual Complaints 155
Table 30: Management of Infusion-related Reactions 156

FIGURES

Figure 1: Schematic Overview of the Study 16
Figure 2: Timeline of Study Dosing and Key Assessments (Year 1) 17
Figure 3: Timeline of Study Dosing and Key Assessments (Years 2-3) 18
Figure 4: TAR-200 45
Figure 5: Loading and Deployment (Insertion) of TAR-200 using the Urinary Placement Catheter (UPC) 78
Figure 6: TAR-200 Removal 79

1. PROTOCOL SUMMARY

1.1. Synopsis

Phase 2b Clinical Study Evaluating Efficacy and Safety of TAR-200 in Combination with Cetrelimab, TAR-200 Alone, or Cetrelimab Alone in Participants with High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Intravesical Bacillus Calmette-Guérin (BCG) who are Ineligible for or Elected Not to Undergo Radical Cystectomy

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 (PMOA). The TAR-200 consists of 2 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 comprises a dual lumen CCI part with 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"). The UPC is a sterile, single-use, transient contact medical device which has been specifically developed for the transurethral insertion of TAR-200 into the bladder. TAR-200 is removed from the bladder transurethrally via cystoscopy and noncutting endoscopic grasping forceps.

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), and enhances pro-inflammatory cytokine production.

KEY OBJECTIVES

PRIMARY OBJECTIVE (Cohorts 1, 2, and 3 only)
To evaluate the overall complete response (CR) rate in participants treated with TAR-200 in combination with intravenous (IV) cetrelimab (Cohort 1), or TAR-200 alone (Cohort 2), or IV cetrelimab alone (Cohort 3), with Carcinoma in Situ (CIS), with or without concomitant high-grade Ta or T1 papillary disease.
PRIMARY OBJECTIVE (Cohort 4 only)
To evaluate disease-free survival (DFS) in participants treated with TAR-200 alone with papillary disease only (Cohort 4).
KEY SECONDARY OBJECTIVES
To evaluate the duration of response (DoR) in participants treated with TAR-200 in combination with IV cetrelimab (Cohort 1), or TAR-200 alone (Cohort 2), or IV cetrelimab alone (Cohort 3) with CIS (with or without concomitant Ta or T1 papillary disease) who achieve a CR.
To determine the overall survival (OS) in all participants.
To assess the safety of TAR-200 with or without IV cetrelimab and IV cetrelimab alone.
To evaluate the pharmacokinetics (PK) of gemcitabine and the PK and immunogenicity of IV cetrelimab when IV cetrelimab is administered with and without TAR-200.

Hypothesis

For Cohorts 1, 2, and 3: Treatment with intravesical TAR-200 in combination with IV cetrelimab, TAR-200 alone, or IV cetrelimab alone in participants with high-risk NMIBC (HR-NMBIC) (CIS with or without papillary disease) unresponsive to prior intravesical BCG therapy will lead to CR and durable CR.

For Cohort 4: TAR-200 alone in participants with papillary disease only (without CIS) unresponsive to prior intravesical BCG therapy will prolong DFS.

OVERALL DESIGN

This is an open-label, parallel-group, multi-center study evaluating the efficacy and safety of intravesical TAR-200 in combination with IV cetrelimab, TAR-200 alone, or IV cetrelimab alone in participants with HR-NMIBC unresponsive to prior intravesical BCG therapy who are either ineligible for or have elected not to undergo radical cystectomy (RC) after making an informed decision. Ineligibility for or reason for refusal of cystectomy will be documented in the electronic case report form (eCRF). All enrolled participants must have received adequate BCG and confirmed CIS [with or without papillary disease] or confirmed papillary disease only (high-grade Ta or any T1, without CIS), within 12 months of completion of the last dose of BCG therapy. All visible papillary disease must be fully resected (absent) prior to randomization (ie, treatment assignment) (residual CIS acceptable for participants eligible for Cohort 1, 2, and 3 only) and documented in the eCRF based on Screening cystoscopy. Adequate BCG therapy is defined as a minimum of 5 of 6 full doses of an induction course (adequate induction) plus 2 of 3 doses of a maintenance course, or at least 2 of 6 doses of a second induction course (Food and Drug Administration 2018). Single-dose perioperative intravesical chemotherapy prior to study treatment is allowed in accordance with institutional guidelines.

There are 4 cohorts in this study: Cohort 1 TAR-200 in combination with IV cetrelimab; Cohort 2 TAR-200 alone; Cohort 3 IV cetrelimab alone; and, added with Amendment 4, Cohort 4 TAR-200 alone. Per previous protocol versions, participants with CIS [with or without papillary disease] were randomly assigned (2:1:1) to receive intravesical TAR-200 in combination with IV cetrelimab (Cohort 1) or TAR-200 alone (Cohort 2) or IV cetrelimab alone (Cohort 3). Following review of the futility data, the Sponsor elected to close further enrollment into Cohorts 1 and 3. Additionally, in accordance with Amendment 3, the Sponsor decided to expand enrollment into Cohort 2 to approximately 80 participants. Participants already enrolled in Cohorts 1 and 3 who are in the Treatment Phase and benefiting from treatment will continue to receive the assigned treatment until the protocol-defined criteria for treatment discontinuation are met (eg, recurrence/progression) (refer to Section 7.1 for discontinuation criteria). All participants, including those in Cohort 1 and 3, who discontinue study treatment should not be considered withdrawn from the study and will continue to be followed for assessments in the Follow-up Phase as described in the Schedule of Activities (Section 1.3).

As of Protocol Amendment 4, the study design includes Cohort 4 of approximately 50 participants with BCG-unresponsive papillary disease only (high-grade Ta or any T1). Enrollment into Cohort 4 may also be discontinued at Sponsor discretion (eg, if Cohort 2 enrollment is completed).

For the purposes of this study, both TAR-200 and IV cetrelimab, alone or in combination, will be referenced as study drug.

NUMBER OF PARTICIPANTS

Per previous protocol versions, a total sample size of 200 participants in a 2:1:1 randomization ratio (Cohort 1: 100 participants, Cohort 2: 50 participants, and Cohort 3: 50 participants) was planned. Following review of data from the futility analysis, the Sponsor has elected to close further enrollment into Cohorts 1 and 3 and expand Cohort 2 to approximately 80 participants.

As of Amendment 4, an additional cohort of approximately 50 participants will be included (Cohort 4).

TREATMENT GROUPS AND DURATION

For Cohort 1, TAR-200 will be dosed every 3 weeks (Q3W) up to the first 24 weeks. Dosing of TAR-200 will then be every 12 weeks through Week 99 (Year 2). Cetrelimab will be dosed at 360 mg IV every 3 weeks (Q3W) through Week 78 (18 months).

For Cohort 2 and Cohort 4, TAR-200 will be dosed Q3W for up to the first 24 weeks on study. Dosing of TAR-200 will then be every 12 weeks through Week 99 (Year 2).

For Cohort 3, cetrelimab will be dosed at 360 mg IV Q3W through Week 78 (18 months).

There is only 1 dose and schedule option for TAR-200. TAR-200 is available in 1 dose only (containing 225-mg free base equivalents of gemcitabine), which will remain indwelling for up to 3 weeks (approximately 21 days) per each dosing cycle. Stopping criteria is allowed based on TAR-200 related adverse events (AEs). There is only 1 dosing and schedule option for IV cetrelimab. Cetrelimab is dosed and scheduled for 360 mg IV Q3W. Dose delays and/or skipped doses are allowed for toxicity management. Guidelines for management of immune-related toxicities are provided.

EFFICACY EVALUATIONS

Participants will be enrolled based on local histopathology and local urine cytology. Confirmed CIS (with or without papillary disease) or papillary only diagnosis based on a bladder biopsy/transurethral resection of bladder tumor (TURBT) conducted during the Screening phase or confirmed CIS (with or without papillary disease) or papillary disease only based on a prior biopsy, at the site or an outside institute, up to 3 months (90 days) prior to Screening, can be used for eligibility assessment. The biopsy with confirmed CIS [with or without papillary disease] or papillary disease only should also be submitted to the central laboratory. Recurrent CIS diagnosis, either during Screening or based on prior biopsy as mentioned above, should be within 12 months of the last dose of BCG. Adequate BCG therapy is defined as a minimum of 5 of 6 full doses of an induction course (adequate induction) plus 2 of 3 doses of a maintenance course, or at least 2 of 6 doses of a second induction course (Food and Drug Administration 2018).

Cystoscopy and urine cytology (all cohorts) will be performed to assess disease response. This will occur every C weeks CCI [Year 1 and Year 2]) for up to Week 99 (2 years) of treatment or until disease persistence, progression, or recurrence as confirmed by positive central urine cytology or local/central pathology showing high-grade disease. Sites should consult with the Sponsor in the event of a positive local biopsy and absent/pending central pathology review before discontinuing study treatment. In Year 3 through the end of study, after the study treatment has ended, cystoscopy and urine cytology will be performed per institutional guidelines and will be collected at least every C weeks. For participants with CR, urine cytology from Year 3 through the end of study will be centrally reviewed for disease response. For participants who discontinue study treatment before Week 99 (Year 2), due to toxicity or reasons other than disease persistence, progression, or recurrence, disease assessments should be performed every C weeks CCI [Year 1 and Year 2]) until the start of subsequent therapy/procedure (eg, radical cystectomy) during the Follow-up Phase. Whenever possible, the same individual should perform cystoscopy throughout the study for a given participant. Unscheduled cystoscopy and biopsy may be performed as clinically indicated. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests. Overall survival status, any procedures (eg, cystectomy), subsequent anti-cancer therapies, and other malignancies will be reported in the eCRF until death, withdrawal of consent, or the end of the study, whichever occurs first.

During the Treatment Phase, voided urine specimens will be collected and submitted for central cytopathologic review to assess for recurrence and/or progression of disease.

On study bladder biopsy/TURBT must be performed at the Week [redacted] and Week [redacted] assessments (inclusive of negative cystoscopy results) for Cohorts 1, 2, and 3 only, and as clinically indicated for all participants during the study, based on local/central urine cytology, to determine the presence or absence of persistent, recurrent, or progressive disease. Biopsy samples will be evaluated by the local histopathology laboratory for clinical management at the discretion of the Investigator; however, all tissue biopsy sampling taken at any timepoint during study conduct will be submitted for a central review of the participant's disease status. Sites should consult with the Sponsor in the event of a positive local biopsy and absent/pending central pathology review before discontinuing treatment. A new low risk/low-grade papillary lesion does not constitute persistent or recurrent disease. Tissue slides/blocks from participants in all cohorts and all timepoints will be sent for central histopathologic review, confirming any high-grade recurrence. Significant discordances between local and central pathology review will result in Sponsor Investigator consultation, with recommendation to disqualify participant from study. Any confirmed new low risk/low-grade papillary lesion identified while on study (as well as at Screening) must be resected to completion by TURBT/bladder biopsy. Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.

Urine samples will be collected every [redacted] weeks [redacted] as described in the SoA table for central assessment of disease response. In addition, voided urine cytology will be locally assessed approximately 3 weeks prior to the Week [redacted] and Week [redacted] cystoscopy assessments [redacted] to assist with biopsy planning (tumor bed biopsies or systematic bladder biopsies). These biopsies should be taken from any suspicious bladder mucosal area (if noted); otherwise, biopsies should be taken from the site(s) of old tumor. Select bladder biopsies should only be performed if urine cytology is suspicious for malignant cells and cystoscopy is negative.

The primary endpoint for Cohorts 1, 2, and 3 is the CR rate in participants with CIS, with or without concomitant high-grade Ta or T1 papillary disease. Duration of Response (DOR) is a key secondary endpoint. The primary endpoint for Cohort 4 is the DFS for BCG-unresponsive papillary disease only.

CR for Cohorts 1, 2, and 3 is defined as at least one of the following:

- Negative cystoscopy and negative (including atypical) urine cytology
- Positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative (including atypical) urine cytology

DFS is defined as the time from the date of first dose of study treatment to the time of one of the following events, whichever occurs first:

1. The first recurrence of high-risk disease (high-grade Ta, any T1 or CIS).
2. Progression, defined as progression to MIBC (T≥2) or to lymph node (N+) or to distant disease (M+), whichever occurs first
3. Death due to any cause

Participants are required to discontinue from study treatment if there is confirmed high-risk disease persistence, recurrence or progression based on central urine cytology and/or central biopsy assessment, or local biopsy/local imaging after consultation with the Sponsor.

Computed tomography (CT)/Magnetic Resonance Imaging (MRI) Scans with contrast (abdomen, pelvis and chest) will be performed at baseline and every [redacted] weeks thereafter until the end of Year 3. Imaging assessment is conducted prior to dosing at defined timepoints. Additionally, unscheduled CT imaging may be performed if clinically indicated. Identical imaging methodology should be used for disease assessment at baseline and throughout the course of the study. Central review of imaging will not be performed.

Patient-reported outcomes (PRO) will be evaluated to complement data collected by other methods to support the clinical data and cost-effectiveness modeling, and contribute to enhanced communication of value to patients, clinicians, regulators, and payers. The PRO endpoints of interest include domain scales

from the European Organization for the Research and Treatment of Cancer-Quality of Life Questionnaire C30 (EORTC-QLQ-C30) and the EORTC Non-Muscle Invasive Bladder Cancer 24 (EORTC-QLQ-NMIBC24). Exploratory analyses of Medical Resource Utilization (MRU) data collected for participants in all cohorts will be performed.

Participants who initiate post-protocol alternative therapies will continue to be followed for OS. Additional therapies will be collected where possible.

PHARMACOKINETIC EVALUATIONS

For TAR-200 (Cohort 1, Cohort 2, and Cohort 4)

Sparse urine sampling will be collected on 3 occasions over the course of the Treatment Phase of the study. One single collection of urine sample will be collected from participants within 24 hours pre-dose at Week 0 Visit. Two pooled 24-hr cumulative urine collections will be collected from participants at Weeks [redacted] or [redacted] or [redacted] and Weeks [redacted] Additionally, serial urine PK sampling will also be collected in approximately 40 participants across Cohorts 1 and 2. Participants in the serial urine PK sampling are not required to complete the sparse urine sampling at Week 0 and Week [redacted]

These urine samples will be collected for assessment of gemcitabine and 2',2'-difluorodeoxyuridine (dFdU) concentrations in urine.

Blood samples will be collected at multiple timepoints (which coincide with sparse urine PK timepoints). These blood samples will be collected for assessment of gemcitabine and dFdU concentrations in plasma.

For Cetrelimab (Cohort 1 and Cohort 3)

Blood for the assessment of cetrelimab PK will be collected at the timepoints specified in the Schedule of Activities.

IMMUNOGENICITY EVALUATIONS

For Cetrelimab (Cohort 1 and Cohort 3)

Blood samples will be collected and serum will be analyzed for antibodies to cetrelimab using a validated immunoassay for anti-drug antibody (ADA) analysis.

BIOMARKER EVALUATIONS

Biomarker samples (tissue, blood, and urine) will be collected from patients treated with TAR-200 in combination with IV cetrelimab, or TAR-200 alone, or IV cetrelimab alone to determine biomarkers that correlate with clinical response. The goal of the biomarker analyses is to understand the mechanism of action and clinical response relationships with IV cetrelimab, and TAR-200 alone and with the combination of TAR-200 and IV cetrelimab. For participants in Cohort 4, biomarker collections will not be performed.

SAFETY EVALUATIONS

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, 12-lead electrocardiogram (ECG), physical examinations (per the Schedule of Activities [SoA], Section 1.3), clinical laboratory tests, and other safety evaluations at specified timepoints.

Any clinically significant abnormalities or toxicities persisting at the end of the study will be followed by the Investigator until resolution or until reaching a clinically stable endpoint.

Safety oversight will be performed by the Study Responsible Physician (SRP) and Independent Data Monitoring Committee (IDMC), which will be composed of individuals with the appropriate expertise. The

IDMC will operate under the rules of 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

The cohorts will be analyzed separately. For Cohorts 1, 2, or 3, the overall CR rate and its 95% exact confidence interval (CI) will be calculated based on binomial distribution. A Z test with normal approximation will be used to compare the CR rate with the historical CR rate (20%) at 2-sided significance level of 5%. No statistical comparison will be performed among the 4 cohorts. A side-by-side descriptive summary of efficacy will be provided to illustrate the contribution of TAR-200 or IV cetrelimab to the efficacy of the combination therapy in participants with CIS [with or without papillary] disease only (Cohorts 1, 2, and 3).

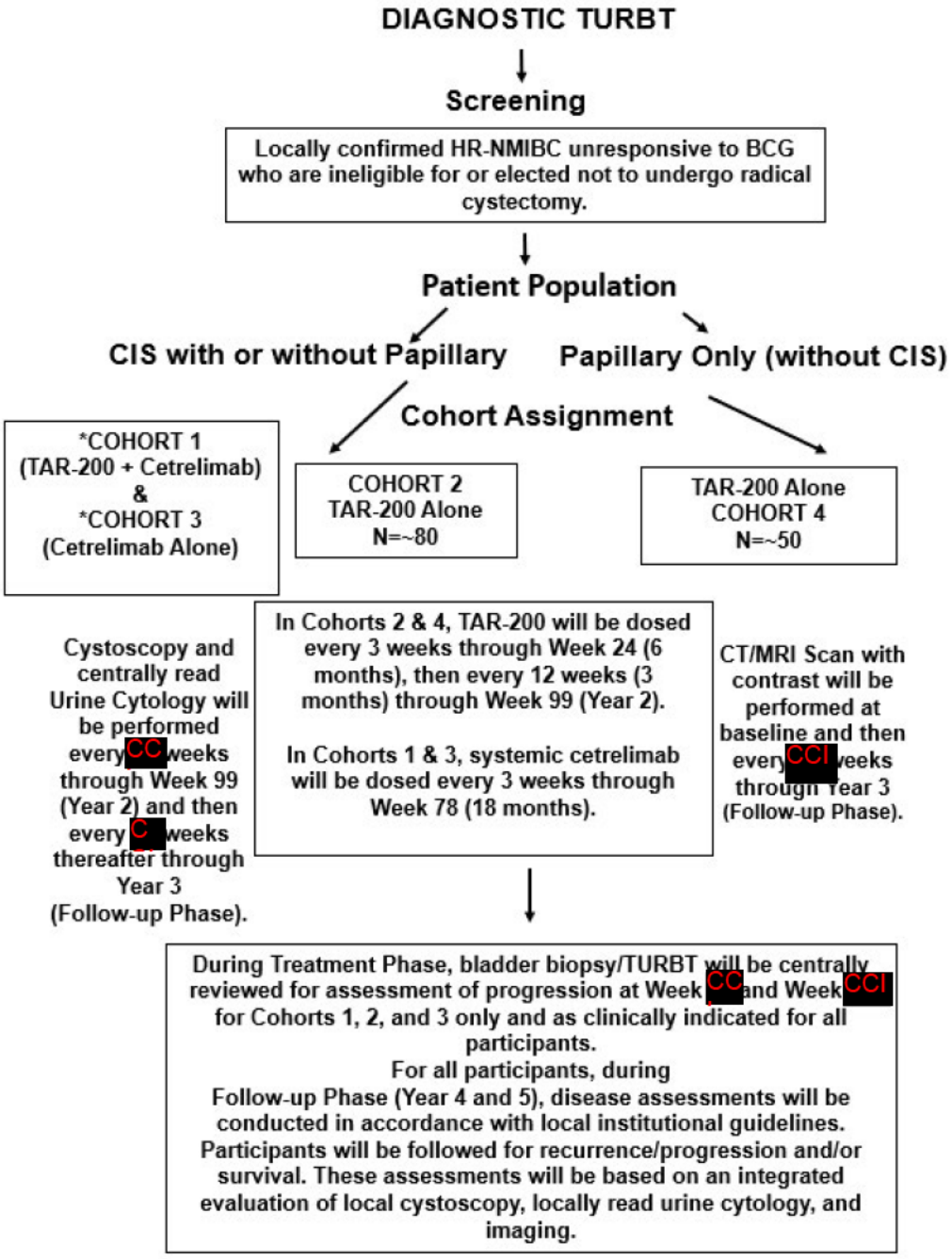
For Cohort 4, the DFS rate at 12 months will be provided using Kaplan Meier estimate. The DFS rate at other timepoints (eg 18 or 24 months) will also be calculated based on the Kaplan-Meier estimate.

A futility analysis was performed after there were 75 evaluable participants from Cohorts 1, 2, and 3 who had adequate disease assessment post-baseline (See Section 9.3 for the definition of evaluable analysis set). Any cohort could be closed for futility if its overall CR rate is less than 20%. Additionally, the IDMC reviewed and evaluated the data from individual cohorts and the totality of the data to provide its recommendation. Following Amendment 3 and the Futility Analysis, Cohorts 1 and 3 were closed for further enrollment and the sample size for Cohort 2 was expanded to approximately 80 participants. The sample size of 80 participants will provide over 95% power to reject the null hypothesis using 2-sided alpha of 0.05 assuming an overall CR rate of 40%. Refer to the “Overall Design” section above for further information on study design updates post futility.

As of Amendment 4, an additional cohort of approximately 50 participants will be included (Cohort 4). The sample size of 50 participants in Cohort 4 will provide 93% probability to have the lower boundary of 95% CI of DFS at 1 year exceeding 35% (or about 78% probability exceeding 40% 1-year DFS), if we assume the 1-year DFS rate is 60%, 5% annual drop out rate, 7-month enrollment and additional 12-month follow-up.

1.2. Schema

Figure 1: Schematic Overview of the Study



Abbreviations: BCG=Bacillus Calmette-Guérin; CT=computed tomography; MRI=magnetic resonance imaging

Abbreviations: BCG=Bacillus Calmette-Guérin, CIS=carcinoma in situ, CT=computed tomography, HR-NMIBC=high-risk non-muscle invasive bladder cancer; IDMC=Independent Data Monitoring Committee, MRI=magnetic resonance imaging; TURBT=transurethral resection of bladder tumor.

*For Cohorts 1 and 3 only, enrollment is closed. Participants randomized to Cohorts 1 or 3 will continue on study as outlined in the Treatment and Follow-up Phase of the Schedule of Activities (Refer to Section 1.3).

Figure 2: CCI

CCI

Figure 3: CCI

CCI

1.3. Schedule of Activities

Table 1: Screening Activities (Cohorts 2 and 4 Only)

Procedures, Tests, & Evaluations	Screening (C Days*)	Randomization C days prior to W0D1	Notes
PROCEDURAL/ADMINISTRATIVE ASSESSMENTS**			*For participants who require repeat biopsy/TURBT and/or repeat imaging during the standard C -day Screening Phase, the Screening Phase may be extended from C days to C days. **Note that participants who are re-screened within C days of the original Screening do not need to repeat screening procedures, with the exception of urine culture and laboratory test result.
Informed Consent	X		Must be obtained before performing any Screening procedures.
Eligibility Confirmation	X		Must be assessed during screening period and confirmed prior to randomization.
Medical History with prior therapies including prior BCG	X		Including history of prior bladder biopsies (including initial TURBT/biopsy), and prior therapies including prior BCG.
Demographics	X		
Randomization (Treatment Assignment)		X	
SAFETY ASSESSMENTS Section 8.11			
Physical examination & ECOG	X		
Vital Signs with Height and Weight	X		Height will be measured at Screening only.
ECG	X		
Hematology, Blood Chemistry, Coagulation Panel, Urinalysis, & Urine Culture Sections 8.11.5 and 10.2, Appendix 2	X		It is recommended that urine culture be obtained with adequate time for treatment of potential positive urine culture during Screening and prior to Week C T3 and HbA1c at screening, then only as clinically indicated. Screening laboratory tests must be within C days prior to the Week C visit. If collected within C days prior to the Week C visit, these laboratory tests may be used in lieu of Week C of the required laboratory tests.
Serology - HIV, HBsAg, HBc, HCV antibody	X		
Serum Pregnancy Test (POCBP) Section 8.11.6	X		
Bladder PVR	X		Participants with a bladder PVR >350-mL after a second attempted voiding will be excluded. PVR measurement must be recorded in the eCRF prior to randomization.
Concomitant Medications	X		
Adverse Events/SAEs (Sections 8.11, 8.11.1, 8.12, 10.4, Appendix 4, and 10.9, Appendix 9)	X	X	
DISEASE ASSESSMENTS Section 8.10.1			
Screening Cystoscopy Section 8.10.1.1	X		All visible papillary disease must be fully resected (absent) prior to randomization (residual CIS acceptable [for participants eligible for Cohorts 1, 2, and 3 only]) and documented in the CRF at Screening cystoscopy. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Urine Cytology Section 8.10.1.2	X		Urine Cytology at Screening will be sent for central review. Additionally, an aliquot of the urine should be taken from the same collections and used for local cytopathologic evaluation to guide clinical management. For participants eligible for Cohort 4 (ie, patients with papillary disease only), local urine cytology at Screening must be negative or atypical (for HGUC).
TURBT (Bladder Biopsy) Section 8.10.1.3	X		At Screening visit, local re-reading of slides is required for participants who are referred from an outside institution. If a biopsy with confirmed CIS (with or without papillary) or papillary disease only was done up to C months prior to screening and within C months of last BCG dose, then additional TURBT/biopsy at during screening is not required. Results from the biopsy showing CIS (with or without papillary) or papillary disease only should be entered in eCRF. For participants who require repeat biopsy/TURBT during the Screening Phase, the Screening Phase may be extended from C days to C days. Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.

Procedures, Tests, & Evaluations	Screening [C] Days*)	Randomization [C] days prior to W0D1	Notes
CT/MRI with contrast (Chest, Abdomen, and Pelvis) Section 8.10.1.4	X		The same methodology should be used for disease assessment at baseline and throughout the course of the study and should be interpreted by the same individual throughout the study. CT/MRI with contrast (Chest, Abdomen, and Pelvis) performed within [C] days prior to the date of ICF will be considered for eligibility review. For participants who require repeat imaging during the standard [C]-day Screening Phase, the Screening Phase may be extended from [C] days to [C] days.
MEDICAL RESOURCE UTILIZATION and HEALTH ECONOMICS			
MRU Section 8.15	X		

Abbreviations: BCG=Bacillus Calmette-Guérin; CIS=carcinoma in situ; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; HBsAg=Hepatitis B virus surface antigen; HbA1c=hemoglobin A1c; HBc=Hepatitis B core antibody; HCV=Hepatitis C virus; HepB=Hepatitis B; HIV=human immunodeficiency virus; MRI=magnetic resonance imaging; MRU=medical resource utilization; POCBP=participant of childbearing potential; PVR=post-void residual; SAE=serious adverse event; TURBT=transurethral resection of bladder tumor; T3=triiodothyronine; UTI=urinary tract infection; W0D1=Week 0, Day 1.

Table 2: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities -Treatment Phase -Week C through Week C (Year C)

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments with the exception of Week C are to be completed within CCI C [redacted]	Notes
SAFETY ASSESSMENTS* Section 8.11		*If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECGs, vital signs, blood draws, and dosing to be conducted last.
Physical Examination (PE) & ECOG	X [redacted] X [redacted] X [redacted] X [redacted] X [redacted] X	A targeted PE and ECOG score will be assessed at timepoints to correlate with disease assessments. It may also be performed at any time on study as clinically indicated.
ECG	ECG may be conducted at any time on study as clinically indicated.	
Vital Signs with weight	X X X X X X X X X X X X X X X X X X	
Hematology, Blood Chemistry, Coagulation Panel, Urinalysis, & Urine Culture Sections 8.11.5 and 10.2, Appendix 2	X X X X X X X X X X X X X X X X X X	Glucose must be fasting while on IV cetrelimab. Coagulation Panel at CCI [redacted] T3 and HbA1c are only required as clinically indicated.
Urine Pregnancy Test (POCBP) (Pre-dose) Section 8.11.6	X X X X X X X X X X X X X X X X X X	If urine pregnancy test is positive, a serum pregnancy test must be performed.
Concomitant Medications	X X X X X X X X X X X X X X X X X X	
Adverse Events/SAEs Sections 8.11, 8.11.1, 8.12, 10.4, Appendix 4, and 10.9, Appendix 9	X	AEs/SAEs should be reported at any time throughout study conduct from the time of informed consent signature to end of Follow-up Safety Visit (ie, 100-Day Safety Follow-up, see Table 4)
Product Quality Complaint and Device Deficiencies Sections 8.12.8, 10.4.6, and 10.10.1	X	Identified PQCs and Device Deficiencies should be reported at any time throughout the Treatment Phase. If a PQC is reported for TAR-200 or IV cetrelimab, or a Device Deficiency is reported for the UPC, the respective product must be retained by the site under the appropriate storage conditions until a shipment request is received from the Sponsor. Instructions will be provided in the Study Reference Manual.
Procedures (Genitourinary and Non-Genitourinary) Section 8.11.8	X	
DISEASE ASSESSMENTS Section 8.10.1		
Assessment Cystoscopy Section 8.10.1.1	X [redacted] X [redacted] X [redacted] X	Antibiotics for standard cystoscopy may be administered in accordance with standard of care. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Urine Cytology Section 8.10.1.2	X [redacted] X* X [redacted] X [redacted] X* X	Urine cytology will be sent for central review. Additionally, an aliquot of the urine should be taken from the same collections at each disease assessment visit and used for local cytopathologic evaluation to guide clinical management. Please refer to the Laboratory Manual for further instructions. *Voided urine cytology collected at the Week C and Week C visits will be locally assessed to assist with biopsy planning (tumor bed biopsies/targeted or systematic bladder biopsies) at the Week C and Week C visits, respectively.

Table 2: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities -Treatment Phase -Week C through Week C (Year C)

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments with the exception of Week C are to be completed within CCI																	Notes
	C																	
TURBT (Bladder Biopsy) Section 8.10.1.3									X							X		Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
CT/MRI with contrast (Chest, Abdomen and Pelvis) Section 8.10.1.4									X							X		
PATIENT REPORTED OUTCOME Section 8.10.2																		
EORTC-QLQ-C30 Section 8.10.2.1	X		X		X				X				X				X	Complete prior to any other assessments of the day. The EORTC QLQ-C30 will be completed before the EORTC QLQ-NMIBC questionnaire.
EORTC-QLQ-NMIBC24 Section 8.10.2.2	X		X		X				X				X				X	
MEDICAL RESOURCE UTILIZATION and HEALTH ECONOMICS																		
MRU Section 8.15	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
STUDY DRUG																		
TAR-200 Insertion Section 6.1.1	X	X	X	X	X	X	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 within CCI On days in which both TAR-200 and IV cetrelimab will be administered, TAR-200 will be inserted at least 45 minutes before the start of or after the completion of cetrelimab IV infusion. If one treatment is held the other may still be administered in consultation with the Sponsor. Consider administering anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 insertion. To mitigate the risk of UTIs participants must receive at least one dose of prophylactic periprocedural antibiotics for TAR-200 insertion or removal. *TAR-200 should not be administered less than 14 days after any procedure resulting in traumatized urothelium during the biopsy (eg, gross hematuria). In the event a visit is scheduled that is within CCI window during the first C weeks, every attempt should be made to maintain the initial Q3W regimen for TAR-200 calculated from the date of first dose (W0D1).
TAR-200 Removal with Cystoscopy Section 6.1.2		X	X	X	X	X	X	X	X					X				X	Consider administering anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 removal. To mitigate the risk of UTIs participants must receive at least one dose of prophylactic periprocedural antibiotics for TAR-200 insertion or removal. When the TAR-200 is removed, it may be replaced immediately per protocol or within the visit window CCI Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.

Table 2: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities -Treatment Phase -Week [redacted] through Week [redacted] (Year [redacted]

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments with the exception of Week 0 are to be completed within [redacted]																		Notes
	0[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
IV Cetrelimab Administration Section 6.1.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	In the event a visit is scheduled that is within [redacted] window, every attempt should be made to maintain the initial Q3W regimen for cetrelimab calculated from the date of first dose (W0D1).

Abbreviations: CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EORTC-QLQ-NMIBC24=European Organisation for Research and Treatment of Cancer -Non-Muscle Invasive Bladder Cancer Questionnaire; HbA1c=hemoglobin A1c; IV=intravenous; MRI=magnetic resonance imaging; MRU=medical resource utilization; PE=physical examination; POCBP=participant of childbearing potential; PQC=product quality complaint; Q3W=every 3 weeks; SAE=serious adverse event; TURBT=transurethral resection of bladder tumor; T3=triiodothyronine; UPC=Urinary Placement Catheter; UTI=urinary tract infection; W0D1=Week 0 Day 1.

Table 3: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities -Treatment Phase -Week 54 through Week 99 (Year 2)

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments are to be completed within [redacted]															Notes
	54	57	60	63	66	69	72	75	78	84	87	88	92	96	99	
SAFETY ASSESSMENTS*																*If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECGs, vital signs, blood draws, and dosing to be conducted last.
Hematology, Blood Chemistry, Coagulation Panel, Urinalysis, & Urine Culture Sections 8.11.5 and 10.2, Appendix 2	X	X	X	X	X	X	X	X	X	X				X		Glucose must be fasting while on IV cetrelimab. Coagulation Panel at [redacted] T3 and HbA1c are only required as clinically indicated.
Urine Pregnancy Test (POCBP) Pre-dose Section 8.11.6	X	X	X	X	X	X	X	X	X	X		X*	X*	X	X	For POCBP, pregnancy testing should be conducted monthly through 6 months after the last dose of study drug and then as outlined in this table. In the event of a positive pregnancy test, the participant must contact the Investigator immediately. If urine pregnancy test is positive at any timepoint, a serum pregnancy test must be performed. *This assessment represents a test to be conducted between study visits.
Physical Examination & ECOG			X				X			X				X		A targeted PE and ECOG score will be assessed at timepoints to correlate with disease assessments and may also be performed at any time on study as clinically indicated.
ECG	ECG may be conducted at any time on study as clinically indicated.															
Vital Signs with weight	X	X	X	X	X	X	X	X	X	X	X			X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X			X	X	
Adverse Events/SAEs Sections 8.11, 8.11.1, 8.12, 10.4, Appendix 4, and 10.9, Appendix 9	X															AEs/SAEs should be reported at any time throughout study conduct from the time of informed consent signature to end of Follow-up Safety Visit (ie, 100-Day Safety Follow-up Visit; see Table 4)
Product Quality Complaint and Device Deficiencies Sections 8.12.8, 10.4.6, and 10.10.1	X	X	X	X	X	X	X	X	X	X	X			X	X	Identified PQCs and Device Deficiencies should be reported at any time throughout the Treatment Phase. If a PQC is reported for TAR-200 or IV cetrelimab, or a Device Deficiency is reported for the UPC, the respective product must be retained by the site under the appropriate storage conditions until a

Table 3: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities -Treatment Phase -Week C through Week C (Year C

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments are to be completed within CCI															Notes
	C															
																shipment request is received from the Sponsor. Instructions will be provided in the Study Reference Manual.
Procedures (Genitourinary and Non-Genitourinary) Section 8.11.8	X															
DISEASE ASSESSMENTS																
TURBT Bladder biopsy Section 8.10.1.3	Only performed when clinically indicated. TURBT specimens from any timepoint should be submitted to central laboratory.															Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests
Assessment Cystoscopy Section 8.10.1.1			X				X			X				X		Antibiotics for standard cystoscopy may be administered in accordance with standard of care. Cystoscopy will be performed at the EOT Visit only if needed for TAR-200 removal. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests..
Urine Cytology Section 8.10.1.2			X				X			X				X		Urine Cytology will be sent for central review. Additionally, an aliquot of the urine should be taken from the same collections at each disease assessment visit and used for local cytopathologic evaluation to guide clinical management. Please refer to the Laboratory Manual.
CT/MRI Scan with contrast (Chest, Abdomen and Pelvis) Section 8.10.1.4							X							X		
PATIENT REPORTED OUTCOME																
EORTC-QLQ-C30, Section 8.10.2.1			X				X			X				X		Complete prior to any other assessments of the day. The EORTC-QLQ-C30 will be completed before the EORTC-QLQ-NMIBC questionnaire.
EORTC QLQ NMIBC24, Section 8.10.2.2			X				X			X				X		
MEDICAL RESOURCE UTILIZATION and HEALTH ECONOMICS																
MRU Section 8.15	X	X	X	X	X	X	X	X	X	X	X			X	X	
STUDY DRUG ADMINISTRATION																
TAR-200 Insertion Section 6.1.1			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 within CCI [redacted] On days in which both TAR-200 and IV cetrelimab will be administered, TAR-200 will be provided at least 45 minutes before the start of or after the completion of cetrelimab IV infusion. If one treatment is held the other may still be administered in consultation with the Sponsor. Consider administering anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 insertion. To mitigate the risk of UTIs participants must receive at least one dose of prophylactic periprocedural antibiotics for TAR-200 insertion or removal. TAR-200

Table 3: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities -Treatment Phase -Week CCI through Week CCI (Year CCI)

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments are to be completed within CCI															Notes
	CCCI															
																should not be administered less than 14 days after any procedure resulting in traumatized urothelium during the biopsy (eg, gross hematuria).
TAR-200 Removal with cystoscopy Section 6.1.2				X				X			X				X	Consider administering anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 removal. To mitigate the risk of UTIs participants must receive at least one dose of prophylactic periprocedural antibiotics for TAR-200 insertion or removal. When the TAR-200 is removed, it may be replaced immediately per protocol or within the visit window CCI [redacted] Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests..
IV Cetrelimab Administration	X	X	X	X	X	X	X	X	X							In the event a visit is scheduled that is within CCI [redacted] window, every attempt should be made to maintain the initial Q3W regimen for cetrelimab calculated from the date of first dose (W0D1).

Abbreviations: CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EORTC-QLQ-NMIBC24=European Organisation for Research and Treatment of Cancer -Non-Muscle Invasive Bladder Cancer Questionnaire; EOT=end of treatment; HbA1c=hemoglobin A1c; IV=intravenous; MRI=magnetic resonance imaging; MRU=medical resource utilization; PE=physical examination; POCBP=participant of childbearing potential; PQC=product quality complaint; Q3W=every 3 weeks; SAE=serious adverse event; TURBT= transurethral resection of bladder tumor; T3=triiodothyronine; UPC=Urinary Placement Catheter; UTI=urinary tract infection; W0D1=Week 0 Day 1

Table 4: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities - Follow-up Phase

Procedures, Tests, & Evaluations	FOLLOW-UP PHASE					
	End of Treatment	30-Day Safety F/U	100 Day Safety F/U	Surveillance F/U[a, b]	Survival F/U[c]	Notes
	At completion or discontinuation of all study drug (+ 1 week).	30 days (±1 week) from the EOT visit	100 days (±1 week) from the EOT visit	[a]Disease assessment follow-up will be performed per institutional guidelines for participants who have ended study drug but have not recurred or progressed, and will be collected at least every C weeks after EOT until disease recurrence or progression, death, withdrawal of consent or the end of the study, whichever occurs first (Section 4.4)	To be conducted every C weeks ±2 weeks	[b]For participants who discontinue study treatment before Week C (Year C, due to toxicity or reasons other than disease persistence/progression/recurrence, disease assessments should be done every C weeks CCI [Year 1] or CCI [Year 2]) before the start of subsequent therapy/procedure (eg, radical cystectomy). [c]All participants will be assessed for survival via a telephone call or other locally approved methods of contact. OS will be documented in the eCRF.
SAFETY ASSESSMENTS						
Hematology, Blood Chemistry, Coagulation Panel, Urinalysis, & Urine Culture	X	X	X	X[a, b]		Glucose must be fasting through the 100-day safety follow-up visit while on cetrelimab. Coagulation studies will not be performed during Year 3. T3 and HbA1c are only required as clinically indicated.
Urine Pregnancy Test (POCBP) Section 8.11.6	X	X	X	X[a, b]		For POCBP, pregnancy testing should be conducted monthly through 6 months after the last dose of study drug and then as outlined in this table. In the event of a positive pregnancy test, the participant must contact the Investigator immediately. If urine pregnancy test is positive at any timepoint, a serum pregnancy test must be performed.
Physical Examination (PE) and ECOG	X	X	X	X		A targeted PE and ECOG score will be assessed at time points to correlate with disease assessments, EOT, and at the 30- and 100-day safety follow-up visit. It may also be performed at any time on study as clinically indicated.
ECG	X					ECGs may be conducted at any time on study as clinically indicated.
Vital Signs with weight	X	X	X	X		
Concomitant Medications	X	X	X	X		
Adverse Events/SAEs Sections 8.11, 8.11.1, 8.12, 10.4, Appendix 4, and 10.9, Appendix 9	X	X	X	X*		AEs/SAEs should be reported at any time throughout study conduct from the time of informed consent signature to end of Follow-up Safety Visit. *All drug-related SAEs beyond 100 days after last dose of study drug should be reported for both treatment groups while participants are in the study Follow-up Phase.
Procedures (Genitourinary and Non-Genitourinary) Section 8.11.8	X	X	X	X	X	Procedures (eg, cystectomy) will be collected through survival follow-up
DISEASE ASSESSMENTS						
TURBT (bladder biopsy) Section 8.10.1.3	TURBT is not required at any specific timepoint during this phase but should be conducted as deemed clinically indicated. TURBT specimens from any time point should be submitted to central laboratory.					Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.

Table 4: Cohort 1 (TAR-200 + IV Cetrelimab) Schedule of Activities - Follow-up Phase

Procedures, Tests, & Evaluations	FOLLOW-UP PHASE					
	End of Treatment	30-Day Safety F/U	100 Day Safety F/U	Surveillance F/U[a, b]	Survival F/U[c]	Notes
	At completion or discontinuation of all study drug (+ 1 week).	30 days (±1 week) from the EOT visit	100 days (±1 week) from the EOT visit	[a]Disease assessment follow-up will be performed per institutional guidelines for participants who have ended study drug but have not recurred or progressed, and will be collected at least every C weeks after EOT until disease recurrence or progression, death, withdrawal of consent or the end of the study, whichever occurs first (Section 4.4)	To be conducted every C weeks ±2 weeks	[b]For participants who discontinue study treatment before Week C (Year C), due to toxicity or reasons other than disease persistence/progression/recurrence, disease assessments should be done every C weeks CCI [Year 1] or CCI [Year 2]) before the start of subsequent therapy/procedure (eg, radical cystectomy). [c]All participants will be assessed for survival via a telephone call or other locally approved methods of contact. OS will be documented in the eCRF.
Assessment Cystoscopy Section 8.10.1.1	X*			X[a, b]		Antibiotics for standard cystoscopy may be administered in accordance with standard of care. *Cystoscopy will be performed at the EOT Visit only if needed for TAR-200 removal. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Urine Cytology Section 8.10.1.2				X[a, b]		Urine Cytology will be sent for central review. For all participants, an aliquot of the urine should be collected for local cytopathologic evaluation. Please refer to the Laboratory Manual for further instructions.
CT/MRI Scan with contrast (Chest, Abdomen and Pelvis Section 8.10.1.4	X*			X[a, b]		*To be performed per Sponsor approval as clinically indicated
PATIENT-REPORTED OUTCOME						
EORTC-QLQ-C30 Section 8.10.2.1	X					Complete prior to any other assessments of the day. The EORTC-QLQ-C30 will be completed before the EORTC-QLQ-NMIBC questionnaire.
EORTC-QLQ NMIBC24 Section 8.10.2.2	X					
MEDICAL RESOURCE UTILIZATION and HEALTH ECONOMICS						
MRU Section 8.15	X	X	X	X[a, b, e]		Until disease recurrence/progression. If the participant ends treatment without a recurrence or progression, continue to collect until disease recurrence or progression with each disease assessment.
LONG-TERM FOLLOW-UP						
Overall Survival Section 8.7	X	X	X	X[a, b]	X	All participants will be assessed for survival via a telephone call or other locally approved methods of contact. Other methods to obtain the data per institutional SOC policy are acceptable. OS will be documented in the eCRF.
Subsequent Anti-Cancer Therapies Section 8.6	X	X	X	X[a, b]	X	
Other Malignancies	X	X	X	X[a, b]	X	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.

Abbreviations: AE=adverse event; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30= European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EORTC-QLQ-NMIBC24= European Organisation for Research and Treatment of Cancer -Non-Muscle Invasive Bladder Cancer Questionnaire; EOT=end of treatment; MRI=magnetic resonance imaging; MRU=medical resource utilization; OS=overall survival; POCBP=participant of childbearing potential; SAE=serious adverse event; SOC=standard of care; TURBT= transurethral resection of bladder tumor; UTI=urinary tract infection

Table 5: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities - Treatment Phase -Week C through Week C (Year C

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments with exception of Week C complete within CCI																	Notes
	C																	
SAFETY ASSESSMENTS* Section 8.11																		*If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECGs, vital signs, blood draws, and dosing to be conducted last.
Physical Examination (PE) & ECOG	X				X				X				X				X		A targeted PE and ECOG score will be assessed at timepoints to correlate with disease assessments. It may also be performed at any time on study as clinically indicated.
ECG	ECG may be conducted at any time on study as clinically indicated.																	
Vital Signs with Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry, Coagulation Panel, Urinalysis, & Urine Culture Sections 8.11.5 and 10.2, Appendix 2	X	X	X	X	X	X	X	X	X				X	X			X	X	Fasting glucose is required. Coagulation Panel CCI T3 and HbA1c are only required as clinically indicated.
Urine Pregnancy Test (POCBP) (Pre-dose) Section 8.11.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	For POCBP, pregnancy testing should be conducted monthly through 6 months after the last dose of study drug and then as outlined in this table. In the event of a positive pregnancy test, the participant must contact the Investigator immediately. If urine pregnancy test is positive at any timepoint, a serum pregnancy test must be performed.
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events/SAEs Sections 8.11, 8.11.1, 8.12, 10.4, Appendix 4, and 10.9, Appendix 9	X																		AEs/SAEs should be reported at any time throughout study conduct from the time of informed consent signature to end of Follow-up Safety Visit (ie, 100-Day Safety Follow-up Visit; see Table 7)
Product Quality Complaint and Device Deficiencies Sections 8.12.8, 10.4.6, and 10.10.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Identified PQCs and Device Deficiencies should be reported at any time throughout the Treatment Phase. If a PQC is reported for TAR-200 or IV cetrelimab, or a Device Deficiency is reported for the UPC, the respective product must be retained by the site under the appropriate storage conditions until a shipment request is received from the Sponsor. Instructions will be provided in the Study Reference Manual.
Procedures (Genitourinary and non-Genitourinary) Section 8.11.8	X																		
DISEASE ASSESSMENTS																			
Assessment Cystoscopy Section 8.10.1.1					X				X				X				X		Antibiotics for standard cystoscopy may be administered in accordance with standard of care. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Urine Cytology Section 8.10.1.2					X			X*	X				X			X*	X		Urine Cytology will be sent for central review. Please refer to the Laboratory Manual. Additionally, an aliquot of the urine should be taken from the same collections at each disease assessment visit and used for local cytopathologic evaluation to guide clinical management. *Voided urine cytology collected at the Week C and Week C visits will be locally assessed to assist with biopsy planning (tumor bed biopsies/targeted or systematic bladder biopsies) at the Week CCI , Week CCI , respectively.

Table 5: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities - Treatment Phase -Week C through Week C (Year C)

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments with exception of Week C complete within CCI																Notes
	C																
TURBT (Bladder Biopsy)* Section 8.10.1.3								X*								X*	*Week 24 and Week 48 TURBT is only required participants in Cohort 2. Unscheduled TURBT may be performed if deemed clinically indicated for all participants. TURBT specimens from any time point should be submitted to central laboratory. Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests
CT/MRI Scan with contrast (Chest, Abdomen and Pelvis) Section 8.10.1.4								X								X	
PARTICIPANT REPORTED OUTCOME																	
EORTC-QLQ-C30 Section 8.10.2.1	X		X		X				X				X			X	Complete prior to any other assessments of the day. The EORTC-QLQ-C30 will be completed before the EORTC-QLQ-NMIBC questionnaire.
EORTC-QLQ- NMIBC 24 Section 8.10.2.2	X		X		X				X				X			X	
MEDICAL RESOURCE UTILIZATION and HEALTH ECONOMICS																	
MRU (Section 8.15)	X	X	X	X	X	X	X	X	X				X	X		X	X	
STUDY DRUG																	
TAR-200 Insertion Section 6.1.1	X	X	X	X	X	X	X	X					X			X*	Consider administering anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 insertion. To mitigate the risk of UTIs participants must receive at least one dose of prophylactic periprocedural antibiotics for TAR-200 insertion or removal. *TAR-200 should not be administered less than 14 days after any procedure resulting in traumatized urothelium during the biopsy (eg, gross hematuria). In the event a visit is scheduled that is within CCI window during the first 24 weeks, every attempt should be made to maintain the initial Q3W regimen for TAR-200 calculated from the date of first dose (W0D1).
TAR-200 Removal with cystoscopy Section 6.1.2		X	X	X	X	X	X	X	X					X			X	Consider administering anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 removal. To mitigate the risk of UTIs participants must receive at least one dose of prophylactic periprocedural antibiotics for TAR-200 insertion or removal. When the TAR-200 is removed, it may be replaced immediately per protocol or within the visit window CCI Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests..

Abbreviations: CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EORTC-QLQ-NMIBC24=European Organisation for Research and Treatment of Cancer -Non-Muscle Invasive Bladder Cancer Questionnaire; HbA1c=hemoglobin A1c; MRI=magnetic resonance imaging; MRU=medical resource utilization; PE=physical examination; POCBP=participant of childbearing potential, PQC=product quality complaint; Q3W=every 3 weeks; SAE=serious adverse event; TURBT= transurethral resection of bladder tumor; T3=triiodothyronine; UPC=Urinary Placement Catheter; UTI=urinary tract infection; W0D1=Week 0 Day 1.

Table 6: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities -Week C through Week C (Year C

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments are to be completed within CCI C																Notes
SAFETY ASSESSMENTS*																	*If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECGs, vital signs, blood draws, and dosing to be conducted last.
Hematology, Blood Chemistry, Coagulation Panel, Urinalysis, & Urine Culture Sections 8.11.5 and 10.2, Appendix 2			X				X				X				X		Fasting glucose is required. Coagulation Panel at CCI [redacted] T3 and HbA1c are only required as clinically indicated.
Urine Pregnancy Test (POCBP) (Pre-dose) Section 8.11.6	X*	X*	X		X*	X*	X		X*	X*	X		X*	X*	X		For POCBP, pregnancy testing should be conducted monthly through 6 months after the last dose of study drug and then as outlined in this table. In the event of a positive pregnancy test, the participant must contact the Investigator immediately. If urine pregnancy test is positive at any timepoint, a serum pregnancy test must be performed. *This assessment represents a test to be conducted between study visits.
Physical Examination & ECOG			X				X				X				X		A targeted PE and ECOG score will be assessed at timepoints to correlate with disease assessments and may also be performed at any time on study as clinically indicated.
ECG	ECG may be conducted at any time on study as clinically indicated.																
Vital Signs with weight			X	X			X	X			X	X			X	X	
Concomitant Medications			X	X			X	X			X	X			X	X	
Adverse Events/SAEs Sections 8.11, 8.11.1, 8.12, 10.4, Appendix 4, and 10.9, Appendix 9	X																AEs/SAEs should be reported at any time throughout study conduct from the time of informed consent signature to end of Follow-up Safety Visit (ie, 100-Day Safety Follow-up Visit; see Table 7)
Product Quality Complaint and Device Deficiencies Sections 8.12.8, 10.4.6, and 10.10.1			X	X			X	X			X	X			X	X	Identified PQCs and Device Deficiencies should be reported at any time throughout the Treatment Phase. If a PQC is reported for TAR-200 or IV cetrelimab, or a Device Deficiency is reported for the UPC, the respective product must be retained by the site under the appropriate storage conditions until a shipment request is received from the Sponsor. Instructions will be provided in the Study Reference Manual.
Procedures (Genitourinary and Non-Genitourinary) Section 8.11.8	X																

Table 6: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities -Week C through Week C (Year C

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments are to be completed within CCI C															Notes
DISEASE ASSESSMENTS *** NOTE: Cohort 2 participants with a CR must have a CCI disease assessment visit at CCI from the date of onset of CR. The CCI disease assessment from onset of CR may occur in lieu of CCI disease assessment, if the two visits are within 6 weeks of each other. The CCI disease assessment post initial CR date will include assessment cystoscopy, urine cytology, TURBT bladder biopsy (if clinically indicated) and CT/MRI with contrast (if applicable).**																
TURBT Bladder biopsy Section 8.10.1.3	*Only performed when clinically indicated. TURBT specimens from any timepoint should be submitted to central laboratory.															Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Assessment Cystoscopy Section 8.10.1.1			X	*	*	*	X*				X				X		Antibiotics for standard cystoscopy may be administered in accordance with standard of care. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Urine Cytology Section 8.10.1.2			X	*	*	*	X*				X				X		Urine Cytology will be sent for central review. Additionally, an aliquot of the urine should be taken from the same collections at each disease assessment visit and used for local cytopathologic evaluation to guide clinical management. Please refer to the Laboratory Manual.
CT/MRI Scan with contrast (Chest, Abdomen and Pelvis) Section 8.10.1.4				*	*	*	X*								X		
PATIENT REPORTED OUTCOME																
EORTC-QLQ-C30, Section 8.10.2.1			X				X				X				X		Complete prior to any other assessments of the day. The EORTC-QLQ-C30 will be completed before the EORTC-QLQ-NMIBC questionnaire.
EORTC QLQ NMIBC24, Section 8.10.2.2			X				X				X				X		
MEDICAL RESOURCE UTILIZATION and HEALTH ECONOMICS																
MRU Section 8.15			X				X				X				X		
STUDY DRUG ADMINISTRATION																
TAR-200 Insertion Section 6.1.1			X				X				X				X		Consider administering anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 insertion. To mitigate the risk of UTIs participants must receive at least one dose of prophylactic periprocedural antibiotics for TAR-200 insertion or removal. TAR-200 should not be administered less than 14 days after any procedure resulting in traumatized urothelium during the biopsy (eg, gross hematuria).

Table 6: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities -Week C through Week C (Year C)

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments are to be completed within CCI																Notes
	C																
TAR-200 Removal with cystoscopy Section 6.1.2				X				X				X				X	Consider administering anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 removal. To mitigate the risk of UTIs participants must receive at least one dose of prophylactic periprocedural antibiotics for TAR-200 insertion or removal. When the TAR-200 is removed, it may be replaced immediately per protocol or within the visit window CCI Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.

Abbreviations: CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EORTC-QLQ-NMIBC24=European Organisation for Research and Treatment of Cancer -Non-Muscle Invasive Bladder Cancer Questionnaire; HbA1c=hemoglobin A1c; IV=intravenous; MRI=magnetic resonance imaging; MRU=medical resource utilization; PE=physical examination; POCBP=participant of childbearing potential; PQC=product quality complaint; SAE=serious adverse event; TURBT=transurethral resection of bladder tumor; T3=triiodothyronine; UPC=Urinary Placement Catheter; UTI=urinary tract infection

Table 7: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities - Follow-up Phase

Procedures, Tests, & Evaluations	FOLLOW-UP PHASE					
	End of Treatment	30-Day Safety F/U	100 Day Safety F/U	Surveillance F/U[a, b]	Survival F/U[c]	Notes
	At completion or discontinuation of all study drug (+ 1 week).	30 days (±1 week) from the EOT visit	100 days (± 1 week) from the EOT visit	[a]Disease assessments will be performed per institutional guidelines for participants who have ended study drug but have not recurred or progressed, and will be collected at least every C weeks after EOT until disease recurrence or progression, death, withdrawal of consent or the end of the study, whichever occurs first (Section 4.4).	To be conducted every C weeks ±2 weeks	[b]For participants who discontinue study treatment before Week C (Year C), due to toxicity or reasons other than disease persistence/progression/recurrence, disease assessments should be done every C weeks CCI [Year 1] or CCI [Year 2]) before the start of subsequent therapy/procedure (eg, radical cystectomy). [c]All participants will be assessed for survival via a telephone call or other locally approved methods of contact. OS will be documented in the eCRF.
SAFETY ASSESSMENTS						
Hematology, Blood Chemistry, Coagulation Panel, Urinalysis, & Urine Culture Sections 8.11.5 and 10.2, Appendix 2	X	X	X	X[a, b]		Fasting glucose is required. Coagulation studies will not be performed during Year 3. T3 and HbA1c are only required as clinically indicated.
Urine Pregnancy Test (POCBP) Section 8.11.6	X	X	X	X[a, b]		For POCBP, pregnancy testing should be conducted monthly through 6 months after the last dose of study drug and then as outlined in this table. In the event of a positive pregnancy test, the participant must contact the Investigator immediately. If urine pregnancy test is positive at any timepoint, a serum pregnancy test must be performed.

Table 7: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities - Follow-up Phase

Procedures, Tests, & Evaluations	FOLLOW-UP PHASE					
	End of Treatment	30-Day Safety F/U	100 Day Safety F/U	Surveillance F/U[a, b]	Survival F/U[c]	Notes
	At completion or discontinuation of all study drug (+ 1 week).	30 days (±1 week) from the EOT visit	100 days (± 1 week) from the EOT visit	[a]Disease assessments will be performed per institutional guidelines for participants who have ended study drug but have not recurred or progressed, and will be collected at least every [C] weeks after EOT until disease recurrence or progression, death, withdrawal of consent or the end of the study, whichever occurs first (Section 4.4).	To be conducted every [C] weeks ±2 weeks	[b]For participants who discontinue study treatment before Week [C] (Year [C] due to toxicity or reasons other than disease persistence/progression/recurrence, disease assessments should be done every [C] weeks [CCI] [Year 1] or [CCI] [Year 2]) before the start of subsequent therapy/procedure (eg, radical cystectomy). [c]All participants will be assessed for survival via a telephone call or other locally approved methods of contact. OS will be documented in the eCRF.
Physical Examination (PE) and ECOG	X	X	X	X		A targeted PE and ECOG score will be assessed at time points to correlate with disease assessments, EOT, and at the 30- and 100-day safety follow-up visit. It may also be performed at any time on study as clinically indicated.
ECG	X					ECGs may be conducted at any time on study as clinically indicated.
Vital Signs with weight	X	X	X	X		
Concomitant Medications	X	X	X	X		
Adverse Events/SAEs Sections 8.11, 8.11.1, 8.12, 10.4, Appendix 4, and 10.10, Appendix 10	X	X	X	X*		AEs/SAEs should be reported at any time throughout study conduct from the time of informed consent signature to end of Follow-up Safety Visit. *All drug-related SAEs beyond 100 days after last dose of study drug should be reported for both treatment groups while participants are in the study Follow-up Phase.
Procedures (Genitourinary and Non-Genitourinary) Section 8.11.8	X	X	X	X	X	Procedures (eg, cystectomy) will be collected through survival follow-up
DISEASE ASSESSMENTS						
TURBT (Bladder Biopsy) Section 8.10.1.3	TURBT is not required at any specific timepoint during this phase but should be conducted as deemed clinically indicated. TURBT specimens from any time point should be submitted to central laboratory.					Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Assessment Cystoscopy Section 8.10.1.1	X*			X[a, b]		Antibiotics for standard cystoscopy may be administered in accordance with standard of care. *Cystoscopy will be performed at the EOT Visit only if needed for TAR-200 removal. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Urine Cytology Section 8.10.1.2				X[a, b]		Urine Cytology will be sent for central review. For all participants, an aliquot of the urine should be collected for local cytopathologic evaluation. Please refer to the Laboratory Manual for further instructions.
CT/MRI Scan with contrast (Chest, Abdomen and Pelvis Section 8.10.1.4	X*			X[a, b]		*To be performed per Sponsor approval as clinically indicated
PATIENT-REPORTED OUTCOME						
EORTC-QLQ-C30	X	X	X			Complete prior to any other assessments of the day. The EORTC-QLQ-C30 will be completed before the EORTC-QLQ-NMIBC questionnaire.
EORTC-QLQ NMIBC24	X	X	X			

Table 7: Cohort 2 and Cohort 4 (TAR-200 Alone) Schedule of Activities - Follow-up Phase

Procedures, Tests, & Evaluations	FOLLOW-UP PHASE					
	End of Treatment	30-Day Safety F/U	100 Day Safety F/U	Surveillance F/U[a, b]	Survival F/U[c]	Notes
	At completion or discontinuation of all study drug (+ 1 week).	30 days CCI from the EOT visit	100 days CCI from the EOT visit	[a]Disease assessments will be performed per institutional guidelines for participants who have ended study drug but have not recurred or progressed, and will be collected at least every C weeks after EOT until disease recurrence or progression, death, withdrawal of consent or the end of the study, whichever occurs first (Section 4.4).	To be conducted every C weeks ±2 weeks	[b]For participants who discontinue study treatment before Week C (Year C due to toxicity or reasons other than disease persistence/progression/recurrence, disease assessments should be done every C weeks CCI [Year 1] or CCI [Year 2]) before the start of subsequent therapy/procedure (eg, radical cystectomy). [c]All participants will be assessed for survival via a telephone call or other locally approved methods of contact. OS will be documented in the eCRF.
MEDICAL RESOURCE UTILIZATION and HEALTH ECONOMICS						
MRU Section 8.15	X	X	X	X[a, b]		Until disease recurrence/progression. If the participant ends treatment without a recurrence or progression, continue to collect until disease recurrence or progression with each disease assessment.
LONG-TERM FOLLOW-UP						
Overall Survival Section 8.7	X	X	X	X[a, b]	X	All participants will be assessed for survival via a telephone call or other locally approved methods of contact. Other methods to obtain the data per institutional SOC policy are acceptable. OS will be documented in the eCRF.
Subsequent Anti-Cancer Therapies Section 8.6	X	X	X	X[a, b]	X	
Other Malignancies	X	X	X	X[a, b]	X	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.

Abbreviations: AE=adverse event; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EORTC-QLQ-NMIBC24=European Organisation for Research and Treatment of Cancer -Non-Muscle Invasive Bladder Cancer Questionnaire; EOT=end of treatment; eCRF=electronic case report form; F/U=follow-up; HbA1c=hemoglobin A1c; MRI=magnetic resonance imaging; MRU=medical resource utilization; OS=overall survival; PE=physical examination; SAE=serious adverse event; POCBP=participant of childbearing potential; SOC=standard of care; TURBT= transurethral resection of bladder tumor; T3=triiodothyronine; UTI=urinary tract infection

Table 8: Cohort 3 (IV Cetrelimab Alone) Schedule of Activities -Treatment Phase -Week C through Week C (Year C C

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments with the exception of Week 0 are to be completed within CCI																	Notes
	C																	
SAFETY ASSESSMENTS Section 8.11																		
Physical Examination (PE) and ECOG	X				X				X				X				X	A targeted PE and ECOG score will be assessed at timepoints to correlate with disease assessments. It may also be performed at any time on study as clinically indicated.
ECG	ECG may be conducted at any time on study as clinically indicated.																	
Vital Signs with weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 8: Cohort 3 (IV Cetrelimab Alone) Schedule of Activities -Treatment Phase -Week C through Week C (Year C

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments with the exception of Week 0 are to be completed within CCI C																		Notes
Hematology, Blood Chemistry, Coagulation Panel, Urinalysis, & Urine Culture Sections 8.11.5 and 10.2, Appendix 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Glucose must be fasting while on IV cetrelimab. Coagulation Panel every CCI [redacted] T3 and HbA1c are only required as clinically indicated.
Urine Pregnancy Test (POCBP) (Pre-dose) Section 8.11.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If urine pregnancy test is positive, a serum pregnancy test must be performed.
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events/SAE Sections 8.11, 8.11.1, 8.12, and 10.9, Appendix 9	X																		AEs/SAEs should be reported at any time throughout study conduct from the time of informed consent signature to end of Follow-up Safety Visit (ie, 100-Day Safety Follow-up Visit; see Table 10)
Product Quality Complaint and Device Deficiencies Sections 8.12.8, 10.4.6, and 10.10.1	X																		Identified PQCs and Device Deficiencies should be reported at any time throughout the Treatment Phase. If a PQC is reported for TAR-200 or IV cetrelimab, or a Device Deficiency is reported for the UPC, the respective product must be retained by the site under the appropriate storage conditions until a shipment request is received from the Sponsor. Instructions will be provided in the Study Reference Manual.
Procedures (Genitourinary and Non-Genitourinary) Section 8.11.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
DISEASE ASSESSMENTS Section 8.10																			
Assessment Cystoscopy Section 8.10.1.1					X				X				X				X		Antibiotics for standard cystoscopy may be administered in accordance with standard of care. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Urine Cytology Section 8.10.1.2					X			X*	X				X			X*	X		Urine Cytology will be sent for central review. Additionally, an aliquot of the urine should be taken from the same collections at each disease assessment visit and used for local cytopathologic evaluation to guide clinical management. Please refer to the Laboratory Manual for further instructions. *Voided urine cytology collected at the Week C and Week C visits will be locally assessed to assist with biopsy planning (tumor bed biopsies/targeted or systematic bladder biopsies) at the Week C and Week C visits, respectively.

Table 8: Cohort 3 (IV Cetrelimab Alone) Schedule of Activities -Treatment Phase -Week C through Week C (Year C)

Procedures, Tests, & Evaluations	TREATMENT PHASE (WEEKS) All assessments with the exception of Week 0 are to be completed within CCI																		Notes
	C																		
TURBT (Bladder Biopsy) Section 8.10.1.3									X								X		Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
CT/MRI with contrast (Chest, Abdomen and Pelvis) Section 8.10.1.4									X								X		
PATIENT REPORTED OUTCOME Section 8.10.2																			
EORTC-QLQ-C30 Section 8.10.2.1	X		X		X				X				X				X		Complete prior to any other assessments of the day. The EORTC-QLQ-C30 will be completed before the EORTC-QLQ-NMIBC questionnaire.
EORTC-QLQ-NMIBC24 Section 8.10.2.2	X		X		X				X				X				X		
MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS																			
MRU Section 8.15	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
STUDY DRUG																			
Cetrelimab Administration Section 6.1.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	In the event a visit is scheduled that is within CCI window, every attempt should be made to maintain the initial Q3W regimen for cetrelimab calculated from the date of first dose (W0D1).

Abbreviations: CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EORTC-QLQ-NMIBC24=European Organisation for Research and Treatment of Cancer -Non-Muscle Invasive Bladder Cancer Questionnaire; HbA1c=hemoglobin A1c; IV=intravenous; MRI=magnetic resonance imaging; MRU=medical resource utilization; PE=physical examination; POCBP=participant of childbearing potential; PQC=product quality complaint; Q3W=every 3 weeks; SAE=serious adverse event; TURBT=transurethral resection of bladder tumor; T3=triiodothyronine; UPC=Urinary Placement Catheter; UTI=urinary tract infection; W0D1=Week 0 Day 1.

Table 9: Cohort 3 (Cetrelimab Alone) Schedule of Activities – Through End of Treatment Phase

Procedures, Tests, & Evaluations	TREATMENT PHASE All assessments are to be completed within CCI CC [redacted]									Notes
SAFETY ASSESSMENTS*										*If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECGs, vital signs, blood draws, and dosing to be conducted last.
Vital Signs with weight	X	X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry, Coagulation Panel, Urinalysis & Urine Culture Sections 8.11.5 and 10.2, Appendix 2	X	X	X	X	X	X	X	X	X	Glucose must be fasting while on IV cetrelimab. Coagulation Panel CCI [redacted]. T3 and HbA1c are only required as clinically indicated.
Physical Examination & ECOG			X				X			A targeted PE and ECOG score will be assessed at timepoints to correlate with disease assessments, EOT, and at the 30- and 100-day safety follow-up visit. It may also be performed at any time on study as clinically indicated.
ECG	ECG may be conducted at any time on study as clinically indicated.									
Urine Pregnancy (POCBP) (Pre-dose) Section 8.11.6	X	X	X	X	X	X	X	X	X	For POCBP, pregnancy testing should be conducted monthly through 6 months after the last dose of study drug and then as outlined in this table. In the event of a positive pregnancy test, the participant must contact the Investigator immediately. If urine pregnancy test is positive at any timepoint, a serum pregnancy test must be performed.
Concomitant Medications	X	X	X	X	X	X	X	X	X	
Adverse Events/SAEs Sections 8.11, 8.11.1, 8.12, 10.4, Appendix 4, and 10.9, Appendix 9	X	X	X	X	X	X	X	X	X	
Product Quality Complaint and Device Deficiencies Sections 8.12.8, 10.4.6, and 10.10.1	X									Identified PQCs and Device Deficiencies should be reported at any time throughout the Treatment Phase. If a PQC is reported for TAR-200 or IV cetrelimab, or a Device Deficiency is reported for the UPC, the respective product must be retained by the site under the appropriate storage conditions until a shipment request is received from the Sponsor. Instructions will be provided in the Study Reference Manual.
Procedures (Genitourinary and Non-Genitourinary) Section 8.11.8	X	X	X	X	X	X	X	X	X	
STUDY DRUG										

Table 9: Cohort 3 (Cetrelimab Alone) Schedule of Activities – Through End of Treatment Phase

Procedures, Tests, & Evaluations	TREATMENT PHASE All assessments are to be completed within CCI									Notes
	CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cetrelimab administration Sections 6.1.3, 6.5.2 and 10.9	X	X	X	X	X	X	X	X	X	
DISEASE ASSESSMENTS										
TURBT (Bladder Biopsy) Section 8.10.1.3	Only performed when clinically indicated. TURBT specimens from any timepoint should be submitted to central laboratory									Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Assessment Cystoscopy Section 8.10.1.1			X				X			Antibiotics for standard cystoscopy may be administered in accordance with standard of care. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Urine Cytology Section 8.10.1.2			X				X			Urine Cytology will be sent for central review. Additionally, an aliquot of the urine should be taken from the same collections at each disease assessment visit and used for local cytopathologic evaluation to guide clinical management. Please refer to the Laboratory Manual.
CT/MRI Scan with contrast (Chest, Abdomen, and Pelvis) Section 8.10.1.4							X			
PATIENT REPORTED OUTCOME										
EORTC-QLQ-C30 Section 8.10.2.1			X				X			Complete prior to any other assessments of the day. The EORTC-QLQ-C30 will be completed before the EORTC-QLQ-NMIBC questionnaire.
EORTC-QLQ NMIBC24 Section 8.10.2.2			X				X			
MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS										
MRU Section 8.15	X	X	X	X	X	X	X	X	X	If the participant ends treatment without a recurrence or progression, continue to collect until disease recurrence or progression with each disease assessment.

Abbreviations: CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EORTC-QLQ-NMIBC24=European Organisation for Research and Treatment of Cancer -Non-Muscle Invasive Bladder Cancer Questionnaire; EOT=end of treatment; HbA1c=hemoglobin A1c; IV=intravenous; MRI=magnetic resonance imaging; MRU=medical resource utilization; PE=physical examination; POCBP=participant of childbearing potential; PQC=product quality complaint; SAE=serious adverse event; TURBT= transurethral resection of bladder tumor; T3=triiodothyronine; UPC=Urinary Placement Catheter; UTI=urinary tract infection

Table 10: Cohort 3 (Cetrelimab Alone) Schedule of Activities: Follow-up Phase

Procedures, Tests, & Evaluations	FOLLOW-UP PHASE					
	End of Treatment	30-Day Safety F/U	100 Day Safety F/U	Surveillance F/U[a, b]	Survival F/U[c]	Notes
	At completion or discontinuation of all study drug (+ 1 week).	30 days CCI from the EOT visit	100 days CCI from the EOT visit	[a]Disease assessment follow-up will be performed per institutional guidelines for participants who have ended study drug but have not recurred or progressed, and will be collected at least every C weeks until disease recurrence or progression, death, withdrawal of consent or the end of the study, whichever occurs first (Section 4.4).	To be conducted every C weeks ±2 weeks	[b]For participants who discontinue study treatment before Week C (Year C), due to toxicity or reasons other than disease persistence/progression/recurrence, disease assessments should be done every CCI CCI [Year 1] or CCI [Year 2]) before the start of subsequent therapy/procedure (eg, radical cystectomy). [c]All participants will be assessed for survival via a telephone call or other locally approved methods of contact. OS will be documented in the eCRF.
SAFETY ASSESSMENT						
Hematology, Blood Chemistry, Coagulation Panel, Urinalysis & Urine Culture Sections 8.11.5 and 10.2, Appendix 2	X	X	X	X[a, b]		Glucose must be fasting through the 100-day safety follow-up visit while on cetrelimab. Coagulation studies will not be performed during Year 3. T3 and HbA1c are only required as clinically indicated.
Urine Pregnancy Test (POCBP) Section 8.11.6	X	X	X	X[a, b]		For POCBP, pregnancy testing should be conducted monthly through 6 months after the last dose of study drug and then as outlined in this table. In the event of a positive pregnancy test, the participant must contact the Investigator immediately. If urine pregnancy test is positive at any timepoint, a serum pregnancy test must be performed.
Physical Examination and ECOG	X	X	X	X		A targeted PE and ECOG score will be assessed at time points to correlate with disease assessments, EOT, and at the 30- and 100-day safety follow-up visit. It may also be performed at any time on study as clinically indicated
ECG	X					ECGs may be conducted at any time on study as clinically indicated.
Vital Signs with weight	X	X	X	X		
Concomitant Medications	X	X	X	X		
Adverse Events/SAEs Sections 8.11, 8.11.1, 8.12, 10.4, Appendix 4, and 10.9, Appendix 9	X	X	X	X*		AEs/SAEs should be reported at any time throughout study conduct from the time of informed consent signature to end of Follow-up Safety Visit *All drug-related SAEs beyond 100 days after last dose of study drug should be reported for both treatment groups while participants are in the study Follow-up Phase.
Procedures (Genitourinary and Non-Genitourinary) Section 8.11.8	X	X	X	X	X	Procedures (eg, cystectomy) will be collected through survival follow-up

Table 10: Cohort 3 (Cetrelimab Alone) Schedule of Activities: Follow-up Phase

Procedures, Tests, & Evaluations	FOLLOW-UP PHASE					
	End of Treatment	30-Day Safety F/U	100 Day Safety F/U	Surveillance F/U[a, b]	Survival F/U[c]	Notes
	At completion or discontinuation of all study drug (+ 1 week).	30 days [redacted] from the EOT visit	100 days [redacted] from the EOT visit	[a]Disease assessment follow-up will be performed per institutional guidelines for participants who have ended study drug but have not recurred or progressed, and will be collected at least every [redacted] weeks until disease recurrence or progression, death, withdrawal of consent or the end of the study, whichever occurs first (Section 4.4).	To be conducted every [redacted] weeks ±2 weeks	[b]For participants who discontinue study treatment before Week [redacted] (Year [redacted], due to toxicity or reasons other than disease persistence/progression/recurrence, disease assessments should be done every [redacted] weeks [redacted] [Year 1] or [redacted] [Year 2]) before the start of subsequent therapy/procedure (eg, radical cystectomy). [c]All participants will be assessed for survival via a telephone call or other locally approved methods of contact. OS will be documented in the eCRF.
DISEASE ASSESSMENTS						
TURBT (bladder biopsy) Section 8.10.1.3	TURBT is not required at any specific timepoint during this phase but should be conducted as deemed clinically indicated. TURBT specimens from any time point should be submitted to central laboratory.					Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Assessment Cystoscopy Section 8.10.1.1				X[a, b]		Antibiotics for standard cystoscopy may be administered in accordance with standard of care. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.
Urine Cytology Section 8.10.1.2				X[a, b]		Urine Cytology will be sent for central review. For all participants, an aliquot of the urine should be collected for local cytopathologic evaluation. Please refer to the Laboratory Manual for further instructions.
CT/MRI Scan with contrast (Chest, Abdomen, and Pelvis) Section 8.10.1.4	X*			X[a, b]		*To be performed per Sponsor approval as clinically indicated
PATIENT-REPORTED OUTCOME						
EORTC-QLQ-C30 Section 8.10.2.1	X	X	X			Complete prior to any other assessments of the day. The EORTC-QLQ-C30 will be completed before the EORTC-QLQ-NMIBC questionnaire.
EORTC-QLQ-NMIBC24 Section 8.10.2.2	X	X	X			
MEDICAL RESOURCE UTILIZATION and HEALTH ECONOMICS						
MRU Section 8.15	X	X	X	X[a, b]		Until disease recurrence/progression. If the participant ends treatment without a recurrence or progression, continue to collect until disease recurrence or progression with each disease assessment.
LONG-TERM FOLLOW-UP						
Overall Survival Status Section 8.7	X	X	X	X[a, b]	X	All participants will be assessed for survival via a telephone call or other locally approved methods of contact. Other methods to obtain the data per institutional SOC policy are acceptable. OS will be documented in the eCRF.
Subsequent Anti-Cancer Therapies	X	X	X	X[a, b]	X	

Table 10: Cohort 3 (Cetrelimab Alone) Schedule of Activities: Follow-up Phase

Procedures, Tests, & Evaluations	FOLLOW-UP PHASE					
	End of Treatment	**30-Day Safety F/U**	**100 Day Safety F/U**	**Surveillance F/U[a, b]**	**Survival F/U[c]**	**Notes**
	At completion or discontinuation of all study drug (+ 1 week).	30 days [redacted] from the EOT visit	100 days [redacted] from the EOT visit	[a]Disease assessment follow-up will be performed per institutional guidelines for participants who have ended study drug but have not recurred or progressed, and will be collected at least [redacted] weeks until disease recurrence or progression, death, withdrawal of consent or the end of the study, whichever occurs first (Section 4.4).	To be conducted every [redacted] weeks ±2 weeks	[b]For participants who discontinue study treatment before Week [redacted] (Year [redacted], due to toxicity or reasons other than disease persistence/progression/recurrence, disease assessments should be done every [redacted] weeks [redacted] [Year 1] or [redacted] [Year 2]) before the start of subsequent therapy/procedure (eg, radical cystectomy). [c]All participants will be assessed for survival via a telephone call or other locally approved methods of contact. OS will be documented in the eCRF.
Section 8.6						
Other Malignancies	X	X	X	X[a, b]	X	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.

Abbreviations: AE=adverse event; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30= European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EORTC-QLQ-NMIBC24= European Organisation for Research and Treatment of Cancer -Non-Muscle Invasive Bladder Cancer Questionnaire; EOT=end of treatment; F/U= follow-up; HbA1c=hemoglobin A1c; MRI=magnetic resonance imaging; MRU= medical resource utilization; OS=overall survival; PE=physical examination; POCBP=participant of childbearing potential; SAE=serious adverse event; SOC=standard of care; TURBT= transurethral resection of bladder tumor; T3=triiodothyronine; UTI=urinary tract infection

Table 11: Sparse Urine Pharmacokinetics - (All Participants in Cohort 1, Cohort 2, and Cohort 4) See Section 8.13.1.1

VISIT	PRIOR TO TAR-200 INSERTION	POST TAR-200 INSERTION
Within 24 Hours Pre-dose at Week C C	X[a] Single Sample Collection	
Anytime between Days 2 to7, following TAR-200 insertion on either Week CCI		X[a] One pooled 24-hour Collection
Anytime between Days 2 to 7, following TAR-200 insertion on either Week CCI		X One pooled 24-hour Collection

Abbreviations: PK=pharmacokinetic
[a]Participants in the serial urine PK sampling are not required to complete the Week C C and Week CCI sparse timepoints.

Table 12: Serial Urine Pharmacokinetics – (approximately 40 Participants Across Cohort 1 and Cohort 2) See Section 8.13.1.2

VISIT	PRIOR TO TAR-200 INSERTION	POST TAR-200 INSERTION
Within 24 Hours Pre-dose at Week C C	X Single Sample Collection	
Beginning at Week C C, on all days from Days 1 through Day 7		X One pooled 24-hour Collection per day
Beginning at Week CCI on all days from Days 1 through Day 7		X One pooled 24-hour Collection per day

Note: It is anticipated that 40 participants in Cohort 1 and Cohort 2 will participate in the serial urine sampling. Sample collections and analysis will only be performed as local regulations permit.

Table 13: Plasma Pharmacokinetics - (All Participants in Cohorts 1 and Cohort 2) See Section 8.13.1.3

VISIT	PRIOR TO TAR-200 INSERTION	POST TAR-200 INSERTION
Within 24 hours Pre-dose at Week C C	X	
Anytime between Days 2 to 7, following TAR-200 insertion on either Week CCI		X One Sample Collection Coincide with sparse Urine PK
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=pharmacokinetic
Note: For the subset of participants included in serial urine sampling, plasma pharmacokinetic collection anytime between Days 2 to 7 of Week 0 will be obtained. Sample collections and analysis will only be performed as local regulations permit.

Table 14: Serum Pharmacokinetics for Cetrelimab- (Cohort 1 and Cohort 3) See Section 8.13.1.4

Time Points	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]
Pre-dose (trough) Draw within 30 minutes before cetrelimab Infusion	X	X	X	X	X	X	X*
End of Infusion (EOI) In the opposite arm; if Central Line, collect from the opposite side of the body	X	X	X	X	X	X	

* One sample to be collected at the Week [redacted] visit.
Note: Sample collection and analysis will only be performed as local regulations permit.

Table 15: Serum Immunogenicity for Cetrelimab- (Cohort 1 and Cohort 3) See Section 8.13.1.4

Time Points	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]
Pre-dose (trough) Draw within 30 minutes before Cetrelimab Infusion	X	X	X	X	X	X*

* One sample to be collected at the Week [redacted] visit.
Note: Sample collections and analysis will only be performed as local regulations permit.

Table 16: Biomarker Tissue Collection – Treatment Phase - (Cohort 1, Cohort 2, and Cohort 3 Only) See Section 8.14

Biomarker	Specimen	Pre-dose	At time of Persistence, Recurrence or Progression
IHC	Tissue from biopsy	X	X
RNA/DNA Sequencing	Tissue from biopsy	X	X

Abbreviations: IHC=immunohistochemistry
Note: For participants in Cohort 4, biomarker collections will not be performed.

Table 17: Biomarker Blood Collection – Treatment Phase - (Cohort 1, Cohort 2, and Cohort 3 Only) See Section 8.14

Biomarker	Specimen	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]	Week [redacted]
Blood biomarker	Whole Blood	X	X	X	X		X	X		
TCR Seq	Whole Blood	X	X	X		X	X	X		

Abbreviations: TCR Seq=T-cell receptor sequencing
Note: For participants in Cohort 4, biomarker collections will not be performed.

Table 18: Biomarker Urine Collection – Treatment Phase - (Cohort 1, Cohort 2, and Cohort 3 Only) See Section 8.14

Biomarker	Specimen	Week C	Week C	Week C	Week C	Week C	Week C	Week CC	Week CC
Urine biomarkers[a]	Urine	X	X	X	X	X	X	X	X

[a] Urine biomarkers will be taken from the residual urine cytology sample.
[b] For Cohorts 1 and 2 only.
Note: For participants in Cohort 4, biomarker collections will not be performed.

Table 19: Biomarker Collection – Follow-up Phase - (Cohort 1, Cohort 2, and Cohort 3 Only) See Section 8.14

Procedures, Tests, & Evaluations	FOLLOW-UP PHASE					
	End of Treatment	30-Day Safety F/U	100 Day Safety F/U	Surveillance F/U	Survival F/U	Notes
	At completion or discontinuation of all study drug (+ 1 week).	30 days (+1 week) from the EOT visit	100 days (± 1 week) from the EOT visit	Samples will be collected at the time of Surveillance F/U visits as described in Table 4 for Cohort 1, Table 7 for Cohort 2, and Table 10 for Cohort 3.	To be conducted every C weeks ±2 weeks	
BIOMARKER URINE COLLECTION						
Urine biomarkers				X		Urine biomarkers will be taken from the residual urine cytology sample.

Abbreviations: F/U=follow-up

2. INTRODUCTION

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 (PMOA). The TAR-200 consists of 2 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 comprises 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 refer to as "UPC"). TAR-200 is removed from the bladder transurethrally via cystoscopy and non-cutting endoscopic grasping forceps.

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 5). Refer to Appendix 2 of the TAR-200 Investigator's Brochure (IB) for further details regarding the UPC.

TAR-200 is a flexible bi-oval shaped like a "pretzel." The product size is visually comparable to the size of an American 25-cent coin or a European 2-Euro coin (Figure 4). It is submerged and freely mobile in the urine while indwelling in the bladder.

Figure 4: TAR-200

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), and enhances pro-inflammatory cytokine production. Two recommended Phase 2 doses (RP2Ds) for intravenous (IV) cetrelimab were established in Part 1 and 2 of Study 63723283LUC1001, an ongoing, multi-center, Phase 1/2 First in Human (FIH) study of IV cetrelimab monotherapy in participants with advanced solid

tumor malignancies. In this study, cetrelimab was administered IV at doses ranging from 80 mg every 2 weeks (Q2W) up to 800 mg once every 4 weeks (Q4W). Dosing 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 IV cetrelimab. The planned dose in this Phase 2b study is 360 mg every 3 weeks (Q3W).

Combining TAR-200 with IV cetrelimab, with TAR-200 local delivery of cytotoxic therapy, may enable tumor-lysis and enhance tumor antigen release.

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."

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 United States (National Cancer Institute 2020). Approximately 550,000 new bladder cancer cases occurred worldwide in 2018 (WCRF 2020). In the United States, the prevalence of people living with bladder cancer was 699,450 in 2016 and the National Cancer Institute estimated that 80,470 new cases and 17,670 deaths occurred in the year 2019 (NCI 2020). Bladder cancer can be clinically classified as either muscle invasive bladder cancer (MIBC) or non-muscle invasive bladder cancer (NMIBC) based on the involvement of the detrusor muscle. About 75% of bladder cancers are nonmuscle invasive at diagnosis and the majority are histologically low-grade (Bray 2018), with approximately 25% of NMIBC patients having high-risk (HR)-NMIBC, defined as high-grade papillary tumor Ta (pTa), papillary tumor Tis (pTis), or papillary tumor T1 (pT1) (Herr 2001). In NMIBC, approximately 70% of patients present as pTa, 20% as pT1, and 10% with carcinoma in situ (CIS) lesions (Bas 2009). The natural history of HR-NMIBC is unpredictable; rates of recurrence vary from 15% to 78%, and rates of progression to muscle invasion and metastasis vary from <1 to 45% (Sylvester 2006). Long-term outcomes suggest that approximately 20% to 25% of these patients die from bladder cancer (Thomas 2013).

The mainstay of treatment for HR-NMIBC is transurethral resection of bladder tumor (TURBT, biopsy only for patients with CIS), followed by intravesical treatment with BCG. Primary radical cystectomy (RC) is an option for some patients. BCG dosing includes an initial induction treatment course, followed by maintenance therapy for up to 3 years (Chang 2016, AJCC 2017, Babjuk 2016). Adjuvant intravesical BCG therapy is employed as a therapeutic treatment for patients with CIS tumors, as well as a prophylactic treatment for patients with high-risk resected Ta or T1 papillary tumors (Lamm 2000).

BCG therapy has been demonstrated to be superior to resection alone for the prevention of recurrence of HR-NMIBC (Shelley 2001). Subsequent meta-analyses have exhibited the superiority of BCG after resection compared with resection alone or compared with intravesical

chemotherapy in preventing recurrences (Han 2006, Shelley 2004). Another meta-analysis showed that intravesical induction and maintenance BCG reduces the risk of disease recurrence by 32% compared with intravesical mitomycin C (MMC) (Malmstrom 2009).

While BCG therapy is often successful at preventing early tumor recurrences in patients with HR-NMIBC, most patients do not maintain sustained remissions (Shelley 2000). BCG treatment eventually fails in up to 50% of patients; almost 50% of these failures occur within the first 6 months (Lightfoot 2011). Thus, many patients will ultimately develop BCG-unresponsive disease.

BCG-unresponsive HR-NMIBC is defined as persistent disease despite adequate BCG therapy, disease recurrence after initially achieving a tumor-free state after adequate BCG, or T1 tumors following a single induction course of BCG (Lerner 2009, Food and Drug Administration 2018). Adequate BCG therapy is defined as a minimum of 5 of 6 full doses of an induction course (adequate induction) plus 2 of 3 doses of a maintenance course, or at least 2 of 6 doses of a second induction course (Food and Drug Administration 2018).

Once the disease progresses to MIBC, prognosis is poor, even with combined-modality therapy, with a 10-year overall survival (OS) of 36%. Hence, RC is considered the standard of care for any patient with BCG-unresponsive high-grade NMIBC (Babjuk 2016). Radical cystectomy entails high morbidity (up to 60%) and negatively affects HRQoL. These complications occur even in high-volume centers of excellence and regardless of surgical technique or approach (Shabsigh 2009). The procedure itself has a mortality rate of 3% (Stein 2001). Hence, some patients refuse surgery. Additionally, some patients are medically unfit for surgery due to such factors as age, poor functional status, high American Society of Anesthesiologists Class Score, medical co-morbidities, and increased body mass index.

Because 30% to 40% of patients will experience recurrence after BCG therapy, and because the utility of RC is limited by various underlying factors previously discussed, there exists a significant clinical need for alternative treatment options following BCG failure. Valrubicin is one of the few intravesical therapies approved by the US Food and Drug Administration (FDA) for the treatment of BCG-refractory CIS in patients who are unfit or unwilling to undergo cystectomy. The complete response (CR) rate following valrubicin treatment is 18% at 6 months; only 4% of patients are disease-free 2 years after therapy (Steinberg 2000).

A study of systemic pembrolizumab monotherapy in patients with BCG-unresponsive HR-NMIBC demonstrated a CR rate of 41.2% at 3 months in participants with CIS with or without papillary disease and a 43.5 % 12-month DFS rate in participants with papillary disease only (Balar 2021; Necchi 2023. Seventeen percent of patients with CIS were disease-free at CCI In a separate study, nadofaragene firadenovec, a non-replicating adenovirus vector harboring the human interferon (IFN) alpha2b gene for intravesical instillation, resulted in a CR rate of 53% at 3 months for CIS and a 43.8% 12-month high-grade recurrence-free survival rate in participants with papillary disease only (Boorjian 2021). However, only 24.3% of patients with CIS were still free of disease at CCI Because these recent advances in the treatment of BCG-unresponsive NMIBC continue to lack long-term disease-free outcomes, there remains a significant unmet need for effective and durable treatments in the BCG-unresponsive HR-NMIBC. Further, papillary disease

represents a significant portion of this disease, and approved treatment options to date are limited to the CIS population.

The TAR-200 platform is an innovative advancement in the field of urologic drug delivery that has the potential to be a CCI [redacted] As an intravesical drug delivery system, the TAR-200 approach may:

- Minimize systemic exposure and associated adverse events (AEs) of current therapies due to continuous low dosing.
- Lower the rate of tumor recurrence.
- Maximize targeted drug exposure within the bladder.
- Improve outcomes of TURBT and improve the response to subsequent immunotherapies/chemotherapies that the patient may receive.
- Reduce the number of urethral catheterizations required with current intravesical treatments and consequently improve the patient's treatment experience and quality of life.

In this clinical study, we hypothesize that metronomic dosing of intravesical gemcitabine delivered via the TAR-200 will not only have marked local cytotoxic effects on HR-NMIBC, but may also increase tumor antigen presentation and tumor antigen specific T-cell activation and maintenance. If these T-cells are activated by co-treatment with systemic cetrelimab, the PD1 inhibitor, enhanced local and systemic anti-tumor activity may result, with benefit in HR-NMIBC patients unresponsive to prior intravesical BCG therapy.

The expected toxicities of IV cetrelimab and TAR-200 are non-overlapping, and the safety of checkpoint inhibitors in combination with systemic gemcitabine has been well-established in the setting of non-small cell lung cancer (NSCLC) (Rizvi 2016). Therefore, in the absence of concerns regarding pharmacokinetic (PK) and pharmacodynamic interactions, the proposed Phase 2b study has been devised to evaluate the efficacy of combination systemic and intravesical therapy in participants with HR-NMIBC unresponsive to prior intravesical BCG therapy. It is believed that this dual immunomodulatory approach will both exploit and enhance the immunogenicity of IV cetrelimab, leading to a safe and potentially effective treatment for patients with a demonstrated clinical need.

2.2. Background

2.2.1. TAR-200 Nonclinical Studies

Nonclinical studies have demonstrated that bladder concentrations of gemcitabine following administration of TAR-200 in minipigs are sufficient to achieve tissue concentrations that are expected to be tumoricidal.

A non-Good Laboratory Practice (non-GLP) toxicology study of TAR-200 in minipigs has demonstrated that average bladder urine concentrations of CCI [redacted] and above are achieved over a 7-day dosing cycle, resulting in no or low plasma levels of gemcitabine. In this study, minimal

changes in hematological tests, clinical chemistry tests, and urinalyses were noted in animals treated with 1 deployment of TAR-200 or 2 sequential 7-day deployments of TAR-200. Histopathologic data in this study indicate that minimal and reversible local changes in the bladder are anticipated following insertion of TAR-200 in participants, assuming urine output is in the typical range. Administration of 2 TAR-200 simultaneously in this study resulted in greater urinary concentrations and more pronounced clinical and histopathological findings.

A GLP toxicology study comparing TAR-200 to placebo demonstrated that quantifiable urine gemcitabine concentrations occurred within 24 hours and levels at or above CCI were generally maintained over a 7-day dosing cycle in minipigs. No quantifiable levels of gemcitabine were observed in plasma. Administration of TAR-200 was associated primarily with mild urothelial inflammation in the bladder based on the hematology, clinical chemistry, gross pathology, and microscopic observations. The urothelial changes tended to be mild in severity and transient as complete resolution was observed following the 14-day recovery period.

Published nonclinical studies evaluating the PK of gemcitabine following intravesical administration indicate that systemic absorption is limited or undetectable in pigs and rabbits (Witjes 2004; Matera 2004). In dogs, systemic absorption was observed, but therapeutic doses were well tolerated (Cozzi 1999). Toxicology studies indicate minimal bladder-specific toxicity and limited systemic toxicity at clinically active doses.

See the TAR-200 Investigator's Brochure (IB) for more information on TAR-200 nonclinical studies.

2.2.2. Cetrelimab Nonclinical Studies

Nonclinical Pharmacology

PD-1 blockade with cetrelimab enhanced T-cell function in vitro, as evidenced by dose dependent increases in pro-inflammatory cytokine levels in mixed lymphocyte reaction (MLR) and cytomegalovirus (CMV) recall assays. In addition, cetrelimab reversed PD-1 mediated suppression of T-cell receptor signaling by promoting nuclear factor of activated T-cells (NFAT)-reporter transcriptional activity in Jurkat T-cell lines. The in vitro activity of cetrelimab was consistent with that observed for nivolumab and pembrolizumab analogues in the MLR, CMV, and NFAT- reporter assays. In vivo, cetrelimab also inhibited tumor growth in human PD-1 knock-in mice bearing MC38 murine colon carcinoma tumors and showed antitumor efficacy consistent with that of a nivolumab analogue.

Toxicology

Data from the 4- and 5-week toxicology studies in cynomolgus monkeys indicate cetrelimab was clinically well tolerated and demonstrated evidence of pharmacology (T-cell dependent antibody response enhancement). No cetrelimab-related effects were noted in cardiovascular, respiratory, or central nervous system during the 5-week study. Primary cetrelimab-related findings noted in 4- and 5-week monkey studies at CCI included slight increases in monocyte counts and prothrombin times in the 4-week study, and slight increases in prothrombin times. In the 5-week study, the no-observed-adverse-effect level was CCI (mean

C_{max} [redacted] and $AUC_{Day29-36}$ [redacted] following the dose on Day 29). Cetrelimab cytokine response in vitro in human blood was similar to other immune-modulatory compounds with a low risk of cytokine release syndrome.

See the cetrelimab IB for more information on cetrelimab nonclinical studies.

2.2.3. TAR-200 Clinical Studies

The clinical development program for TAR-200 consists of 4 prospective, open-label Phase 1b clinical studies, 2 Phase 2 studies (including this study), and 2 Phase 3 studies evaluating TAR-200 in bladder cancer participants. These studies are described in the sections that follow. Refer to the IB for further details on the completed and ongoing TAR-200 clinical studies and published clinical studies investigating intravesical gemcitabine in urothelial carcinoma. As of 12 January 2023, approximately [redacted] participants have been treated with TAR-200 alone and approximately [redacted] participants have been treated with the TAR-200 + IV cetrelimab combination in TAR-200 clinical studies in participants with NMIBC or MIBC.

2.2.3.1. Clinical Development Plan in Muscle Invasive Bladder Cancer

Phase 1 Studies in Patients With MIBC

Study TAR-200-101 (NCT02722538) was a prospective, multi-center, 2-arm, open-label, Phase 1b study of gemcitabine delivered intravesically by TAR- 200 to participants with MIBC (stage cT2 to T3b) prior to undergoing RC. Safety, tolerability, preliminary efficacy, and PK were evaluated. Twenty-three participants underwent at least 1 dosing cycle and 20 participants completed both dosing cycles. This study demonstrated that TAR-200 had encouraging anti-tumor activity in MIBC (Daneshmand 2022). Overall, administration of TAR-200 was well tolerated in the study. This study was completed on 02 May 2019.

Phase 1b Study TAR-200-104 (NCT03518320) was a prospective, multi-center, open-label study evaluating the combination of TAR-200 and nivolumab in participants with MIBC who were scheduled for RC and ineligible for or refusing platinum-based neoadjuvant chemotherapy. Participant were to receive 4 consecutive 21-day dosing cycles of TAR-200, with nivolumab administered by IV infusion within 3 days of each placement of TAR-200, prior to RC. Enrollment and dosing were voluntarily suspended in July 2019 due to business reasons. This early study termination was not due to safety concerns. This study was completed on 11 December 2019.

Study TAR-200-103 (NCT03404791) was a prospective, multi-center, open-label Phase 1b study of participants with MIBC who were medically unfit for RC and ineligible to receive or refuse cisplatin-based systemic chemotherapy. The study evaluated 4 consecutive 21-day dosing cycles followed by one 21-day dosing cycle every 3 months for 3 cycles (Tyson 2021). Overall, administration of TAR-200 was well tolerated in this study. This study was completed on 15 September 2022.

Additional descriptions of each study's design, population, dose regimen, and primary objectives are provided in Table 1 of the TAR-200 IB.

Phase 2 Study 17000139BLC2002 - Ongoing

This is a global, prospective, multicenter, open-label, randomized Phase 2 study of TAR-200 in combination with IV cetrelimab and IV cetrelimab alone in participants with MIBC (cT2-T4a, N0, M0) who are scheduled for RC and are ineligible for or refusing platinum-based neoadjuvant chemotherapy. This study seeks to evaluate the percentage of participants with a pathologic CR (ypT0N0) derived from analysis of RC bladder specimens. This study is ongoing with planned enrollment of 160 participants.

Phase 3 Study 17000139BLC3001 - Ongoing

This is a global, prospective, multi-center, open-label, randomized Phase 3 study of the efficacy and safety of intravesical TAR-200 plus IV cetrelimab versus concurrent chemoradiotherapy in participants with diagnosis of MIBC (cT2-T4a, N0, M0), who are ineligible or refuse RC. This study seeks to evaluate if combination treatment with intravesical TAR-200 and IV cetrelimab in participants with cT2-T4a, N0, M0 MIBC will lead to improved bladder intact event- free survival (BI-EFS) as compared with participants receiving concurrent chemoradiotherapy. This study is ongoing with planned enrollment of CCI participants.

Phase 3 Study 17000139BLC3002 - Ongoing

This is a global, prospective, multi-center, open-label, randomized Phase 3 study of the efficacy and safety of intravesical TAR-200 plus IV cetrelimab or TAR-200 alone versus intravesical BCG in participants with BCG-naïve HR-NMIBC. This study seeks to evaluate if combination treatment with intravesical TAR-200 and IV cetrelimab or TAR-200 alone in participants with with BCG-naïve HR-NMIBC will lead to improved EFS as compared with participants receiving intravesical BCG. This study is ongoing.

2.2.3.2. Clinical Development Plan in Non-Muscle Invasive Bladder Cancer

Phase 1b Study TAR-200-102 (NCT02720367)

TAR-200-102 (NCT02720367) was a prospective, multi-center, open-label, Phase 1b study of gemcitabine delivered intravesically by TAR-200 to 12 participants with recurrent low- or intermediate-risk (IR)-NMIBC between diagnosis and TURBT. This window-of-opportunity study evaluated the safety, tolerability, and preliminary anti-tumor effects of continuous release of intravesical gemcitabine as delivered by TAR-200 over 2 dosing cycles, prior to undergoing TURBT. Administration of TAR-200 was well tolerated in this study. This study was completed on 03 March 2020.

Additional descriptions of the study design, population, dose regimen, and primary objectives are provided in Table 1 of the TAR-200 IB.

2.2.4. Cetrelimab Clinical Studies

Clinical experience with cetrelimab in humans to date is based on data from 9 clinical studies, 3 monotherapy studies (63723283LUC1001, 63723283HPB1001, and 63723283LUC1002 [Part 1]) and 6 combination studies, non-inclusive of those with TAR-200 (63723283LUC1002

[Part 2], 54767414MMY2036, 64091742PCR2002, 42756493BLC2002, 56021927PCR2032, and 64407564MMY1005).

As of the clinical cut-off date of 01 September 2022, up to CCI participants had received at least one dose of cetrelimab in cetrelimab studies (excluding studies in combination with TAR-200). Of these, CCI participants were treated for cancer (selected advanced cancers including NSCLC, melanoma, renal, bladder, small cell lung cancer [SCLC], gastric/esophageal cancer, high-level microsatellite instability or mismatch-repair deficiency colorectal cancer [MSI-H/dMMR CRC], metastatic castration-resistant prostate cancer, metastatic or locally advanced urothelial cancer, and multiple myeloma), and at least CC participants were treated for bladder cancer in studies 63723283LUC1001 and 42756493BLC2002 (refer to the cetrelimab IB).

In addition, as of the cut-off date of 12 January 2023, CCI participants with early bladder cancer had been treated with cetrelimab (alone or in combination with TAR-200) in TAR-200 studies. For studies in combination with TAR-200, refer to Section 2.2.5.

In an ongoing FIH open-label, multi-center, Phase 1/2 study (63723283LUC1001), participants with selected solid tumor types who previously received or were ineligible for standard treatment options were enrolled. For the most comprehensive clinical information regarding cetrelimab IV, refer to the cetrelimab IB.

Part 1 of Study 63723283LUC1001 evaluated dose escalation cohorts and PK/pharmacodynamics cohorts of cetrelimab administered IV. Part 1 established the IV RP2D, which may be administered at either 240 mg Q2W or 480 mg Q4W. In Part 2, initiated on 03 May 2017, the IV cetrelimab RP2D dose of 240 mg Q2W was evaluated in selected solid tumor types, including NSCLC, melanoma, renal cancer, bladder cancer, SCLC, gastric/esophageal cancer, and MSI-H/dMMR CRC. The purposes of dose expansion in Part 2 are to further characterize the safety and to assess the antitumor activity of the IV RP2D of cetrelimab.

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 CCI treated participants was CCI with CC participants having a confirmed response of CR or partial response (PR). The complete benefit rate (CBR) by RECIST 1.1 for all treated participants was CCI, with CC participants having a confirmed response of CR, PR, or stable disease for at least 24 weeks from the start of treatment. CCI participants CCI experienced at least 1 treatment-emergent adverse event (TEAE); 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=CC participants; melanoma=CCI participants; bladder=CC participants; renal cell=CC participants; SCLC: CC participants; MSI-H/dMMR CRC=CC participants; other=participants).

After a single IV infusion of cetrelimab, mean C_{max} ranged from CCI cetrelimab to CCI cetrelimab. Mean $AUC_{0\text{-}336h}$ ranged from CCI

cetrelimab to [redacted] cetrelimab. The linear increase in C_{max} and AUC with dose suggests dose dependency and dose proportionality for the IV dose range that has been evaluated in Study 63723283LUC1001. Mean $t_{1/2}$ after a single IV infusion ranged from [redacted] to [redacted] hours, or [redacted] to [redacted] days.

As of the PK data cut-off date of 03 December 2019 the PK analysis included a total of [redacted] 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 [redacted] days, indicating that steady state of serum cetrelimab concentration would be reached around approximately [redacted] weeks in advanced cancer patients, similar to endogenous immunoglobulins. Full PD-1 receptor occupancy with cetrelimab was sustained for both 240 mg IV Q2W and 480 mg IV Q4W. The IV RP2Ds for cetrelimab (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 cetrelimab in Study 63723283LUC1001 was low, [redacted] ([redacted]. The [redacted] participants with positive antibody titers were included in Part 2 and received 240 mg IV cetrelimab Q2W. [redacted] 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. [redacted] 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.

For this study (17000139BLC2001), cetrelimab will be dosed at 360 mg Q3W IV to align with the dosing frequency of TAR-200. The Q3W regimen can be supported based on population PK modeling and simulation of cetrelimab, which demonstrated that the steady-state C_{trough} and C_{max} of IV cetrelimab attained is between the values from the 2 established IV RP2Ds (240 mg Q2W and 480 mg Q4W).

For the most comprehensive nonclinical and clinical PK information regarding cetrelimab, refer to the IB for additional details.

2.2.5. Combination Therapy

In addition to this study, TAR-200 in combination with IV cetrelimab is currently being evaluated in 2 ongoing studies: 17000139BLC3001 (NCT04658862) in patients with MIBC who are not receiving RC, and 17000139BLC2002 (NCT04919512) in patients with MIBC who are scheduled for RC and are ineligible for or refusing platinum-based neoadjuvant chemotherapy (see Section 2.2.3.1). However, no formal data on tolerability, safety, PK, or efficacy on this combination in humans are available to date. As of 12 January 2023, [redacted] participants have been treated with at least one dose of the TAR-200 + IV cetrelimab combination in the 3 studies.

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 HNT 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 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 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 [redacted]
5. CCI [redacted] CCI [redacted] 016);
6. Activated effector CD4+ T-cells increased 3- to 4-fold with intravesical gemcitabine perfusion in rat models. Additionally, the $T_{regulatory}$ to $T_{effector}$ ratio improved with gemcitabine treatment, favoring enhanced CD4 effector T-cell activity (Giesing 2018);
7. Activated effector CD8+ populations increased 2- to 3-fold with intravesical gemcitabine perfusion in rat models. The ratio of $T_{effector}$:$T_{regulatory}$ also increased with gemcitabine treatment, favoring increased CD8 activity (Giesing 2018);
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 patients with pancreatic cancer receiving gemcitabine, the ratio of $T_{effector}$:$T_{regulatory}$ was increased, myeloid derived suppressor cells (MDSCs) were decreased, TGFβ-1 levels were reduced, and the proliferative ability of T-cells was unaffected (Eriksson 2016);
9. In rat models, tumors implanted in both the bladder wall and subcutaneously (SC) in the flank at the same time exhibited a high implant rate, growing rapidly and reproducibly. The growth of the flank tumor was arrested after the first dose of gemcitabine in the bladder; growth attenuation persisted even after halting this first dose. Significant reduction or complete ablation of SC flank tumors was observed in all animals completing the second intravesical treatment. These data suggest a potential immune priming effect of gemcitabine. (Giesing 2018).
10. CCI [redacted]

CCI [redacted]

2.3. Benefit-Risk Assessment

The local delivery of gemcitabine is known to be active in transitional cell carcinoma of the upper and lower genitourinary tract. There has been broad human experience with intravesical gemcitabine in the management of patients with all-risk non-muscle invasive transitional cell carcinoma. These studies have shown that prolonged dwell time and repeated exposure to intravesical gemcitabine results in meaningful pathologic CR rates, which are in turn associated with more durable outcomes in delaying the time to disease recurrence. Intravesical gemcitabine delivery is currently limited by dose delivery and voiding cycles, 2 issues that TAR-200 may mitigate by virtue of its rational, continuous release design.

Multiple Phase 1/2 HR-NMIBC studies employing a 6-week induction course with weekly or twice weekly 40 mg/mL doses of intravesical gemcitabine have shown promising initial responses to treatment. However, despite these responses, durable responses at 1 to 2 years in patients who have recurred after prior BCG therapy are poor. Given that monthly maintenance with gemcitabine has resulted in improved durable responses, the SWOG 0353 trial was designed to assess the effectiveness of repeat intravesical gemcitabine exposure for intermediate- and high-risk patients who failed prior intravesical BCG therapy (Skinner 2013). Most of these patients were either unfit for or refusing RC as definitive treatment.

The SWOG 0353 study demonstrated the utility of regular repeated exposure to intravesical gemcitabine and the correlation between bladder drug exposure time and pathologic outcomes (Skinner 2013). Forty-seven eligible patients who received any treatment were evaluable for response. Of these patients, 42 (89%) had high-risk disease, including high-grade papillary disease alone (12 Ta and 2 T1), CIS alone (20) or with associated papillary disease (4 Ta and 4 T1). At the initial 3-month evaluation, 47% of patients were free of disease. At 12 months, 13 evaluable patients (28%) remained free of disease. The 24-month estimated recurrence free survival (RFS) was 21%.

Based upon this experience of intensive intravesical gemcitabine exposure in BCG-refractory patients, the authors suggest that the wide variation in response to intravesical gemcitabine may be due to differences in dosing and schedules. This is likely a direct result of the short bladder dwell times of instillations and the local toxicities experienced by those receiving supra-therapeutic doses of gemcitabine.

Despite the frequent use of intravesical instillations of chemotherapeutic agents in NMIBC, this approach also suffers from the inability to uniformly expose the bladder urothelium to drug for longer than 1 to 2 hours. Given that the cell-cycle time of higher-grade urothelial tumors may be 48-72 hours in duration, episodic delivery of short-term instillations falls well short of the desired exposure to impact and derange growing cancer cells.

Intravesical gemcitabine has exhibited activity and a good safety profile in the setting of NMIBC (Shelley 2012). Clinical studies of TAR-200 in participants with various stages of organ-confined urothelial carcinoma have demonstrated good tolerability of intravesical dosing.

As of 25 February 2023, approximately [redacted] participants have been treated with TAR-200 alone in 4 early development TAR-200 monotherapy clinical studies (TAR-200-101, TAR-200-102, TAR-200-103, and TAR-200-104), and approximately [redacted] participants have been treated with at least 1 dose of the combination TAR-200 with IV cetrelimab in 3 clinical studies (17000139BLC3001, 17000139BLC2002, and this study; see Section 2.2.3).

Safety and efficacy results from this ongoing study, 17000139BLC2001 were reviewed by the IDMC on 3 occasions (03 February 2022, 29 July 2022, and 14 April 2023). The Futility Analysis data was reviewed by the IDMC on 14 April 2023, and the IDMC recommended to continue the study. Overall, results of the pre-specified futility analysis demonstrated activity and safety of TAR-200 and cetrelimab in patients with HR-NMIBC and supported the continued development in this setting (Daneshmand 2023).

The safety and efficacy of cetrelimab in immune-sensitive advanced cancers was found to be consistent with those of other known anti-PD-1 antibodies. The combination of TAR-200 and cetrelimab is anticipated to not have any overlapping toxicities. Accounting for the measures taken to minimize risk to participants of this study, the potential risks identified in association with TAR-200 in combination with cetrelimab are justified by the anticipated benefits that may be afforded to participants with NMIBC unresponsive to BCG who are ineligible for or refusing RC.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective (Cohorts 1, 2, and 3 Only)	
• To evaluate the overall CR rate in participants treated with TAR-200 in combination with IV cetrelimab (Cohort 1), or TAR-200 alone (Cohort 2), or IV cetrelimab alone (Cohort 3), with Carcinoma in Situ (CIS), with or without concomitant high-grade Ta or T1 papillary disease.	• Overall CR rate will be measured by determining the proportion of participants without presence of high-grade disease using results from cystoscopy and centrally read urine cytology at any timepoint.
Primary Objective (Cohort 4 Only)	
• To evaluate DFS in participants treated with TAR-200 alone with papillary disease only (Cohort 4 only).	• DFS will be measured as the time from the date of first dose of study treatment to either the time of the first recurrence of high-risk disease, progression, or death due to any cause, whichever occurs first. Twelve-month DFS rate will be determined.
Secondary	
• To evaluate the duration of response (DOR) in participants treated with TAR-200 in combination with IV cetrelimab (Cohort 1), or TAR-200 alone (Cohort 2), or IV cetrelimab alone (Cohort 3) with CIS (with or without concomitant Ta or T1 papillary disease) who achieve a CR.	• DOR is defined as the date of first CR achieved to the date of first evidence of recurrence or progression or death, using cystoscopy, centrally read bladder biopsy and urine cytology, and imaging, if available. Twelve-month DOR will be determined.
• To determine the overall survival (OS) in all participants.	• OS, defined as the time from the date of first dose of study treatment to death; if a participant has not died at the time of analysis, the participant will be censored at the date last known alive.
• To evaluate the pharmacokinetics (PK) of gemcitabine and major metabolite 2',2'difluorodeoxyuridine (dFdU) in urine and plasma in TAR-200 in combination with IV cetrelimab (Cohort 1), or TAR-200 alone (Cohort 2 and Cohort 4).	• Gemcitabine and dFdU concentrations in urine and plasma.
• To evaluate the PK and immunogenicity of IV cetrelimab in serum when IV cetrelimab is administered with and without TAR-200.	• Serum concentration and incidence of anti-cetrelimab antibodies.
• To evaluate health-related quality of life (HRQoL) in all participants.	• Change from baseline and time to symptom deterioration in EORTC-QLQ-C30 and EORTC- QLQ-NMIBC24.

Objectives	Endpoints
• To assess the safety and tolerability of participants receiving TAR-200 in combination with IV cetrelimab (Cohort 1), or TAR-200 alone (Cohort 2 and Cohort 4), or IV cetrelimab alone (Cohort 3).	• Frequency and grade of adverse events (AEs) (according to Common Terminology Criteria for Adverse Events [CTCAE] version 5.0). • Laboratory abnormalities: CTCAE grades comparing baseline to the worst post-baseline value; other safety data, such as vital signs, will be considered as appropriate.
Exploratory	
• To determine the incidence of and time to cystectomy (TTC) in the study in all participants.	• The incidence of and time to cystectomy for recurrent or progressive urothelial carcinoma will be measured in the study.
• To identify biomarkers (DNA, RNA, protein) in blood, urine and tissue samples that elucidate mechanisms of action and predict response to TAR-200 in combination with IV cetrelimab (Cohort 1), or TAR-200 alone (Cohort 2), or IV cetrelimab alone (Cohort 3); and its' association with RFS, in participants with Ta/T1/CIS BCG-unresponsive HR-NMIBC.	• Expression of immune markers by immunohistochemistry (IHC) or alternate methods. • Molecular subtyping and expression of immune signatures by RNA sequencing (RNA seq). • Peripheral immune cell profiling and characterization of T cell receptor (TCR) repertoire. • Markers of intrinsic and acquired resistance from pretreatment and on study tissue, urine, and blood samples (circulating tumor DNA analysis, DNA and RNA sequencing).
• To characterize the impact of medical resource utilization (MRU) in all participants.	• Number of participants with type and length of inpatient stay and overall medical encounters.
• To explore the relationships between PK, Pharmacodynamic, adverse event profile, and antitumor activity in all participants.	• Quantitative relationship between PK parameters, Pharmacodynamic parameters, and safety/efficacy parameters.

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

HYPOTHESIS

For Cohorts 1, 2, and 3: Treatment with TAR-200 in combination with IV cetrelimab, TAR-200 alone, or IV cetrelimab alone in participants with HR-NMIBC (CIS with or without papillary disease) unresponsive to prior intravesical BCG therapy will lead to CR and durable CR.

For Cohort 4: TAR-200 alone in participants with papillary disease only (without CIS) unresponsive to prior intravesical BCG therapy will prolong DFS.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, parallel-group, multi-center study evaluating the efficacy and safety of intravesical TAR-200 in combination with IV cetrelimab, TAR-200 alone, or IV cetrelimab alone

in participants with HR-NMIBC (CIS [with or without papillary] or papillary only) unresponsive to prior intravesical BCG therapy who are either ineligible for or have elected not to undergo RC after making an informed decision. Ineligibility for or reason for refusal of cystectomy will be documented in the eCRF. All enrolled participants must have received adequate BCG therapy and confirmed CIS (with or without papillary disease) or confirmed papillary disease only (high-grade Ta or any T1), within 12 months of completion the last dose of BCG therapy. All visible papillary disease must be fully resected (absent) prior to randomization (residual CIS acceptable for participants eligible for Cohorts 1, 2, and 3 only) and documented in the eCRF based on Screening cystoscopy. Adequate BCG therapy is defined as a minimum of 5 of 6 full doses of an induction course (adequate induction) plus 2 of 3 doses of a maintenance course, or at least 2 of 6 doses of a second induction course (Food and Drug Administration 2018). Single-dose peri-operative intravesical chemotherapy prior to study treatment is allowed in accordance with institutional guidelines.

There are 4 cohorts in this study:

- Cohort 1 TAR-200 in combination with IV cetrelimab in participants with CIS with or without papillary disease.
- Cohort 2 TAR-200 alone in participants with CIS with or without papillary disease.
- Cohort 3 IV cetrelimab alone in participants CIS with or without papillary disease.
- Cohort 4 TAR-200 alone in participants with papillary disease only.

As of this Amendment 4, an additional cohort of participants with papillary disease only will be assigned to receive TAR-200 alone (Cohort 4). New participants with CIS (with or without papillary disease) will continue to be assigned to Cohort 2. No new participants are being enrolled in Cohorts 1 or 3. Each cohort will be analyzed separately, and no statistical comparison will be performed between the 4 cohorts. A side-by-side descriptive summary of efficacy will be provided to illustrate the contribution of TAR-200 or IV cetrelimab to the efficacy of the combination therapy.

For the purposes of this study, both TAR-200 and cetrelimab, alone or in combination, will be referenced as study drug.

- For Cohort 1, TAR-200 will be dosed Q3W for up to the first 24 weeks (6 months). Dosing of TAR-200 will then be every 12 weeks through Week 99 (Year 2). Each TAR-200 will be removed after a 3-week dwell time through Week 99 (Year 2). Cetrelimab will be dosed at 360 mg IV Q3W through Week 78 (18 months).
- For Cohort 2 and Cohort 4, TAR-200 alone will be dosed Q3W for up to the first 24 weeks (6 months) on study. Dosing of TAR-200 will then be every 12 weeks through Week 99 (Year 2).
- For Cohort 3, cetrelimab will be dosed at 360 mg IV Q3W through Week 78 (18 months).

There is only one dose and schedule option for TAR-200. TAR-200 is available in one dose only (containing 225-mg free base equivalents of gemcitabine) and will remain indwelling for up to 3 weeks (approximately 21 days) per each dosing cycle. Stopping criteria are allowed based on TAR-200 related AEs. There is only 1 dose and schedule option for IV cetrelimab. Cetrelimab is dosed and scheduled for 360 mg IV Q3W. Dose delays and/or skipped doses are allowed. Guidelines for management for immune-related toxicities are provided.

Each TAR-200 releases gemcitabine into the bladder during the indwelling period, with the majority being delivered within the first 7 days. The first dosing regimen evaluated as part of Phase 1b study TAR-200-101 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. To allow the remaining amount of drug (20% to 30%) in the system to continue to release into bladder urine, the indwelling period was later extended from 7 to 21 days (3 weeks). In addition to potentially improving efficacy, extension of the indwelling period allowed for removal of the previous system and placement of a new system to occur on the same visit, reducing the number of office visits for the participant. This additional residence time is not expected to result in a significant difference in terms of tolerability, as the concentration of gemcitabine remaining in the TAR-200 after 7 days is low, and the rate of release of additional gemcitabine after Day 7 is minimal. The safety of 3-week (21-day indwelling) dosing cycles has been studied in prior Phase 1b clinical studies (TAR-200-103/NCT03404791, TAR-200-104/NCT03518320) and has been generally well tolerated based on data from these studies (refer to the IB).

Cystoscopy and urine cytology (all cohorts) will be performed to assess for disease response. This will occur every CC weeks CCI [Year 1 and Year 2]) for up to 2 years of treatment or until disease persistence, progression, or recurrence as confirmed by positive central urine cytology or local/central pathology showing high-grade disease. Sites should consult with the Sponsor in the event of a positive local biopsy and absent/pending central pathology review before discontinuing study treatment. In Year 3 through the end of study, after the study treatment has ended, cystoscopy and urine cytology will be performed per institutional guidelines and will be collected at least every CC weeks C months). These assessments will be based on an integrated evaluation of local cystoscopy and centrally read urine cytology. For participants with CR, urine cytology from Year 3 through the end of study will be centrally reviewed for disease response. For participants who discontinue study treatment before Week 99 (Year 2) due to toxicity or reasons other than disease persistence, progression, or recurrence, disease assessments should be performed CCI weeks CCI [Year 1 and Year 2]) before the start of subsequent therapy/procedure (eg, radical cystectomy) during the Follow-up Phase. Whenever possible, the same individual should perform cystoscopy throughout the study for a given participant. Unscheduled cystoscopy and bladder biopsy may be performed as clinically indicated. Overall survival status, any procedures (eg, cystectomy), subsequent anti-cancer therapies, and other malignancies will also be reported in the eCRF until death, withdrawal of consent, or the end of the study, whichever occurs first.

During the Treatment Phase, voided urine specimens will be collected and submitted for central cytopathologic review to assess for recurrence and/or progression of disease.

CT/MRI Scans with contrast (abdomen, pelvis, and chest) will be performed at baseline and every [redacted] weeks thereafter until the end of Year 3. Imaging assessment is conducted prior to dosing at defined timepoints. Additionally, unscheduled CT imaging may be performed if clinically indicated. Identical imaging methodology should be used for disease assessment at baseline and throughout the course of the study. Central review of imaging will not be performed.

Participants will be enrolled based on local histopathologic assessment and local urine cytology. Confirmed CIS (with or without papillary) and papillary only diagnosis based on a bladder biopsy/TURBT conducted during the Screening phase or confirmed CIS (with or without papillary) and papillary disease only based on a prior biopsy, at the site or an outside institute, up to 3 months (90 days) prior to Screening, can be used for eligibility assessment. The biopsy with confirmed CIS (with or without papillary) or confirmed papillary disease only should also be submitted to the central laboratory. Recurrent CIS diagnosis, either during Screening or based on prior biopsy as mentioned above, should be within 12 months of the last dose of BCG.

On study bladder biopsy/TURBT must be performed at baseline and the Week [redacted] and Week [redacted] assessments (inclusive of negative cystoscopy results) for Cohorts 1, 2, and 3 only, and as clinically indicated for all cohorts during the study, based on local/central urine cytology, to determine the presence or absence of persistent, recurrent, or progressive disease. Biopsy samples will be evaluated by the local histopathology laboratory for clinical management at the discretion of the Investigator; however, any tissue biopsy sampling will be submitted for a central review of the participant's disease status. Sites should consult with the Sponsor in the event of a positive local biopsy and absent/pending central pathology review before discontinuing treatment. A new low risk/low-grade papillary lesion does not constitute persistent or recurrent disease. Tissue slides/blocks from participants in all cohorts with any locally confirmed low or high-risk recurrence, or progression, will be sent for central histopathologic confirmation. Significant discordances between local and central pathology review will result in Sponsor Investigator consultation, with recommendation to disqualify participant from study. Any confirmed new low risk/low-grade papillary lesion must be resected to completion by TURBT/bladder biopsy, as is feasible, both prior to Screening and during study participation.

Cystoscopy during Screening will still be required to determine if bladder accessibility is adequate for insertion of TAR-200 and to ensure that any papillary disease has been completely excised. Participants are required to discontinue from study treatment if there is confirmed high-risk disease persistence, recurrence, or progression based on central urine cytology and/or central biopsy assessment or local biopsy/local imaging after consultation with the Sponsor. Once a participant demonstrates a high-risk recurrence or progression, that participant will be followed for OS. Per the study design, if a cytopathologic diagnosis of suspicious for high-grade urothelial carcinoma (SHGUC) is resulted from an instrumented urine collection in the absence of a tissue diagnosis of HGUC, a voided urine specimen will be collected and centrally assessed to confirm recurrence and/or progression of disease.

Biomarker assessments will include exploratory DNA, RNA, and protein analyses using archival or fresh biopsy tissue, blood, and urine. Gemcitabine concentrations will be measured in plasma

and urine for PK analysis. Safety assessments will include adverse event reports, physical examinations, clinical laboratory tests, and vital sign measurements. Product Quality Complaints (PQCs) will also be collected for participants who receive TAR-200 and/or IV cetrelimab study drug (Cohort 1, Cohort 2, Cohort 3, and Cohort 4) (refer to Section 10.4.6).

The primary endpoint for Cohorts 1, 2, and 3 is the CR rate for BCG-unresponsive HR-NMIBC (CIS with or without papillary disease). CR is defined as:

- Negative cystoscopy and negative (including atypical) centrally read urine cytology
- Positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative (including atypical) centrally read urine cytology.

Duration of Response (DOR) is a key secondary endpoint for Cohorts 1, 2, and 3.

The primary endpoint for Cohort 4 is the DFS rate for BCG-unresponsive papillary disease only. DFS will be measured as the time from the date of first dose of study treatment to the time of one of the following events, whichever occurs first:

1. The first recurrence of high-risk disease (high-grade Ta, any T1 or CIS).
2. Progression, defined as progression to MIBC (T≥2) or to lymph node (N+) or to distant disease (M+), whichever occurs first.
3. Death due to any cause

Study Treatment After Futility Analysis

An IDMC is commissioned for this study. Refer to Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations for details.

The IDMC will meet at pre-specified analysis and as specified in the IDMC charter to review the data and to make a recommendation. The Sponsor will determine whether to close any of the cohorts, to close the study, or to continue the study unchanged (see Section 9.5). If any cohort is closed, patients on treatment in that cohort will be able to continue to receive the assigned treatment until the protocol-defined criteria for treatment discontinuation are met (eg, recurrence/progression). Following review of the futility data, the Sponsor elected to close further enrollment into Cohorts 1 and 3. Additionally, in accordance with Amendment 3, the Sponsor decided to expand enrollment into Cohort 2 to approximately 80 participants. Participants already enrolled in Cohorts 1 and 3 who are in the Treatment Phase and benefiting from treatment will continue to receive the assigned treatment until the protocol-defined criteria for treatment discontinuation are met (eg, recurrence/progression) (refer to Section 7.1 for discontinuation criteria). All participants, including those in Cohort 1 and 3, who discontinue study treatment should not be considered withdrawn from the study and will continue to be followed for assessments in the Follow-up Phase as described in the Schedule of Activities (Section 1.3).

As of this Amendment 4, the study design includes Cohort 4 of approximately 50 participants with BCG-unresponsive papillary disease only (high-grade Ta or any T1). Enrollment into Cohort 4 may also be discontinued at Sponsor discretion (eg, if Cohort 2 enrollment is completed).

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

Diversity and Inclusion

Cancer affects all population groups, 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, certain groups continue to be at increased risk of developing or dying from particular cancers.

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

Details of the diversity metrics and goals will be outlined in the Sponsor's Diversity Plan.

4.2. Scientific Rationale for Study Design

In a previous Phase 1b clinical study with TAR-200 (TAR-200-101/ NCT02722538), participants received 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. To allow the remaining amount of drug (20% to 30%) in the TAR-200 to continue to release into bladder urine, the indwelling period was later extended to 21 days. In addition to potentially improving efficacy, extension of the indwelling period to allow removal of the previous TAR-200 and placement of a new TAR-200 to occur on the same visit will reduce the number of office visits for the participant. This additional residence time is not expected to result in a significant difference in terms of tolerability as the concentration of gemcitabine remaining in the TAR-200 after 7 days is minimal.

Biomarker Collection

Biomarker samples will be collected to evaluate the mechanism of action of cetrelimab and TAR-200 to help to explain interindividual variability in clinical outcomes, and to help identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the pharmacodynamics (PD) of cetrelimab and TAR-200 and aid in evaluating the intervention-clinical response relationship.

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

Patient-reported outcome (PRO) data complement data collected by other methods to support the clinical data contributing to enhanced communication of value to patients, clinicians, regulators, and payers. The PRO endpoints of interest include domain scales from the EORTC-QLQ-C30 and the EORTC-QLQ-NMIBC24. These PRO measures will be administered to test the hypothesis that treatment with TAR-200 in combination with IV cetrelimab, or TAR-200 alone or IV cetrelimab alone maintains HRQoL as measured by time to symptom and functional deterioration

by a prespecified meaningful change threshold. PRO data will be collected as outlined in the Schedule of Activities (Section 1.3), to understand how the endpoints change over time, with treatment, and with the clinical state of the participant.

Medical Resource Utilization Data Collection

Treatment of NMIBC with TAR-200 in combination with IV cetrelimab or TAR-200 alone or IV cetrelimab alone may result in lower utilization of healthcare resources. Exploratory analyses of MRU data collected for participants in Cohort 1 and Cohort 2 and Cohort 3 and Cohort 4 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. Consent/assent may be documented through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences.

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 participants, the amount of blood collected is less than the American Red Cross standard blood donation of 500 mL over 60 days (2019) and is aligned with World Health Organization blood donation guidelines (2019).

4.3. Justification for Dose

4.3.1. TAR-200 Dose Selection

There is only 1 dose option for this study as TAR-200 is available in 1 dose only (containing 225 mg free base equivalents of gemcitabine), which will remain indwelling for up to 3 weeks per each dosing cycle of 21 days. In the first year of the study, TAR-200 will be dosed Q3W for up to the first 24 weeks (6 months) on study. Dosing of TAR-200 will be every 3 months thereafter through Week 99 (Years 1 and 2). Following the first year of study treatment with TAR-200 (ie, after Week 51), participants will continue to undergo a 3 week dosing cycle every 3 months (Year 2), until a cumulative maximum of 14 dosing cycles (inclusive of the 10 administered in the first year) have been administered.

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 with short duration dosing (Cattel 2006).

The first dosing regimen evaluated as part of Phase 1b study TAR-200-101 consisted of two 7-day dosing cycles with a 14-day recovery period in between dosing cycles. This regimen was found to be well tolerated by the study participants. To allow the remaining amount of drug CCI in the system to continue to release into bladder urine, the indwelling period was later extended from 7 to 21 days (3 weeks). In addition to potentially improving efficacy, extension of the indwelling period allowed for removal of the previous system and placement of a new system to occur on the same visit, reducing the number of office visits for the participant. This additional residence time is not expected to result in a significant difference in terms of tolerability as the 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 3 week (21-day indwelling) TAR-200 dosing cycles has been evaluated in 2 Phase 1b clinical studies (TAR-200-103/NCT03404791 [ongoing], TAR-200-104/NCT03518320) and has been generally well tolerated to date based on data from these studies.

4.3.2. Cetrelimab Dose Selection

The recommended monotherapy dose for IV cetrelimab is based on clinical activity in the Phase 1 Study 63723283LUC1001. The identified RP2D regimens of cetrelimab are 240 mg Q2W and 480 mg Q4W administered intravenously. The IV cetrelimab monotherapy RP2D regimen selection was based on an acceptable safety profile, similarity to other anti-PD-1 monoclonal antibodies, and preliminary evidence that target concentrations are achieved.

For this study, IV cetrelimab will be dosed at 360 mg Q3W to align with the dosing frequency of TAR-200. The Q3W regimen is supported based on population PK modeling and simulation of IV cetrelimab, which demonstrated that the steady-state C_{trough} and C_{max} of IV cetrelimab attained is between the values from the 2 established RP2Ds (240 mg Q2W and 480 mg Q4W).

4.4. End of Study Definition

End of Study Definition

The end of study/study completion is considered as either 2.5 years after the last participant is randomized or 6 months after all participants have either completed or discontinued treatment, have withdrawn consent from the study, are lost to follow-up, or died, whichever occurs first. 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.

Participant Completion of Treatment Definition

A participant will have completed treatment for Cohort 1, Cohort 2, and Cohort 4, when they have completed treatment through Week 99 (removal of the TAR-200); and for Cohort 3, when they

have completed treatment through Week 78. Participants who prematurely discontinue study treatment for any reason before completion of the treatment phase will not be considered to have completed the study treatment.

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 must continue to be followed for protocol-specified disease assessments and follow-up procedures. 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 enroll participants with HR-NMIBC (CIS [with or without papillary disease] and papillary disease only). Screening for eligible participants will be performed within [redacted] days before randomization Screening procedures (Section 8.1), should be completed according to the timing provided in the Schedule of Activities (Section 1.3). Refer to Section 5.4, Screen Failures, for conditions under which the repeat of any Screening procedure is allowed.

The inclusion and exclusion criteria for randomizing 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 randomizing 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:

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

2. Criterion modified per Amendment 1

   2.1 Criterion modified per Amendment 2

   2.2 Criterion modified per Amendment 3

   2.3 Criterion modified per Amendment 4

   2.4 Histologically confirmed diagnosis of persistent or recurrent HR-NMIBC, CIS (OR Tis) [AJCC, 2017], with or without papillary disease (T1, high-grade Ta) or papillary disease only (high-grade Ta or any T1 and absence of CIS), within 12 months of completion of the last dose of BCG therapy, in patients who have received adequate BCG (see inclusion criterion #6). Mixed histology tumors are allowed if urothelial differentiation (transitional cell histology) is predominant. However, the presence of neuroendocrine, micropapillary, signet ring cell, plasmacytoid, or sarcomatoid features will make a participant ineligible. For participants with lamina propria invasion (T1) on the screening biopsy/TURBT, muscularis propria must be present in order to rule out MIBC.

3. Criterion modified per Amendment 2

   3.1 Criterion modified per Amendment 4

   3.2 All visible papillary disease must be fully resected (absent) prior to randomization (residual CIS is acceptable for participants eligible for Cohorts 1, 2, and 3 only) and documented in the eCRF at Screening cystoscopy. For patients with papillary disease only (Cohort 4), local urine cytology at screening must be negative or atypical (for HGUC).

4. Participants must be willing to undergo all study procedures (eg, multiple cystoscopies from Screening through the end of study and TURBT/bladder biopsy for assessment of recurrence/progression).

5. Participants must be ineligible for or have elected not to undergo radical cystectomy.

6. Criterion modified per Amendment 2

   6.1 BCG-unresponsive high-risk NMIBC after treatment with adequate BCG therapy defined as a minimum of 5 of 6 full doses of an induction course (adequate induction)

plus 2 of 3 doses of a maintenance course, or at least 2 of 6 doses of a second induction course.

7. All AEs associated with any prior surgery and/or intravesical therapy must have resolved to CTCAE version 5.0 Grade <2 prior to screening.

8. Participants must sign the informed consent form (ICF) indicating that he or she 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.

9. Eastern Cooperative Oncology Group (ECOG) performance status Grade 0, 1, or 2.

10. Criterion modified per Amendment 1

    10.1 Criterion modified per Amendment 2

    10.2 Criterion deleted per Amendment 4

11. Criterion modified per Amendment 3

    11.1 Criterion modified per Amendment 4

    11.2 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) ≥1,000/mm^3
        ii. Platelet count ≥ 75,000/mm^3
        iii. Hemoglobin ≥ 8.0 g/dL

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

    c. Renal function:

        Creatinine clearance ≥30 mL/min calculated using the Cockcroft-Gault formula (See Section 10.14, Appendix 14).

12. Criterion modified per Amendment 1

    12.1 Criterion modified per Amendment 2

    12.2 Criterion modified per Amendment 3

12.3 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. A female participant must be either of the following (as defined in Section 10.5; Appendix 5: Contraceptive 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: Contraceptive 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:

- agree 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 drug.
- not be breastfeeding (including participants 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 drug. 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 of 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: Contraceptive 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. 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.

A male participant must also:

- agree to not donate sperm for the purpose of reproduction during the study and for at least 6 months after the last dose of study drug
- not plan to father a child while enrolled in this study or within 6 months after the last dose of study drug.

13. Criterion modified per Amendment 1

13.1 A female participant of childbearing potential must have a negative serum test (at screening) and a negative urine test 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).

14. Criterion added per Amendment 2

14.1 Participants must be willing and able to adhere to the lifestyle restrictions specified in this protocol

5.2. Exclusion Criteria

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

1. Criterion modified per Amendment 3

1.1 Presence or history of histologically confirmed, muscle invasive, locally advanced, nonresectable, or metastatic urothelial carcinoma (ie, T2, T3, T4, and/or Stage IV).

2. Criterion modified per Amendment 1

2.1 Criterion modified per Amendment 2

2.1 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.

3. Criterion modified per Amendment 1

3.1 Criterion modified per Amendment 3

3.2 Active malignancies (ie, progressing or requiring treatment change in the last 24 months prior to randomization) other than the disease being treated under study.

Potential allowed exceptions include the following (others may be allowed with Sponsor approval):

a. skin cancer (non-melanoma or melanoma) that is considered completely cured.

b. non-invasive cervical cancer that is considered completely cured.

c. adequately treated lobular carcinoma in situ (LCIS) and ductal CIS

d. history of localized breast cancer and receiving antihormonal agents

e. history of localized prostate cancer (N0M0) and receiving androgen deprivation therapy

f. Localized prostate cancer (N0M0):

i. with a Gleason score of 6, treated within the last 24 months or untreated and under surveillance,

ii. with a Gleason score of 3+4 that has been treated more than 6 months prior to full study Screening and considered to have a very low risk of recurrence,

iii. or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.

4. Criterion modified per Amendment 1

4.1 Criterion modified per Amendment 2

4.2 Presence of any bladder or urethral anatomic feature (eg, urethral stricture) that, in the opinion of the Investigator, may prevent the safe insertion, indwelling use, removal of TAR-200, or passage of a urethral catheter for intravesical chemotherapy, or administration of intravesical BCG. Participants with tumors involving the prostatic urethra in men will be excluded

5. Evidence of bladder perforation during diagnostic cystoscopy.

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

7. Criterion modified per Amendment 1

7.1 Participants should not have a history of acute ischemic heart disease within 30 days of cohort assignment, or history of uncontrolled cardiovascular disease including any of the following in the 3 months prior to Screening:

a. unstable angina,

b. myocardial infarction,

c. ventricular fibrillation,

d. Torsades de Pointes,

e. cardiac arrest, or known congestive New York Heart Association Class III-IV heart failure,

f. cerebrovascular accident,

g. transient ischemic attack, or

h. pulmonary embolism or other venous thromboembolism in the 3 months prior to Screening.

8. A history of clinically significant polyuria with recorded 24-hour urine volumes greater than 4000 mL.

9. Criterion deleted per Amendment 4

10. Criterion modified per Amendment 1

10.1 Criterion modified per Amendment 3

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

11. Criterion modified per Amendment 1

11.1 Criterion modified per Amendment 3

11.2 Active infection requiring systemic IV therapy within 14 days prior to randomization (see Exclusion Criterion No. 23 for information regarding UTI).

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

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

15. Criterion modified per Amendment 1

15.1 Received serial intervening intravesical chemotherapy or immunotherapy from the time of pre-screening (diagnostic) or Screening (completion) cystoscopy/Transurethral Resection of Bladder Tumor (TURBT) to starting study treatment. Peri-operative intravesical chemotherapy prior to study is allowed per institutional guidelines.

16. Prior therapy with an anti-programmed-cell death 1 (PD-1), anti-PD-ligand 2 (L2) agent, or with an agent directed to another co-inhibitory T-cell receptor.

17. Criterion deleted per Amendment 4

18. Not recovered from toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration).

19. Criterion deleted per Amendment 4

20. 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).

21. Criterion modified per Amendment 1

    21.1 Criterion modified per Amendment 3

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

22. Criterion modified per Amendment 1

    22.1 Active hepatitis B or C infection (for example, participants with history of hepatitis C infection but undetectable hepatitis C virus polymerase chain reaction [PCR] test and participants with history of hepatitis B infection with positive HBsAg antibody and undetectable PCR are allowed).

23. Criterion modified per Amendment 1

    23.1 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. 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 $>10^5$ CFUs may be eligible.

24. Criterion deleted per Amendment 4

25. Criterion deleted per Amendment 4

26. Known hypersensitivity to gemcitabine (or other drug excipients) or chemically- related drugs. Refer to the TAR-200 IB for information on excipients.

27. Criterion modified per Amendment 1

    27.1 Known hypersensitivity to the TAR-200 device constituent or the (TAR-200) UPC materials. Refer to the TAR-200 IB for information on TAR-200 device constituent and

UPC materials. Refer to the TAR-200 IB for information on TAR-200 device constituent and UPC materials.

28. Criterion modified per Amendment 1

    28.1 Criterion modified per Amendment 2

    28.2 Evidence of radiographic features associated with pulmonary fibrosis/advanced interstitial lung disease (Investigators may consult a pulmonologist in case of equivocal findings) or active non-infectious pneumonitis.

29. Participants must not have active tuberculosis.

31. Major surgery within 4 weeks before Screening (TURBT is not considered major surgery).

32. 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.

33. 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 drug is given such that he or she 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 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 CCI [redacted]

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.

The participant identification and enrollment log will be treated as confidential and will be filed by the Investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re- screened 1 time. A participant who is a screen failure may be re-screened, 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. 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, a new participant number must be assigned. Note that participants who are re-screened within 60 days of the original Screening do not need to repeat screening procedures as per Table 1, with the exception of urine culture and laboratory assessments.

5.5. Criteria for Temporarily Delaying Administration of Study Treatment

TAR-200 Investigational Product

Dose modifications with TAR-200 can only be achieved by early removal due to the nature of TAR-200. TAR-200 may be removed early or TAR-200 insertion may be skipped for management of adverse events: see Section 6.5.1, for the conditions under which TAR-200 will either not be inserted or will be removed early and for the conditions under which participants will be permanently discontinued from TAR-200. If the TAR-200 is removed, it may be replaced immediately per protocol or within CCI

Cetrelimab

Dose delay 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

For the purpose of this study, 'study drug' refers to both JNJ-17000139 (TAR-200) and JNJ-63723283 (cetrelimab). Study treatment administration must be captured in the source documents and the eCRF.

TAR-200 and IV cetrelimab will be manufactured and provided under the responsibility of the Sponsor. Refer to the 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. For a description of study drugs refer to Table 20.

Table 20: Description of Study Drugs

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	CCI (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 cystoscope (a rigid cystoscope can be utilized for removal when clinically needed)	The CCI product CCI is further CCI injection to make CCI 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/Auxillary Medicinal Product (NIMP/AxMP)	No	No
Sourcing	Provided by the Sponsor	Provided by Sponsor

Study Treatment Name	TAR-200	IV Cetrelimab
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 [redacted] 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.

Abbreviations: IP=investigational product; IV=intravenous; UPC=Urinary Placement Catheter

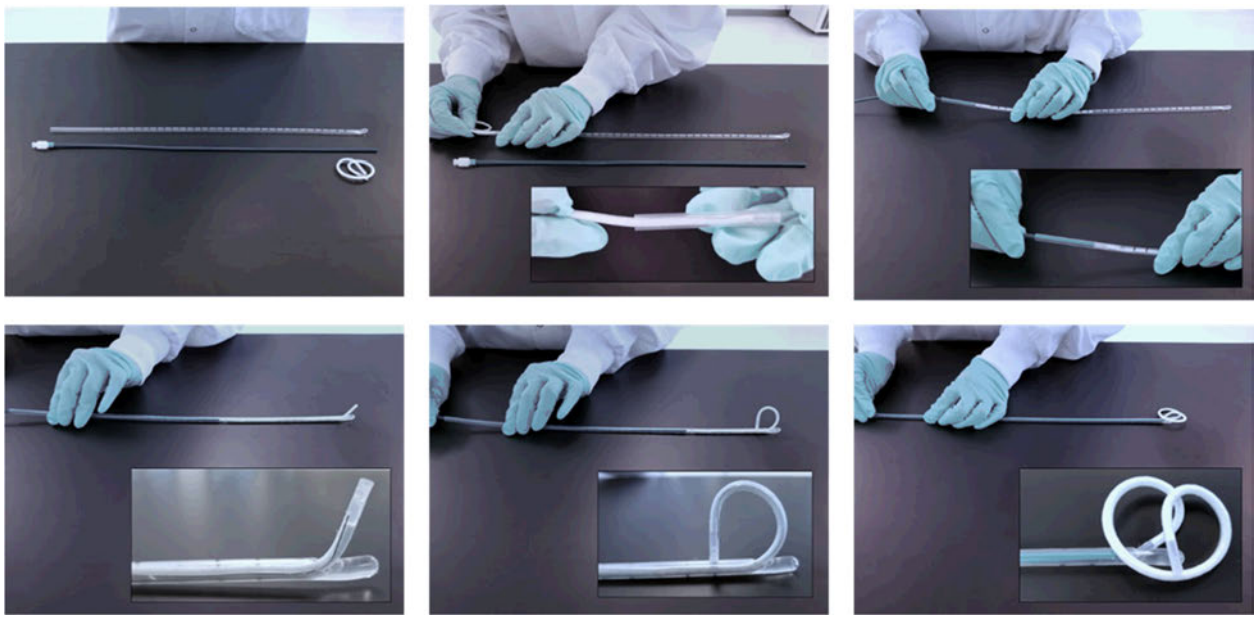
6.1. TAR-200 and Cetrelimab Study Drug Dosing

Participants will receive either TAR-200 in combination with IV cetrelimab (Cohort 1) or TAR-200 alone (Cohort 2 or Cohort 4) or IV cetrelimab alone (Cohort 3).

6.1.1. TAR-200 Insertion

The UPC consists of 2 components, a clear shaft and a green stylet. The UPC shaft is placed via the urethra into the bladder with position confirmed by urine return. The bladder should not be completely empty of urine when TAR-200 is inserted. TAR-200 is loaded linearly 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 TAR-200 through the UPC shaft. The TAR-200 emerges at the exit port as it is being fully deployed into the bladder. The TAR-200 is deployed into the bladder and returns to its original “pretzel” form. Figure 5 below portrays a benchtop illustration of the TAR-200 insertion procedure.

Figure 5: Loading and Deployment (Insertion) of TAR-200 using the Urinary Placement Catheter (UPC)



Abbreviations: IFU=Instructions for Use

Note: The above pictures represent a benchtop illustration of the TAR-200 insertion procedure. Refer to the 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 post-insertion cystoscopy would provide a visual assessment of TAR-200 to safeguard that the intravesical drug delivery system is in its "pretzel-like" 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, nonsteroidal anti-inflammatory drugs (NSAIDS), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 insertion. After insertion of TAR-200, ensure that the participant consumes adequate liquids as reduced fluid consumption may exacerbate urinary symptoms.

To mitigate the risk of UTIs, participants must receive at least 1 dose of prophylactic periprocedural antibiotics for TAR-200 insertion or removal. Complete instructions for TAR-200 insertion are provided in the Instructions for Use (IFU). Antibiotics for standard cystoscopy and TURBT may be administered in accordance with standard of care.

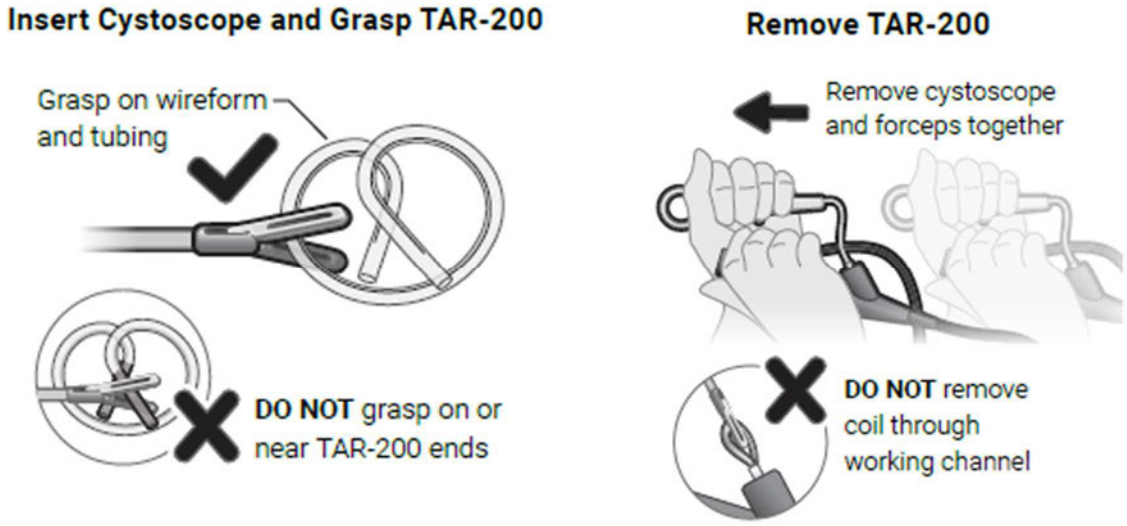
The TAR-200 should generally be placed after all other assessments required at that visit. Note that on days in which both TAR-200 and IV cetrelimab will be administered, TAR-200 will be inserted at least CCI before the start or after the completion of cetrelimab IV infusion.

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

When the TAR-200 is removed, it may be replaced immediately per protocol or within CCI [redacted] The TAR-200 should generally be removed after all other assessments required at that visit and prior to the next TAR-200 insertion, if a TAR-200 insertion is required at that visit. A flexible cystoscope should be used for the removal of TAR-200 with a non-cutting grasping forceps and must be performed by a trained healthcare provider. A rigid cystoscope can be utilized for TAR-200 removal when clinically needed. TAR-200 should be grasped fully and removed from the bladder under direct visualization, not through a cystoscope's working channel. Consider administering anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 removal. To mitigate the risk of UTI's, participants must receive at least 1 dose of prophylactic periprocedural antibiotics at the time of TAR-200 removal. Complete instructions for TAR-200 removal are provided in the IFU. A graphical representation of removal is presented in Figure 6.

Figure 6: 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 following removal of the TAR-200. Refer to the IB.

6.1.3. Cetrelimab Administration

Cetrelimab will be dosed at 360 mg Q3W IV to align with the dosing frequency of TAR-200 until Week 78 (Cohort 1 and Cohort 3) or until the participant has disease recurrence or progression, intolerable toxicity, withdraws consent, there is a decision by the Investigator to discontinue treatment, or the study is terminated, whichever occurs first. The dosing of IV cetrelimab may be delayed and/or skipped to allow for the resolution of any adverse event 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, IV cetrelimab administration should be completed at least CCI before or infusion 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 (eg, acetaminophen) may be administered for subsequent infusions if an infusion reaction is observed with IV cetrelimab. Participants who progress or recur with high-risk disease will perform an end of study visit and undergo treatment in accordance with the treating physician's decision.

6.1.4. Combination Products

All TAR-200 deficiencies (including failure, malfunction, improper or inadequate design, manufacturer error, use error, and inadequate labeling) shall be documented and reported by the Investigator throughout the study. These deficiencies will be reported as PQC (see Section 10.4, Appendix 4) and will be reviewed by the Sponsor and reported in accordance with local legislation (see Section 10.10, Appendix 10).

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 received and any discrepancies are reported to Sponsor immediately and resolved before use of TAR-200. TAR-200 systems 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 trained Investigators or trained and credentialed designees may insert or remove TAR-200. Refer to the IFU for instructions on placement and removal of TAR-200. A disposable, one-time use UPC is co-packaged with each system and is used to insert TAR-200 into the bladder. Refer to the IFU for information on insertion and removal. Refer to the IFU and 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 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 infusion. Only participants enrolled in the study may receive cetrelimab and only trained Investigators or trained and credentialed designees may prepare and dose the IV cetrelimab. Refer to the Investigational

Product Preparation Instructions (IPPI) or the SIPPM for additional information and stepwise guidance on IV 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

The Investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the participant must be documented on the intervention administration form. All study drugs 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 intervention must be handled in strict accordance with the protocol and the container label(s) 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. When the study site is an authorized destruction unit and study treatment supplies are destroyed on-site, this must also be documented on the intervention return form.

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

Study intervention should be dispensed under the supervision of the Investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study treatment must not be dispensed again, even to the same participant. Study intervention 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 treatments are provided in the IFU for TAR-200 and in the IPPI for IV cetrelimab.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

As of Protocol Amendment 4, participants will be assigned to receive TAR-200 alone in either 1 of 2 cohorts based on disease stage: Cohort 2 (for participants with CIS [with or without papillary]) or Cohort 4 (for participants with papillary disease only).

Blinding

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

6.4. Study Treatment Compliance

TAR-200 will be inserted and removed from the bladder by documented and trained Investigators or designees. The date of each insertion and each removal will be recorded in the source documents and recorded in the appropriate eCRF.

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 the IV infusion, 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. Prophylactic administration of anticholinergics, NSAIDS, and bladder analgesics should also be considered. 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 or removal. Antibiotics for standard cystoscopy and TURBT may be administered in accordance with standard of care.

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

6.5.1.2. TAR-200 Dose Modification and Missed Dosing Cycles

During the induction period (Week 0 to Week 24), TAR-200 insertion may be delayed or skipped for management of related AEs. The Sponsor should be notified of any TAR-200 drug delays or skipped dose and directly consulted prior to discontinuation of TAR-200 at any time during the study. In participants who have achieved CR (based on urine cytology and/or biopsy), TAR-200 drug delays may not exceed 4 months from the last centrally assessed CR. TAR-200 drug delays exceeding 4 months from the last CR will result in permanent discontinuation of TAR-200.

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

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

A skipped dose is defined as a TAR-200 insertion that is not administered within the study window as described in the SoA (Section 1.3), and is not due to study discontinuation.

There is only 1 dose option for this study, as TAR-200 is available in 1 dose only. Dose modifications are not permitted due to the nature of TAR-200, except for early removal, delayed placement (ie, a missed dosing cycle), or discontinuation of TAR-200.

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 placed due adverse events 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 placement timepoint, assuming the participant no longer meets the participant stopping safety criteria at that time.

TAR-200 Participant Stopping Safety Criteria

If a participant discontinues TAR-200 before the end of the Treatment Phase, the participant must commit to a clinic visit to have the TAR-200 removed (unless dosing of IV cetrelimab is still ongoing in which case EOT visit will be performed after completion of IV cetrelimab).

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

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

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

- Grade ≥2 hematuria.
- Grade ≥2 clinical and cystoscopic signs of aseptic cystitis.
- Incomplete or complete 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/mm3, platelet count <50,000/mm3).
- Severe or medically significant but not immediately life-threatening opportunistic infections that require hospitalization or result in prolongation of hospitalization.
- Grade ≥2 active urinary tract infection that the Investigator believes to be clinically significant.

TAR-200 Discontinuation

TAR-200 must be removed and the participant discontinued from study drug if the following occur:

- Grade ≥2 allergic reaction (shortness of breath, generalized edema, etc) related to the TAR-200 constituent materials (CCI drug (gemcitabine), excipients (CCI UPC materials CCI
- Grade 4 drug-related toxicity other than the AEs described above.

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 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 immune-related AE (irAE) management.

6.5.2.2. Cetrelimab Dose Modification

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 must be followed for management. Treatment with IV cetrelimab may continue unless the criteria for discontinuation of study drug are met (Cetrelimab Discontinuation, see below).

Cetrelimab Dose Delay

A skipped dose is defined as a 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 treating physician and in consultation with the Sponsor, treatment 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), for which resolution to ≤Grade 2 is required for subsequent treatment. Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline. If the toxicity does not resolve to ≤Grade 1 or baseline (or ≤Grade 2 for those above) within 12 weeks of identification of the toxicity, discontinuation of IV cetrelimab is recommended unless agreement to continue dosing is reached by the Sponsor's Medical Monitor or designee and

the Investigator. TAR-200 dosing alone may continue if the Investigator and Sponsor's Medical Monitor agree.

The following study drug-related irAEs will require dose delay:

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

Cetrelimab Dose Discontinuation

A participant must discontinue study drug 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 12 weeks
- A treatment-related AE does not resolve to Grade ≤1 or baseline within 12 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 drug discontinuation at the discretion of the treating physician
- Any non-hematologic treatment-related event occurs a second time at Grade ≥3 severity.
- Grade ≥3 (or recurrent Grade 2) pneumonitis/ILD.
- 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.
- Immune-mediated encephalitis.
- Grade ≥3 uveitis

- Recurrence of Grade 3 of other immune-mediated adverse reactions (eg, myocarditis, myositis, myasthenia gravis, pancreatitis, and gastritis)
- The Investigator believes that for treatment-emergent toxicity it is in the best interest of the participant to discontinue IV cetrelimab. Participants may continue to receive TAR-200 (Cohort 1)

If a participant's study drug is discontinued, this will not result in automatic withdrawal of the participant from the study. Following treatment discontinuation, the participant should complete the EOT Visit. Once a participant discontinues treatment with IV cetrelimab, the participant may not be retreated with the study drug. If IV cetrelimab is permanently discontinued, then treatment with TAR-200 (Cohort 1) may be continued with Sponsor agreement.

Discontinuation of study treatment is described in Section 7.1.

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

Participants will be instructed that study treatment will not be made available to them after they have completed/discontinued study treatment.

No continued access will be proposed for this study as study treatment concludes after removal of TAR-200 at Week 99 for Cohorts 1, 2, and 4, and after IV cetrelimab administration at Week 78 for Cohort 3, and participants will be followed on study during the Follow-up Phase. At the end of their participation in the study, the participants will be instructed that they should return to their primary physician to determine SOC, if applicable. The only exception would be if continued access is a requirement per local regulation.

6.7. Treatment of Overdose

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

Intravesical instillations of chemotherapeutic agents, including gemcitabine, are frequently used in the treatment of NMIBC. TAR-200 continuously delivers gemcitabine at an average of CC mg/day over the first 7 days (with the remainder expected to be released daily after Day 7) for a maximum of 225 mg, a dose that is significantly less than the doses in standard high-dose gemcitabine instillations used 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 classic intravesical gemcitabine instillation doses traditionally employed. Finally, participant voiding of the bladder urine upon the subsequent voiding cycle would subsequently eliminate this gemcitabine volume from the participant's bladder, limiting the dwell time of this drug load.

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

In the event of an overdose of TAR-200 or IV cetrelimab, the Investigator or treating physician should:

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

6.8. Concomitant Therapy

Any medication (including over-the-counter [OTC]) or prescription medicines, vitamins, or herbal supplements), therapy (including palliative procedures), or vaccine that the participant is receiving at the time of randomization 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

Gemcitabine may potentiate the effects of antithrombotic medications (thrombolytics, anticoagulants, and anti-platelet agents); therefore, the Investigators should monitor participants who are administered these medications closely for risks of increased bleeding. Anticoagulation should be used with caution in this patient population due to procedural interventions.

To mitigate the risk of UTIs, participants must receive at least one dose of prophylactic periprocedural antibiotics for TAR-200 insertion or removal. Antibiotics for standard cystoscopy and TURBT may be administered in accordance with standard of care.

Concomitant therapies, Relevant Procedures (including genitourinary events and procedures), and Healthcare encounters must be recorded throughout the study, beginning with informed consent and through the 100 Day Safety Follow-up visit. Concomitant therapies should also be recorded in conjunction with new or worsening SAEs that meet the criteria outlined in Serious Adverse Events in Section 8.12.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or OTC 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.

6.8.1. 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 non-cancer 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. Anticoagulation should be used with caution in this patient population due to procedural interventions.

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 [H_2] 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.

6.8.2. 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 JNJ-63723283 or hormonal therapy (hormone replacement therapy is acceptable)]; however, supportive care agents, including denosumab, bisphosphonates, and hormonal agents are allowed.
- Other immunosuppressant agents, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumor necrosis factor α (TNF-α) blockers, should not be given while the participant 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 should not be administered within 30 days of the initiation of study treatment (refer to Section 5.2), during study treatment, and for 90 days following completion of study treatment (non-live or non-replicating vaccines such as annual inactivated influenza or COVID-19 vaccine, or monkeypox are allowed). Note: specifically, for COVID-19 vaccines, refer to Section 10.8, Appendix 8: Study Conduct During a Natural Disaster.

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

7. DISCONTINUATION OF STUDY DRUG AND/OR STUDY

7.1. Discontinuation of Study Drug

A participant's study drug must be discontinued if:

- The participant withdraws consent to receive study drug.
- The Investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study drug.
- The participant becomes pregnant.
- Noncompliance with study drug or schedule.
- The participant recurs or progresses with high-risk disease.
- The Sponsor closes the study.
  - The Sponsor reserves the right to close the enrollment or the study or close the study site at any time for any reason at the sole discretion of the Sponsor, eg, in case of poor enrollment, unacceptable risk, intolerable toxicity, or change in the risk/benefit profile; this might include recurrence of AEs of which character, severity, or frequency is new in comparison to the existing risk profile. Also, data derived from other clinical trials or toxicology studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study. If in the judgment of the Investigator, the participant is benefiting from study drug and has not yet completed the protocol defined study drug treatment schedule, the participant may have an opportunity to continue with study drug treatment per the protocol defined administration schedule.

If a participant permanently discontinues study drug for any reason before the end of the Treatment Phase, the participant must commit to a clinic visit to have the TAR-200 removed and perform an EOT Visit (unless dosing of IV cetrelimab is still ongoing in which case EOT visit will be performed after completion of IV cetrelimab). All efforts will be made to continue to follow participants in the Follow-up Phase of the study (safety follow-up visit, the disease assessment visits and OS) through the end of study as described in the Schedule of Activities (Section 1.3).

The primary reason for study drug 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.

7.2. Discontinuation of Study

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

- Withdrawal of consent
- Lost to follow-up

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 records.

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, but the participant must commit to a clinic visit to have the TAR-200 removed (if applicable).

7.3. 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, telephone contact, 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.

- If a participant notifies an Investigator that he/she would like to withdraw consent from the study, the Investigator should discuss any potential medical risks of withdrawal and must schedule a TAR-200 removal (if required), and a final evaluation.
- Efforts will be made to continue follow-up of participants who withdraw prematurely, especially with respect to disease progression and survival through the end of study 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. 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.

7.4. Withdrawal from the Future Use of Research Samples

The participant may withdraw consent for use of samples for future research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3.5, 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 ICF.

7.5. 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, and caregivers.

A participant will be considered lost to follow-up if he or she 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 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, and 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, fax, 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.

7.6. 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. Date of death will be entered the eCRF.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3), 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: ECGs, vital signs, blood draws, and dosing to be conducted last. Blood collections for PK 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); 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. Imaging should be performed prior to dosing. In Cohort 1, placement of TAR-200 and administration of cetrelimab do not need to occur on the same day but should occur CCI [redacted] 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 and completed before any other tests, procedures, or consultations to prevent influencing participant perceptions. Refer to the PRO completion guidelines for instructions on the administration of PROs. MRU data will also be collected. Refer to Section 8.15, Medical Resource Utilization and Health Economics, for details.

Some testing may be performed by mobile study personnel when allowable per country/territory regulations. Site visits may be replaced with telephone visits during a natural disaster, with site visits resuming as soon as possible thereafter (See Section 10.8, Appendix 8: Guidance on Study Conduct During a Natural Disaster for Enrolled Participants).

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Screening criteria must be entered in the eCRF and reviewed and approved by the Sponsor prior to randomization. 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.

Home Health Care and Telehealth Visits

Some testing may be performed by mobile study personnel when allowable per country/territory regulations. Site visits may be replaced with telephone visits during a major disruption, eg, natural disaster, pandemic, regional crises, or if clinically appropriate and with Investigator and Sponsor agreement. Refer to Section 10.8, Appendix 8: Study Conduct During a Natural Disaster for additional details.

Home health care and telehealth visits may be implemented by or with approval from the Sponsor and per the clinical judgment of the Investigator, where feasible and permissible by local policy.

Participants for whom there is no safety concern may have home health care and telehealth (conducted via phone or video conference) visits.

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 instructions above are applicable for collection of biomarker and PK samples. For collection and handling of other samples, local laboratories should follow local procedures, and for handling of central lab samples, the Laboratory Manual that will be provided should be followed. 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
- Cetrelimab IB
- TAR-200 IB
- Pharmacy manual/study SIPPM
- TAR-200 IFU
- Cetrelimab IPPI
- Laboratory Manual
- NCI-CTCAE Version 5.0
- Electronic PRO (ePRO) completion guidelines
- Tablet for on-site ePRO completion
- Interactive voice response system (IVRS)/ Interactive web response system IWRS Manual
- eDC Manual
- Participant Wallet cards

8.1. Screening

All participants must sign the ICF prior to any protocol required procedures being conducted. The Screening Phase includes the interval between signing the ICF and the day the participant is assigned to their respective cohort. The standard Screening Phase is planned for [redacted] days. For participants who require repeat biopsy/TURBT and/or repeat imaging during the standard [redacted]-day Screening Phase, the Screening Phase may be extended from [redacted] days to [redacted] days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the Screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, disease assessment) and obtained before signing the main-study ICF may be used for Screening or baseline 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 in the appropriate eCRF and reviewed and approved by the Sponsor prior to randomization. Confirmed CIS (with or without papillary) or papillary only diagnosis based on a biopsy/TURBT conducted during the Screening phase or confirmed CIS (with or without papillary) or papillary disease only based on a prior biopsy, at the site or an outside institute, up to 3 months (90 days) prior to Screening, can be used for eligibility assessment. The biopsy with confirmed CIS (with or without papillary) or papillary disease only should also be submitted to the central laboratory. Recurrent CIS diagnosis, either during Screening or based on prior biopsy as mentioned above, should be within 12 months of the last dose of BCG.

Immediate post-operative intravesical chemotherapy prior to study treatment is allowed in accordance with institutional guidelines.

An Assessment Cystoscopy will be performed during the [redacted]-day Screening period for the following assessments:

- To assess bladder burden of disease
- Ensure that no underlying anatomical abnormality is found that could prevent safe insertion, indwelling use, or removal of TAR-200
- Assess for abnormal urothelium (eg, evidence of radiation cystitis) that would preclude participation

The participant's previous anticancer therapies including prior BCG therapies, 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. Additionally, eligibility TURBT with diagnostic details and the participants reason for refusal or ineligibility for cystectomy will also be recorded in the source documents and collected in the eCRF. Tests with results that fail eligibility requirements may be repeated once during Screening if the Investigator believes the results to be 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. For participants who are re-screened within 60 days of the original Screening do not need to repeat Screening procedures, with the exception of urine culture and laboratory test result.

8.1.1. Participant Referrals from an Outside Institution

Participant referrals from an outside institution will be required to have their tissue biopsy (TURBT) slides re-read at the investigative site by the local pathologist.

8.1.2. Bladder Post-Void Residual

The bladder PVR will be measured at the Screening visit per the study site's institutional guidelines (ie, bladder scan, catheterization). At the Screening visit, participants with a bladder PVR >350 mL after attempted second voiding will be excluded from the study. PVR measurement must be recorded in the eCRF prior to randomization.

8.2. Treatment Phase

Participants should receive initial dosing of study treatment within 7 days following randomization. The Treatment Phase (Week 0) will begin following random assignment into the study and is the period a participant received study drug (Cohort 1: TAR-200 + IV cetrelimab or Cohort 2: TAR-200 alone or Cohort 3: IV cetrelimab alone or Cohort 4: TAR-200 alone [participants with papillary disease only]). Randomization must not occur more than 7 days prior to Week 0. Treatment may continue until the participant has disease recurrence or progression, intolerable toxicity, withdraws consent, there is a decision by the Investigator to discontinue treatment, or the study is terminated, whichever occurs first. All PRO 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 either TAR-200 or IV cetrelimab. 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 with Sponsor approval.

Administration of IV cetrelimab and the placement of TAR-200 need not occur on the same day but should occur within CCI If 1 treatment is held, the other may still be administered in consultation with the Sponsor.

Cetrelimab administration will take place Q3W through Week 78 for Cohort 1 and Cohort 3 per the Schedule of Activities (Section 1.3).

The first infusion of IV cetrelimab should be administered over 60 (±10) minutes. In the absence of IRRs, subsequent infusions may be administered intravenously over 30 (-5/+10) minutes. Study drug is to be administered under the supervision of qualified site staff. For the first infusion, vital signs should be monitored immediately before the start of the infusion, every 15 to 20 minutes during the infusion, at the end of infusion (EOI) (+10 min), and 2 hours (±15 min) after the EOI. 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 IV cetrelimab, vital signs should be monitored immediately pre-dose, once during infusion at any time during the 30 minute (-5/+10 minutes) infusion, and at the EOI (+10 min).

Dose modification of IV cetrelimab is not permitted. Dose delay is the primary method for managing cetrelimab-related toxicities. If IV cetrelimab administration is delayed beyond CC [redacted] (Schedule of Activities, Section 1.3), then the dose will be considered a missed dose (see Section 6.5).

Cohort 1, 2, and 4: TAR-200 insertion will take place Q3W for the first 6 months (Week 0 to Week 24) on study and then every 3 months thereafter through study Year 2 (Week 36 to Week 99) per the Schedule of Activities (Section 1.3). Periprocedural prophylactic antibiotics should be administered around the time of cystoscopy) to reduce the risk of procedure related UTI. TAR-200 is co-packaged with the UPC. Participants will undergo insertion of TAR-200 into the bladder using the provided UPC in accordance with the IFU. All Investigators or healthcare provider 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. The TAR-200 may be replaced immediately per protocol or within the CCI [redacted] The TAR-200 insertion does not require a negative urine culture.

In all cohorts, for participants who end study drug at the protocol defined timepoint for both TAR-200 and IV cetrelimab and have not progressed, disease assessments through the end of study will be in accordance with the institutional guidelines and will be collected at least every CC [redacted] weeks C [redacted] -month) intervals through the end of study. These disease assessments will be based on an integrated evaluation of local cystoscopy, locally read urine cytology, and OS.

Throughout the Treatment Phase, the Investigator will assess response to study drug using findings from cystoscopy, bladder biopsy, centrally read urine cytology, and CT/MRI Scan with contrast through Year 3. Biopsy via a TURBT of visible lesions will be required if identified during cystoscopy. Efficacy assessments are described further in Section 8.10. For participants who complete study drug or discontinue study drug prior to the protocol defined timepoint without documented disease recurrence or progression, every effort should be made to continue monitoring their disease status according to the disease assessment schedule, until (1) the start of new anticancer treatment, (2) disease recurrence or progression, (3) withdrawal of consent, (4) death, or (5) the end of the study, whichever occurs first. Participants who recur or progress will continue to be followed for OS.

8.3. End of Treatment Visit

EOT is defined as the day the decision was made to permanently discontinue all study treatment.

- For Cohort 1, last dose is defined as the date of final TAR-200 removal or the last dose of IV cetrelimab was administered, whichever occurs later.
- For Cohorts 2 and 4, last dose is defined as the date of final TAR-200 removal.
- For Cohort 3, last dose is defined as the date the last dose of IV cetrelimab was administered.

An EOT visit will be performed after a participant's permanent discontinuation of study drug, either at the protocol defined EOT or for any other reason before that protocol defined timepoint. If the EOT visit coincides with a regular study visit, the EOT evaluations will be conducted in lieu of the regular visit assessments, and the data will be entered in the EOT visit in the eCRF. If a participant decides to discontinue treatment with TAR-200 between study visits (eg, during the indwelling period of a TAR-200 system), the Investigator must ensure the participant returns for removal of the TAR-200 system (if applicable).

Participants who discontinue study treatment should not be considered withdrawn from the study. The participant will continue to be followed for assessments described in the Schedule of Activities (Section 1.3). If the participant refuses to return for clinic visits or is unable to do so, every effort should be made to contact him/her or a knowledgeable informant by telephone to determine participant survival every 12 weeks through end of study. Each participant will be followed through end of study, unless he/she has died or withdrawn consent, or the study is terminated.

8.4. 30-Day Safety Follow-up Visit

The 30-Day safety follow-up visit should be performed 30 days (± 1 week) after the EOT visit (or after the last dose of study drug if the EOT visit was not performed) and to report any AEs that occur during that time. Reasonable efforts should be made to have the participant return for the safety follow-up visit.

8.5. 100-Day Safety Follow-up Visit

The 100-Day safety follow-up visit should be performed 100 days (± 1 week) after EOT visit (or after the last dose of study drug if the EOT visit was not performed) and to report any AEs that occur during that time. Reasonable efforts should be made to have the participant return for the safety follow-up visit. All AEs and SAEs must be reported up until at least 100 days after the last dose of study drug, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer (refer to Section 8.12.1 for further information).

The 100-safety day follow-up visit may be combined with another scheduled visit (ie, disease assessment visit); however, both sets of data must be collected and entered the eCRF.

8.6. Follow-up Phase

For participants who do not demonstrate disease recurrence or progression by the end of study drug treatment, disease status will be assessed in accordance with the institutional guidelines and will be collected at least every CCI (C month intervals) until disease recurrence or progression, death, withdrawal of consent or the end of the study, whichever occurs first. For participants who recur or progress while on study drug or during the follow-up phase, subsequent anti-cancer therapies and other malignancies will be collected in the eCRF and these participants will continue to be followed for cystectomy and OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

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

8.8. End of Study

The end of study will be achieved when the end of study definition, as outlined in Section 4.4, is met. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final participant's survival assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

8.9. Unscheduled Visits

Clinic visits not described in the schedule of activities 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.

8.10. Efficacy Assessments

Cohort 2 participants with a CR must have a CCI disease assessment visit at CCI from the date of onset of CR. The CCI disease assessment from onset of CR may occur in lieu of CCI disease assessment, if the two visits are within 6 weeks of each other. The CCI disease assessment post initial CR date will include assessment cystoscopy, urine cytology, TURBT bladder biopsy (if clinically indicated) and CT/MRI with contrast (if applicable).

8.10.1. Disease Assessments

8.10.1.1. Cystoscopy

Cystoscopy (all cohorts) will be performed as at Screening, and then every CCI weeks CCI [Year 1 and Year 2]), including at a visit at CCI post initial CR, for up to 2 years of treatment or until disease persistence, progression, or recurrence or as confirmed by positive central urine cytology or local/central pathology showing high-grade disease. Sites should consult with the Sponsor in the event of a positive local biopsy and absent/pending central pathology review before discontinuing study treatment. In Year 3 through the end of study, after the study treatment has ended, cystoscopy will be performed per institutional guidelines and will be collected at least every CCI weeks. For participants with CR, urine cytology from Year 3 through the end of study will be centrally reviewed for disease response. For participants who discontinue study treatment before Week 99 (Year 2), due to toxicity or reasons other than disease persistence, progression, or recurrence, cystoscopy should be performed every CCI weeks CCI [Year 1 and Year 2 to Year 3]) before the start of subsequent therapy/procedure (eg, radical cystectomy) during the Follow- up Phase. Whenever possible, the same individual should perform cystoscopy throughout the study for a given participant. Additionally, unscheduled cystoscopy may be performed if clinically indicated. Cystoscopy technology for bladder visualization (eg, white light, blue light) will be documented in the eCRF. Every effort should be made to use the same technology with a given

participant throughout the study. Redacted cystoscopy reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.

Consider administering anticholinergics, nonsteroidal anti-inflammatory drugs (NSAIDs), and bladder analgesics such as phenazopyridine, prior to or after TAR-200 removal. To mitigate the risk of UTIs, participants must receive at least one dose of periprocedural prophylactic antibiotics for any TAR-200 insertion or removal. Antibiotics for standard cystoscopy and TURBT may be administered in accordance with standard of care.

8.10.1.2. Urine Cytology

Urine specimens will be collected throughout the course of the study at specific timepoints in the SoA, including at a visit at CCI post initial CR, for a central cytopathologic assessment for all cohorts. Voided urine specimens will be collected and submitted for central cytopathologic review to assess for recurrence and/or progression of disease. Central review will be performed by a CAP/CLIA accredited laboratory, and a diagnostic report will be issued that may be used to guide clinical management at the Investigator's discretion. Additionally, an aliquot of the urine should be taken from the same collections and used for local cytopathologic evaluation to guide clinical management. Per the study design, if a cytopathologic diagnosis of SHGUC is resulted from an instrumented urine collection in the absence of a tissue diagnosis of HGUC, a voided urine specimen will be collected and centrally assessed to confirm recurrence and/or progression of disease.

Urine cytology does not need to be negative or atypical at Screening for participants with CIS. For participants with high-grade Ta/any T1 papillary disease diagnosis at Screening, an interval Screening urine cytology should be either atypical or negative for high-grade urothelial cancer, prior to randomization, to ensure a disease-free state at the initiation of study treatment.

Voided urine cytology will be locally assessed approximately 3 weeks prior to the Week CCI and Week CCI cystoscopy assessments CCI to assist with biopsy planning (tumor bed biopsies or systematic bladder biopsies). Local urine cytology results will be entered into the eCRF.

In Year 3 through the end of study, after the study treatment has ended, urine cytology will be performed per institutional guidelines and will be collected at least every CCI weeks. For participants with CR, urine cytology from Year 3 through the end of study will be centrally reviewed for disease response. For participants who discontinue study treatment before Week 99 (Year 2), due to toxicity or reasons other than disease persistence, progression, or recurrence, disease assessments should be performed CCI weeks CCI [Year 1 and Year 2 to Year 3]) before the start of subsequent therapy/procedure (eg, radical cystectomy) during the Follow-up Phase.

8.10.1.3. TURBT (Bladder Biopsies)

In accordance with the protocol, a cystoscopic biopsy is defined as 1) TURBT and/or 2) cystoscopic cold-cup biopsy. Confirmed CIS or papillary only diagnosis based on a bladder

biopsy/ TURBT conducted during the Screening phase or confirmed CIS or papillary disease only based on a prior biopsy, at the site or an outside institute, up to 3 months (90 days) prior to Screening, can be used for eligibility assessment. The biopsy with confirmed CIS or papillary disease only should also be submitted to the central laboratory. Recurrent CIS diagnosis, either during Screening or based on prior biopsy as mentioned above, should be within 12 months of the last dose of BCG. For all biopsies/TURBT specimens, the pathology report should document whether muscularis propria (detrusor muscle) is present. For patients with lamina propria invasion (T1) on the Screening biopsy/TURBT, muscularis propria must be present in order to rule out MIBC. Assessment cystoscopy during Screening will still be required to ensure bladder accessibility is adequate for insertion of TAR-200 and that any papillary disease has been completely excised. For Cohorts 1, 2, and 3, the Week [redacted] and Week 48 [redacted] bladder biopsy/TURBT assessments will be performed to determine the presence or absence of recurrent/progressive disease. Additionally, a TURBT may be performed at any time as clinically indicated for all participants.

Biopsies should be taken from any suspicious bladder mucosal area (if noted); otherwise, biopsies must be taken from the site(s) of old tumor. Voided urine cytology will be locally assessed approximately 3 weeks prior to the Week [redacted] and Week [redacted] week cystoscopy assessments [redacted] to assist with biopsy planning (tumor bed biopsies or systematic bladder biopsies). The pre-biopsy Week [redacted] and Week [redacted] local voided urine cytology will be documented in the eCRF. Systematic bladder biopsies should only be performed if urine cytology is suspicious for malignant cells and cystoscopy is negative. At any time, TURBT (biopsy) will be performed if clinically indicated to confirm local disease progression suspected from cystoscopy and prior to administration of further TAR-200. Antibiotics for standard cystoscopy and TURBT may be administered in accordance with standard of care. Biopsy samples will be evaluated by the local histopathology laboratory for clinical management at the discretion of the Investigator; however, all tissue biopsy sampling will be submitted for a central review of participant's disease status. Local histopathology results will be entered into the eCRF. Sites should consult with the Sponsor in the event of a positive local biopsy and absent/pending central pathology review before discontinuing treatment. A new low risk/low- grade papillary lesion does not constitute persistent or recurrent disease. Tissue slides/blocks from participants in all cohorts with any locally confirmed low or high-risk recurrence, or progression, will be sent for central histopathologic confirmation. Significant discordances between local and central pathology review will result in Sponsor Investigator consultation, with recommendation to disqualify participant from study. Any confirmed new low risk/low-grade papillary lesion must be resected to completion by TURBT/bladder biopsy, as is feasible, both prior to Screening and during study participation.

Redacted pathology reports (or equivalent) and other source documentation, may be required by the Sponsor for review and/or to address health authority requests.

8.10.1.4. CT/MRI Scan with Contrast

It is a preference for a CT Scan with contrast to be utilized instead of MRI. However, if a CT Scan with contrast cannot be done, a CT Scan without contrast may be performed. MRI may be used in the instance that neither the CT Scan with or without contrast may be performed. If iodinated IV

contrast is contraindicated, perform an MRI scan of the abdomen and pelvis using Gadolinium IV contrast, unless contraindicated. CT Scan with contrast will be performed during Screening to evaluate participants for the presence of locally advanced disease to the upper urinary tract or extravesical disease in the pelvis, abdomen, and/or chest. CT/MRI with contrast (Chest, Abdomen, and Pelvis) performed within 90 days prior to the date of ICF may be considered for eligibility review. All scheduled CT Scan assessments will be performed as indicated in the Schedule of Activities, including at a visit at CCI post initial CR , if applicable (Section 1.3). Unscheduled imaging may be performed if clinically indicated. Local CT/MRI imaging should be evaluated by the same individual throughout the study to limit inter-reviewer variability and the same methodology should be used for disease assessment at baseline and throughout the course of the study. Central review for imaging will not be performed.

Other diagnostic modalities should not be used exclusively to assess disease status in the absence of CT/MRI confirmation.

Magnetic Resonance Imaging Conditional Compatibility:

TAR-200 is magnetic resonance conditional. A participant with TAR-200 can be scanned safely in a magnetic resonance system immediately after placement 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.

Refer to the Laboratory Manual for instructions on sample handling.

8.10.2. Patient-Reported Outcomes

Health-related Quality of Life Assessments

8.10.2.1. EORTC-QLQ-C30

CCI [redacted]

[redacted].

8.10.2.2. EORTC-QLQ-NMIBC24

CCI [redacted]

8.11. Safety Assessments

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, and other safety evaluations at specified timepoints as described in the Schedule of Activities. AEs and SAEs will be collected from the time of the ICF signature to the end of 100-day safety follow-up visit.

Any clinically significant abnormalities or toxicities persisting at the end of the study will be followed by the Investigator until resolution or until reaching a clinically stable endpoint.

Adverse events will be reported and followed by the Investigator as specified in Section 8.12, 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.

8.11.1. Immune-Mediated Adverse Events

Every AE must be assessed by the Investigator regarding whether it is considered immune-mediated per Section 10.9, Appendix 9: Guidelines for Management of Immune-Related Adverse Events and Adverse Events of Clinical Interest. 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.

8.11.2. Physical Examinations

A complete physical examination including head, ears, eyes, nose, throat, and neck, cardiovascular, respiratory, abdomen, musculoskeletal, skin, and genitourinary systems will be performed at the Screening Visit only. Targeted physical examination will be performed at other

timepoints per the Schedule of Activities (Section 1.3). Physical exams may be performed at any time as clinically indicated. Height is assessed at the Screening Visit only. Weight will be measured at each study visit. The Investigator must review physical examination results and record any clinically relevant changes in either the medical history form or the adverse event form of the eCRF, as appropriate.

8.11.3. Vital Signs

Vital signs will be assessed per the Schedule of Activities (Section 1.3). Blood pressure (systolic and diastolic), heart rate, temperature, and weight will be assessed. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

The Investigator must review and record vital signs results in the eCRF and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

8.11.4. Electrocardiograms

12-lead ECGs will be performed as specified in the Schedule of Activities (Section 1.3), Screening and EOT. 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 arms or legs.

8.11.5. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in 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.

Prior to dosing, laboratory tests are to be completed per the protocol schedule of activities. Screening laboratory tests must be within 14 days prir to the Week 0 visit. If collected within 5 days prior to the Week 0 visit, these laboratory tests may be used in lieu of Week 0 of the required laboratory tests. TAR-200 insertions do not require a negative urine culture. 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 enrollment 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 Appendix 2: Clinical Laboratory Tests.

8.11.6. Pregnancy Testing

Pre-dose urine or serum samples will be obtained for β-hCG pregnancy testing in female participants of childbearing potential at timepoints indicated in the Schedule of Activities (Section 1.3). Females who are not of documented childbearing potential do not require a pregnancy test (Section 10.5). 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 in serum. The TAR-200 insertion and IV cetrelimab infusion will be done only upon confirmation of a negative pregnancy test. For POCBP, pregnancy testing should be conducted monthly (ie, between study visits) through 6 months after the last dose of study drug/study drug comparator, and at disease assessments in Year 4 and 5, per institutional guidelines.

8.11.7. ECOG Performance Status

CCI [redacted] The scoring information is provided in Section 10.7, Appendix 7: ECOG Performance Status Scale.

8.11.8. Genitourinary and Non-Genitourinary Procedures

Genitourinary events and procedures and all non-genitourinary procedures will be assessed at each visit through the 100-day safety follow-up visit. All events related to the genitourinary system must be captured as an adverse event and if a procedure is performed, it will be captured on the genitourinary or non-genitourinary procedure form.

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

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, 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.

AEs 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.

For study treatment that meets the definition of a combination product, malfunctions or deficiencies of a device constituent will be reported as a PQC (Section 10.4.6 and 10.10.2).

AEs be followed by the investigator as specified in Section 10.4 and graded according to the NCI CTCAE Version 5.0. Further details on AEs, SAEs, and PQCs 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).

8.12.1. 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 Main-study ICF is obtained until 100 days after the participant's last dose of study drug. 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 drug 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.

Serious Adverse Events

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 or within 24 hours of their knowledge of the event as required by local regulations.

SAEs, including those spontaneously reported to the Investigator within 100 days after the last dose of study drug, 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 , 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 their knowledge of the event as required by local regulations. The initial and follow-up reports of a SAE should be transmitted electronically or by facsimile (fax).

Device Deficiencies of the UPC and PQCs associated with TAR-200 or IV cetrelimab will be reported on the PQC form.

8.12.2. 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 adverse event 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 adverse events for which the participant is not specifically questioned.

8.12.3. 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 Deficiencies as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including 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.

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

The Sponsor assumes responsibility for appropriate reporting of adverse events 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. Device-related safety reporting (regarding UPC) will be done according to local and regional legislation where required, including the MDCG-2020-10/1 and 2 Guidance in line with Regulation (EU) 2017/745 in the EU. See Section 10.4, for additional information regarding SAE attribution and reporting.

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. All SAEs reported from study sites will be reviewed and assessed case by case by the Sponsor.

Refer to Section 10.13, Appendix 13 for a list of anticipated events. Note that the list of anticipated events is pertinent for reporting to the US FDA, US-based IECs/IRBs and Investigators only.

8.12.5. 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 the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study drug 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.

8.12.6. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Progression of disease should not be considered nor should be reported as an AE (or SAE). However, signs and symptoms of disease progression or of clinical sequelae resulting from disease progression/lack of efficacy that are determined by the Investigator to be of clinical significance 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).

8.12.7. Adverse Events of Special Interest

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

8.12.8. Product Quality Complaints (PQCs) and Medical Device Deficiencies

The TAR-200 used in this study is a combination product and therefore any malfunctions or deficiencies of the device constituent will be reported as PQC according to Section 10.4.6. All PQCs related to TAR-200 and IV cetrelimab 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 Section 10.10) and will be reviewed by the Investigator and Sponsor and reported in accordance with local legislation (see Section 10.10). If a PQC is reported for TAR-200 or IV cetrelimab, or a Device Deficiency is reported for the UPC, the respective product must be retained by the site under the appropriate storage conditions until a shipment request is received from the Sponsor. Refer to the IFU and IPPI as applicable for additional instructions.

NOTE: If an AE/SAE is reported as a consequence of the Device Deficiency, follow the processes outlined in Section 8.12, 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.

8.13. 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.

8.13.1. Evaluations

8.13.1.1. Sparse Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1, Cohort 2, and Cohort 4)

Sparse samples will be collected for assessment of gemcitabine and dFdU concentrations in urine.

One single collection of urine samples will be collected from participants within 24 hours pre-dose at Week 0 Visit. Two pooled 24-hr cumulative urine collections will be collected from participants as indicated below.

- One pooled 24-hour urine collection anytime between Days 2 to 7, following TAR-200 insertion on either Week CCI
- One pooled 24-hour urine collection anytime between Days 2 to 7, following TAR-200 insertion on either Week CCI
- 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. The 40 participants in the serial urine sampling are not required to complete the Week 0 and Week 3, 6, or 9 sparse timepoints as the serial urine sampling will meet these requirements.

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 one-day delay in drug release. Limited drug release occurs after 1 week. 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.

8.13.1.2. Serial Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 and Cohort 2)

- Serial urine samples for assessment of gemcitabine and dFdU concentrations in urine will also be collected according to the following schedule (also see SoA, Section 1.3) in approximately 40 participants across Cohorts 1 and 2. It is anticipated that 40 participants will participate in the serial urine sampling. 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. For these 40 participants, the Sparse Pre-dose timepoints at Week 0 and Week CCI do not need to be collected as this serial urine sampling will meet these requirements.
- One single urine sample collection, within 24 hours Pre-dose at Week 0.
- Beginning at Week 0, on all days from Day 1 through Day 7 (one pooled 24-hr cumulative urine collection per day).

- Beginning at Week [redacted], on all days from Day 1 through Day 7 (one pooled 24-hr cumulative urine collection per day).

Daily urine output over this sampling period in these approximately 40 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.

8.13.1.3. Plasma PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 and Cohort 2)

Blood samples will be collected from participants at the following 3 timepoints (which coincide with PK urine sparse sampling timepoints):

- Within 24 hours Pre-dose at Week 0.
- One sample collected between Days 2-7 following TAR-200 insertion on either Week [redacted] placements.
- One sample collected between Days 2-7 following TAR-200 insertion on either Week [redacted] placements.

Timepoints should coincide with sparse urine PK sample collection in individual participants. These blood samples will be collected for assessment of gemcitabine and dFdU concentrations in plasma.

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

Plasma and urine samples will be analyzed to determine concentrations of gemcitabine and dFdU using validated liquid chromatography/tandem mass spectrometry (LC/MS/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.

8.13.1.4. Serum PK/Immunogenicity Samples for Cetrelimab (Cohort 1 and Cohort 3)

Blood for the assessment of cetrelimab serum PK, including C_{min} (pre-infusion) and C_{max} (EOI), and anti-cetrelimab antibodies (ie, ADA) will be collected at the timepoints specified in the Schedule of Activities. All pre-infusion trough samples should be drawn within 30 minutes before IV cetrelimab infusion in the opposite arm. Post-infusion PK samples are collected from the arm opposite from infusion site at the EOI. Time of EOI will be documented in the eCRF. Blood samples will be processed to obtain serum for measurement of cetrelimab concentration by a validated analytical method by the Sponsor.

Serum Immunogenicity Samples for IV cetrelimab are to be collected. Blood samples will be collected, and serum will be analyzed for antibodies to cetrelimab using a validated immunoassay for ADA analysis. The incidence of antibodies against cetrelimab will be summarized for all participants who received at least one administration of study drug.

Additional details are provided in the Laboratory Manual. The exact date and time of dosing (including start and stop time of IV infusion and volume infused) 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. Biomarkers

Biomarker samples (tissue, blood, and urine) will be collected to evaluate the mechanism of action of TAR-200 in combination with IV cetrelimab, TAR-200 alone or IV cetrelimab alone in participants with HR-NMIBC (CIS with or without papillary disease). Samples may help to identify population subgroups that respond differently to TAR-200 in combination with IV cetrelimab, TAR-200 alone, or IV cetrelimab alone. The goal of the biomarker analyses is to understand the mechanism of action and clinical response relationships with TAR-200 in combination with IV cetrelimab, TAR-200 alone, or IV cetrelimab alone. For participants in Cohort 4, biomarker collections will not be performed.

Tissue for Immune Biomarkers, Molecular Subtyping, and Mutational Profiling

Tissue collected on study will be used to assess the baseline immune marker status, molecular subtype and mutational profile of participants' tumors, as well as identify changes in the tumor in response to study drug with TAR-200 in combination with IV cetrelimab, or TAR-200 alone, or IV cetrelimab alone. Tissue samples collected from participants at persistence, recurrence or progression will be used to assess molecular changes from baseline and understand resistance markers.

The following analyses may be performed:

- IHC analysis of immune markers on the TURBT samples.
- RNA sequencing on tumor specimens to conduct molecular subtyping and to evaluate changes after study drug. Whole exome sequencing may also be performed on the TURBT specimen at Screening.
- DNA mutation profiling to explore molecular markers of response and resistance
- The correlation of immune markers to clinical response of study drug (TAR-200 in combination with IV cetrelimab, or TAR-200 alone, or IV cetrelimab alone).

Circulating Biomarkers

Blood and urine samples for circulating biomarkers may be collected pre-dose at timepoints specified in the Schedule of Activities (Section 1.3).

Peripheral Immune Cell Profiling

Profiling of peripheral immune cells and determination of activation status will be performed in blood samples collected on study. T-cell and Treg enumeration and T-cell activation status will be assessed. Profiling of additional immune cell types, eg, natural killer cells (NK) and MDSCs may also be performed in blood samples.

The diversity of the T-cell receptor (TCR) repertoire will be determined in blood samples collected on study by performing TCR sequencing.

Circulating Tumor DNA

Urine for analysis of circulating tumor DNA (ctDNA) will be collected at multiple timepoints on study. ctDNA are fragments of DNA shed in urine.

Analysis of ctDNA offers the potential of a non-invasive method to assess the emergence of potential molecular markers of resistance.

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

Adjustments in the timing of biomarker collections may cease or timepoints may be modified during the study based on emerging data. However, the number of biomarker sampling will not increase.

Residual samples of blood, tissue, or urine 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.

8.15. Medical Resource Utilization and Health Economics

MRU 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 surgical procedures, and other 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 are outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

The statistical hypothesis for Cohorts 1, 2 and 3 is that the combination of TAR-200 and IV cetrelimab, TAR-200 alone, or IV cetrelimab alone will lead to a higher overall CR rate than observed in historical studies with chemotherapy (20% based on Valrubicin data described in Section 2.1, ie, $H_0 \leq 20\%$ vs. $H_a > 20\%$) in the population with CIS unresponsive to intravesical BCG therapy who are ineligible for or have elected not to undergo radical cystectomy.

The statistical hypothesis for Cohort 4 is that TAR-200 alone will lead to a 1-year DFS higher than 40% in the population with papillary disease only (high grade Ta or any T1) unresponsive to intravesical BCG therapy who are ineligible for or have elected not to undergo radical cystectomy.

9.2. Sample Size Determination

Per previous versions of the protocol, the sample size of 100 participants would provide over 90% power to reject the null hypothesis assuming an overall CR rate of 55% (Cohort 1) and the sample size of 50 participants will provide about 90% power assuming an overall CR rate of 40% (Cohorts 2 and 3), using 2-sided alpha = 0.05. After the futility analysis, the adjusted sample size of 80 participants for Cohort 2 will provide over 95% power to reject the null hypothesis at 2-sided alpha of 0.05. Table 21 describes the point estimate and its 95% exact confidence interval (two-sided) at selected number of participants with CR based on 80 participants in Cohort 2.

Table 21: Point Estimate and the 95% Exact Confidence Interval based on 80 Participants

Number of participants with CR	Observed CR rate	95% exact CI (2-sided)
40	50%	(39%, 61%)
44	55%	(43%, 66%)
48	60%	(48%, 71%)
52	65%	(54%, 75%)
56	70%	(59%, 80%)
60	75%	(64%, 84%)

CR=complete response; CI=confidence interval

The sample size of 50 participants in Cohort 4 will provide 93% probability to have the lower boundary of 95% CI of DFS at 1 year exceeding 35% (or about 78% probability exceeding 40% 1-year DFS), if we assume the 1-year DFS rate is 60%, 5% annual drop out rate, 7-month enrollment and additional 12-month follow up.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	Participants who were not screen failures and were assigned to an intervention group
Full	All enrolled participants who received at least one dose of study treatment.
Safety	All enrolled participants who received at least 1 dose of study treatment.

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

All enrolled participants in Cohorts 1, 2, and 3 will have confirmed CIS at enrollment and will be stratified based upon the presence or absence of concomitant papillary disease. The cohorts will be analyzed separately. There will be no formal comparison between the 4 cohorts. A side-by-side descriptive summary of efficacy will be provided to illustrate the contribution of TAR-200 or IV cetrelimab to the efficacy of the combination therapy in participants with CIS [with or without papillary] disease (Cohorts 1, 2, and 3).

9.4.2. Primary Endpoints

Primary Estimand for Cohorts 1, 2, and 3

- Population: participants with HR-NMIBC CIS unresponsive to intravesical BCG therapy who are ineligible for or have elected not to undergo RC.
- Variable: overall CR.

- Study Drug: TAR-200 in combination with IV cetrelimab, or TAR-200 alone, or IV cetrelimab alone.
- Intercurrent event: subsequent therapy. Hypothetical Strategy: Response after this intercurrent event will not be considered as a response.
- Summary: overall CR rate.

The primary efficacy endpoint, overall CR rate, is defined as the percentage of participants achieving a CR at any time post-treatment.

For Cohort 1, 2, and 3, the overall CR rate and its 95% exact confidence interval (CI) will be calculated based on binomial distribution. A Z test with normal approximation will be used to compare the CR rate with 20%.

The primary analysis will be performed approximately 6 months after treatment initiation of the last participant in Cohorts 1, 2, or 3. An additional analysis will be conducted approximately 1 year from the time of onset of last CR in Cohort 2.

Primary Estimand for Cohort 4

- Population: participants with HR-NMIBC papillary disase only unresponsive to intravesical BCG therapy who are ineligible for or have elected not to undergo RC.
- Variable: disease-free surivival (DFS)
- Study Drug: TAR-200 alone
- Intercurrent event: subsequent therapy. Hypothetical Strategy: censor DFS event occurred after subsequent therapy, as if the participants had continued treatment as planned and had not switched to subsequent anticancer therapies
- Summary: DFS rate

The primary efficacy endpoint for Cohort 4, DFS, is defined as the time from first dose of treatment to recurrence, progression or death due to any reason.

The distribution (median and Kaplan-Meier curves) of DFS will be provided using Kaplan Meier estimate. DFS rate at 12 months , 18 months, and 24 months will also be calculated based on the Kaplan-Merier estimate.

Two pre-specified analyses will be performed approximately 9 and 15 months after treatment initiation of the last participant in Cohort 4, respecitvely. Additional analysis may be performed if specified in the SAP.

9.4.3. Secondary Endpoints

Duration of response (DoR) is defined from the date of first CR achieved to the date of first evidence of recurrence or progression or death (whichever is earlier) for participants who achieve a CR. Participants who are free from recurrence, progression, or death will be censored at the last disease assessment. DoR rate will be estimated using the Kaplan-Meier method and the estimate of DoR at 1 year will be provided. Response at Weeks 24 and 48 will be assessed by cystoscopy,

centrally read bladder biopsy (for Cohorts 1, 2, and 3 only) and urine cytology, and imaging (if available).

OS is defined from the date of first dose of study treatment to the date of the participant's death. If the participant is alive or the vital status is unknown, then the participant's data will be censored at the date the participant was last known to be alive. The distribution (median and Kaplan-Meier curves) of OS will be provided using Kaplan-Meier estimates for all the randomized population.

Patient-reported Outcome (PRO) Assessments

The EORTC-QLQ-C30 and EORTC-QLQ-NMIBC24 will be descriptively summarized at each timepoint. Change from baseline of PRO endpoints will also be summarized descriptively over time.

Time to symptom deterioration in EORTC-QLQ-C30 and EORTC-QLQ-NMIBC24 will be analyzed descriptively.

9.4.4. Exploratory Endpoints

Time to cystectomy (TTC) is defined as the time from the date of first dose of study treatment to the date of the cystectomy. For participants who have not received cystectomy, data will be censored at the last study assessment. The distribution (median and Kaplan-Meier curves) of TTC will be provided using Kaplan-Meier estimates for all the randomized population.

Biomarkers Analyses

Associations between baseline levels and changes from baseline in select markers and the 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.

Medical Resource Utilization and Health Economics Analyses

Medical resource utilization and health economics will be descriptively summarized by intervention group.

The analysis of other exploratory endpoints will be provided in the Statistical Analysis Plan.

9.4.5. Safety Analyses

All safety analyses will be made on the Safety Analysis Set.

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 new or worsening AEs with onset date and time after the first dose through 100 days after the last study drug administration or prior to the start of subsequent anticancer therapy/procedure (eg, radical cystectomy), whichever is

earlier, or the follow-up AE (linked to an existing TEAE) with onset date and time beyond 100 days after the last dose of study intervention but prior to the start of subsequent therapy or any AE that is considered treatment-related regardless of the start date of the event, is considered to be treatmentemergent. All reported TEAEs will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment cohort.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study drug due to an adverse event, or who experience a SAE.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst AE grade experienced by the participant during the study will be provided as shift tables.

Clinical Laboratory Tests

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

Electrocardiograms

ECG measurements are taken at baseline and end of treatment visits. ECG interpretations (clinically significant, not clinically significant) will be summarized at baseline and end of treatment visits by cohort.

Vital Signs

Vital signs including temperature, pulse/heart rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically.

9.4.6. Other Analyses

An IDMC will be established as noted in Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

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 listing. For serial urine PK, PK parameters will be listed and summarized

using descriptive statistics. Details of the analyses will be described in the Clinical Pharmacolgoy 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 listed and summarized 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.

Immunogenicity Analyses

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 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. 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.

9.5. Interim Analysis

An IDMC will be established as noted in Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

A futility analysis was planned after 75 evaluable participants had adequate disease assessment post-baseline (Refer to Section 9.3 for the definition of evaluable analysis set). Any cohort could be terminated for futility if its overall CR rate is less than 20%.

On CCI, the IDMC reviewed and evaluated the data from the pre-specified futility analysisand recommended to continue the study with none of the cohorts meeting the futility threshold.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

ADA	anti-drug antibody
ADE	adverse device effects
ADL	activities of daily living
AE	adverse events
ALT	alanine aminotransferase
ASMP	Anticipated Events Safety Monitoring Plan
AST	aspartate aminotransferase
AUC	area under the curve
AxMP	Auxiliary Medicinal Product
BCG	Bacillus Calmette-Guérin
β-hCG	β-human chorionic gonadotropin
CCI	company confidential information
CIS	carcinoma in situ
CMV	cytomegalovirus
CPK	creatine phosphokinase
CRC	colorectal cancer
CRF	case report form
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
CyTOF	mass cytometry
dFdU	2',2'-difluorodeoxyuridine
dMMR	mismatch repair deficiency
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form(s)
eDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core
EORTC-QLQ-NMIBC24	European Organisation for Research and Treatment of Cancer-Non-Muscle Invasive Bladder Cancer
ECOG	Eastern Cooperative Oncology Group
EOI	end of infusion
EOT	end of Treatment
ePRO	electronic PRO
FDA	Food and Drug Administration
FIH	First in Human
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
HCV	hepatitis C
HIV	human immunodeficiency virus
HGUC	High-Grade Urothelial Carcinoma
HR-NMIBC	high-risk Non-muscle Invasive Bladder Cancer
HRQoL	health-related quality of life
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFU	Instructions for use
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	Investigational Medicinal Product

IPPI	Investigational Product Preparation Instructions
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous
LC/MS/MS	liquid chromatography/tandem mass spectrometry
mAb	monoclonal antibody
MIBC	muscle invasive bladder cancer
MRU	medical resource utilization
MSI	microsatellite instability
NCA	National Competent Authorities
NIMP	Non-Investigational Medicinal Product
NMIBC	Non-muscle Invasive Bladder Cancer
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
OTC	over the counter
PBMCs	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PMOA	primary mode of action
POCBP	participant of childbearing potential
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
PVR	Post-Void Residual
RBC	red blood cell
RC	radical cystectomy
RFS	Recurrent Free Survival
SAC	Safety Assessment Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SHGUC	Suspicious for High-Grade Urothelial Carcinoma
SJS/TEN	Stevens-Johnson syndrome/toxic epidermal necrolysis
SoA	Schedule of Activities
SOC	standard of care
SRP	study responsible physician
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TTC	time to cystectomy
Treatment Phase	period of time where a participant receives study drug
TURBT	transurethral resection of bladder tumor
UADE	unanticipated adverse device effect
UPC	Urinary Placement Catheter
USADE	unanticipated serious adverse device effect
UTI	urinary tract infection
W0D1	Week 0 Day 1
WBC	white blood cell

10.2. Appendix 2: Clinical Laboratory Tests

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

Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="2">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count (RBC)
Hemoglobin
Hematocrit</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="2">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.</td></tr>
<tr><td>Clinical Chemistry</td><td>Sodium
Potassium
Phosphate
Calcium
Albumin
Creatinine
Glucose (Fasting)
Total Protein
Thyroid Stimulating Hormone (TSH)
Triiodothyronine (T3*)
Free Thyroxine (T4)
HbA1c (at screening only)
*T3 is required at Screening and then only as clinically indicated.</td><td>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</td></tr>
<tr><td rowspan="2">Routine Urinalysis</td><td><u>Dipstick</u>
Specific gravity
pH
Glucose
Protein
Blood
Nitrite</td><td rowspan="2"><u>Sediment (if dipstick result is abnormal)</u>
Red blood cells
White blood cells
Epithelial cells
Crystals
Casts
Bacteria</td></tr>
<tr><td><u>Urine Culture</u></td></tr>
</table>

Laboratory Assessments	Parameters
Other Tests	• Serum Pregnancy Testing for participants of childbearing potential only • Serology (at Screening) 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 PCR viral levels to rule out active infection is required Hepatitis C virus (HCV) antibody: if positive, further testing quantitative PCR viral levels to rule out active infection is required • Coagulation Panel Prothrombin Time (PT) Activated Partial Thromboplastin Time (APTT) International Normalized Ratio (INR)

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 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 subInvestigators
- Documentation of subInvestigator 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 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 subInvestigators 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 Prestudy Documentation (above) and contracts for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant (or a legally acceptable representative) must give 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 must be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy. Informed consent may be obtained remotely. Refer to the Monitoring Guidelines.

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 must 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.

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.

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.

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 information about, and where required per applicable regulations, 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. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries.

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, or make requests concerning his or her personal data in accordance with applicable data protection law. 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. In the event of a data security breach, the Sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

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 IV cetrelimab and TAR-200, to understand urothelial cancer, to understand differential drug responders, and to develop tests/assays related to IV 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 7.4, Withdrawal from the Future Use of Research Samples).

10.3.6. Committees Structure

Independent Data Monitoring Committee

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, serious adverse events (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 cetrelimab and TAR-200 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 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 cetrelimab and TAR-200, 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 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 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 (multi-center) 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. In the event that 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 multi-center 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 multi-center 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 multi-center 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 interim results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order 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, and periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a local 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 may review 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 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 electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the Sponsor.

Data must be entered into 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) tool. If corrections to a eCRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- 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; intervention 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 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 study 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 another 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 CRF.

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 for Medicinal Products

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 on 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 AEs under Section 8.12.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event 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, adverse events include those resulting from insufficient or inadequate IFU, deployment, implantation, installation, or operation, or any malfunction of the device. It includes any adverse event resulting from use error or from intentional misuse of the investigational device.

Serious Adverse Event

An 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 an 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 must 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. This also includes the situation when treatment-invoked signs and symptoms of disease progression are determined by the Investigator to be more likely related to the study treatment than being expected from the underlying disease.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For cetrelimab and TAR-200, the expectedness of an adverse event 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.

Adverse Events and SAEs relatedness should be specified in the eCRF as related or not related to the TAR-200 + IV cetrelimab, TAR-200 alone or IV cetrelimab alone, or due to the procedure of the insertion (including the UPC) or removal of the TAR-200 (gemcitabine). If an AE or SAE is determined to be related to the UPC, go to Section 10.10, Appendix 10 for specific information regarding reporting requirements.

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 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; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention 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 intervention indicated.

Grade 5 Death related to AE.

* 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.

ADL=activities of daily living
Note: A semi-colon indicates 'or' within the description of the grade.

The Investigator should 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 treatment 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) 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 participant 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 CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the CRF.

10.4.5. Procedures

All Adverse Events

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 CRF. 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 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 study
- Investigator's name and 24-hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

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 a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (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 adverse event 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 intervention period.

Expected progression of disease should not be considered an adverse event (or SAE). However, if determined by the Investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment 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 a SAE Form, which must be completed and reviewed by a physician from the study site and transmitted in a secure manner to the Sponsor immediately, without undue delay or within 24 hours of their knowledge of the event as required by local regulations. The initial and follow-up reports of a 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 treatment 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, 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 appropriate storage conditions until a shipment request is received from the Sponsor (see SIPPM).

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 8.12.5, 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.

10.5.1. Definitions

Participant of Childbearing Potential (POCBP)

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

Participant 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 women 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 a participant on HRT, the participant will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if they wish 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, premenarchal participant experiences menarche) or the risk of pregnancy changes (eg, a participant who is not heterosexually active becomes active), the 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 should 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 should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

10.5.2. Examples of Contraceptives

10.5.2.1. HIGHLY EFFECTIVE METHODS [a](Failure rate of <1% per year when used consistently and correctly.)

USER INDEPENDENT - Highly Effective Methods.

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- 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 woman 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.*)

USER DEPENDENT - Highly Effective Methods

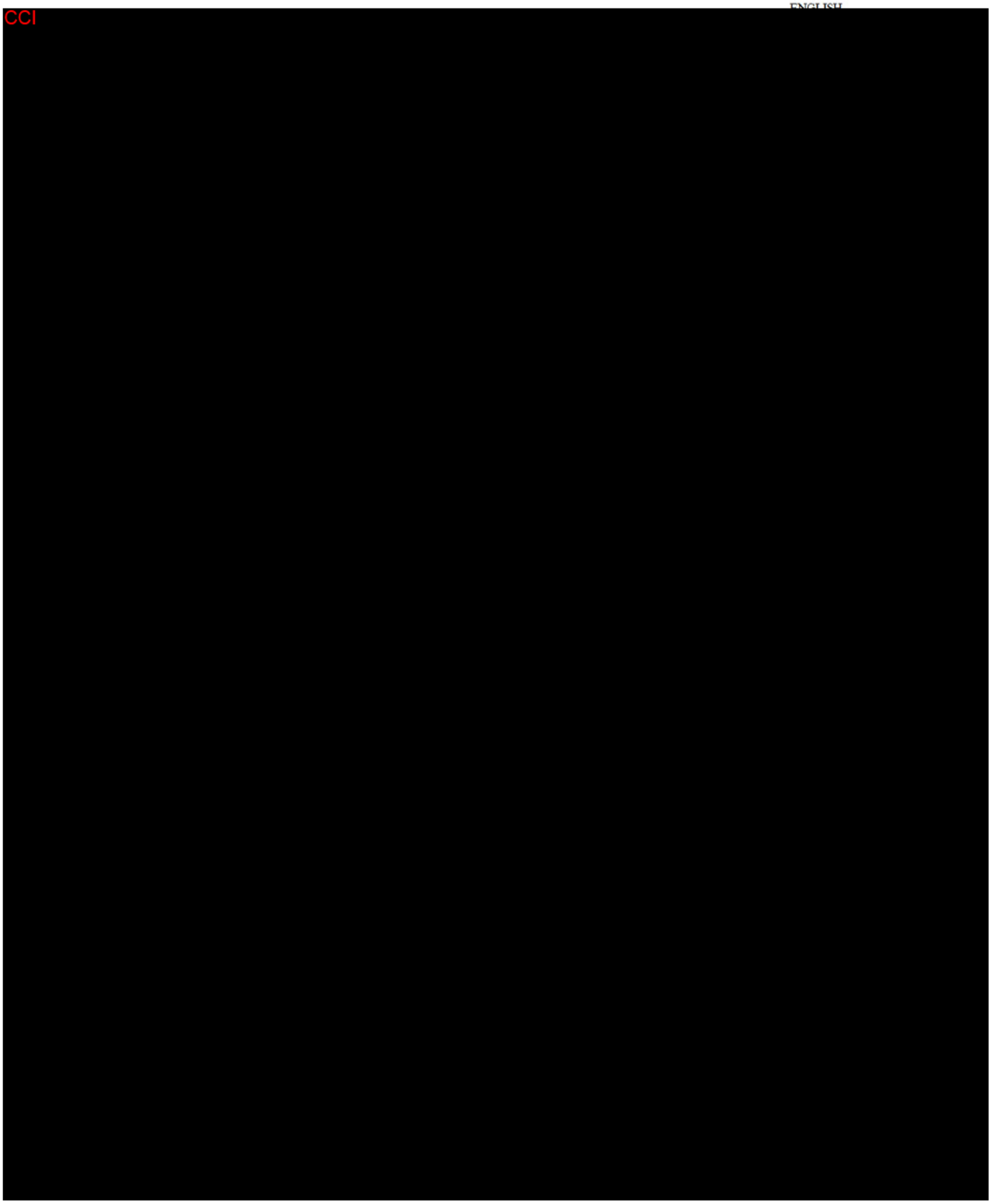
- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - oral
  - injectable
- Sexual abstinence

  (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.

10.6. Appendix 6: PRO Questionnaires

ENGLISH



ENGLISH

CCI

[redacted]

CCI

ENGLISH

CCI

10.7. Appendix 7: ECOG Performance Status Scale

CCI

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.

10.8. Appendix 8: 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 or quarantine by participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or 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 judgment 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.

If, as a result of the COVID-19 pandemic scheduled visits cannot be conducted in person at the study site, they 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 this 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 due to COVID-19 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.

Note: Administration of non-live vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed before or during this study. For guidance on vaccination, please refer to National Comprehensive Cancer Network (NCCN). Preliminary recommendations of the NCCN COVID-19 Vaccination Advisory Committee* Version 1.0 1/22/2021. NCCN https://www.nccn.org/covid-19/pdf/COVID- 19_Vaccination_Guidance_V1.0.pdf (2021), Garassino, M. C. et al. The European Society for Medical Oncology (ESMO) call to action on COVID-19 vaccinations and patients with cancer: Vaccinate. Monitor. Educate. Ann. Oncol. https://doi.org/10.1016/j.annonc.2021.01.068 (2021), and Desai et al COVID-19 vaccine guidance

for patients with cancer participating in oncology clinical trials Nature Reviews Vol 18; 313 https://doi.org/10.1038/s41571-021-00487-z.

Guidance specific to this protocol:

- Regarding the COVID-19 vaccination, the Sponsor has conducted a risk-benefit assessment for this study and determined that there is no anticipated safety concern for the concomitant use of COVID-19 vaccines. 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 eCRF. 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.

10.9. 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 immune-related adverse event (irAEs) that differ in nature, severity and duration as compared with 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 IV 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 immunosuppressive agents 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 6.5.2.

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 22.

Table 22: 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 consult 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 to 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 related to ALT/AST) should be further evaluated to exclude a diagnosis of treatment-emergent sclerosing cholangitis. An evaluation may include ultrasound liver, cholangiography and referral to gastroenterologist and/or hepatologist. Management of immune-related hepatic AEs is provided in Table 23.

Table 23: 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 to 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 to 2.0 mg/kg/d methylprednisolone IV or IV equivalent; start prophylactic antibiotics; consult gastroenterologist **Persistence >3 days or recurrence:** add mycophenolate mofetil 1 to 2 g bid if infectious cause 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: bid=twice a day; 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 24.

Table 24: Management of Immune-related Endocrinopathies

For guidelines for delaying a dose, refer to Section 6.5	
Asymptomatic TSH abnormality	**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. In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care. In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy. **With abnormal laboratory and pituitary scan:** 1.0 to 2.0 mg/kg/d methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy; consider prophylactic antibiotics **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 laboratory 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	Rule out sepsis. **Immediately:** initiate/stress dose of IV steroids with mineralocorticoid activity; fluids IV; consult endocrinologist.

For guidelines for delaying a dose, refer to Section 6.5	
current illness)	**Adrenal crisis ruled out:** treat as symptomatic endocrinopathy.
Type 1 diabetes mellitus (if new onset, including DKA) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)	For T1DM or Grade 3 to 4 Hyperglycemia: Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3 to 4 hyperglycemia associated with metabolic acidosis or ketonuria. Evaluate participants with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and serum or plasma C-peptide fasted.
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 needs 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; T4=thyroxine; 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 therapy. 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. However, more serious skin toxicities, including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and bullous rashes have been reported in rare instances with use of other checkpoint inhibitors. Rash with blisters, mucosal involvement, or bullous formation should trigger suspicion for the potential for a more serious cutaneous adverse reaction.

In some cases, rash and pruritus resolved without intervention. 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 25.

Table 25: Management of Rash

For guidelines for delaying a dose, refer to Section 6.5.	
Grade 1 to 2	**Immediately:** Symptomatic therapy (eg, antihistamines, topical steroids, avoid skin irritants) **Persistence ≥2 weeks or recurrence:** consider skin biopsy; consider 0.5 to 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 to 4	**Immediately:** consult dermatologist; consider skin biopsy; start 1.0 to 2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics, and monitor closely for progression for severe cutaneous adverse reaction (SCAR) **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 needs to be considered

Abbreviation: 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 26.

Table 26: 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 to 3	Monitor creatinine every ≤3 days **Immediately:** start 0.5 to 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 to 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 needs to be considered

Abbreviation: 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 27.

Table 27: 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 to 1.0 mg/kg/d methylprednisolone IV or oral equivalent **Worsening:** treat as Grade 3 to 4
Grade 3 to 4	**Immediately:** consult neurologist; treat symptoms according to institutional standards; start 1.0 to 2.0 mg/kg/d methylprednisolone IV or IV equivalent; prophylactic antibiotics **Worsening or atypical presentation:** consider immunoglobulins IV (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 needs to be considered

Abbreviation: IV=intravenous

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 28.

Table 28: Management of Pulmonary Adverse Events

For guidelines for delaying a dose, refer to Section 6.5	
Grade 1	Monitor for symptoms every 2 to 3 days; consider pulmonary and infectious-disease consult; re-image Q3W **Worsening:** treat as ≥Grade 2
Grade 2	Monitor symptoms daily; re-image every 1 to 3 days; pulmonary and infectious-disease consultation; consider bronchoscopy and lung biopsy; consider empiric antibiotics; consider hospitalization **Immediately:** start 1.0 to 2.0 mg/kg/d methylprednisolone IV or oral equivalent; prophylactic antibiotics **Persistence for 2 weeks or worsening:** treat as Grade 3 to 4 **Improvement to ≤ Grade 1 or baseline:** taper steroids over at least 4 weeks
Grade 3 to 4	Hospitalize; pulmonary and infectious-disease consult; consider bronchoscopy and lung biopsy **Immediately:** 1 to 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; IVIG=immunoglobulins IV; Q3W=every 3 weeks

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 29.

Table 29: 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 to 4
Grade 2	
Grade 3 to 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. Cardiovascular Events

Cardiovascular toxicities reported in anti-PD-1 therapy include myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis. Presenting symptoms can include fatigue, myalgias weakness, chest pain, shortness of breath and can be masked by or occur concomitantly with other irAEs (eg, pneumonitis, thyroid disease).

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

Because cetrelimab 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, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Management of IRRs is provided in Table 30.

All CTCAE Grade 3 or 4 IRRs should be reported immediately, without undue delay or within 24 hours of their knowledge of the event (as required by local regulations) to the Sponsor's Medical Monitor and reported as an SAE if criteria are met.

Table 30: 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 that 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 CRF.
Grade 3 to 4	**Stop infusion**; start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous 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 pruritus 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: CRF=case report form; IV=intravenous

10.9.13. 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 6.5.2, 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 6.1.2, TAR-200 Insertion).
- The definitions and procedures detailed in this Appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical investigation of medical devices.
- Both the Investigator and the Sponsor will comply with all local and regional medical device reporting requirements.
- 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.

10.10.1. Definitions (UPC only)

Adverse Event	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	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	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	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	An unanticipated serious adverse device Effect (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, for details on severity grading

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 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).

An assessment of severity grade will also be made by the participant according to the National Cancer Institute Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (NCI PRO-CTCAE Version 1.0). Note that there will be no data reconciliation between the PRO-CTCAE outcome measurement and adverse event clinical database.

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 4 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 Deficiencies 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.

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 of their knowledge of the event as required by local regulations. • 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 eCRF 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 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. Device Deficiency associated with a SAE: 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 than 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), 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 (Section 10.10.4).

10.10.4. Sponsor Reporting Requirements (UPC Only)

There are certain SAEs/SADEs and Device Deficiencies that will be reported to the regulatory authorities and IRBs/IECs as required by regional and local legislation. Specific requirements by region are listed in the sections below.

Reporting from the Sponsor to the National Competent Authorities (NCAs) in the European Union (Article 80(2) of Regulation (EU) 2017/745):

The following events are considered reportable to NCAs:

- 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 2 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: 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.

10.12. Appendix 12: Hepatitis B Virus Screening

The following hepatitis B virus (HBV) screening guide is to be used to determine participant eligibility (see Section 5.1 and Section 5.2), for the study:

- Individuals who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Individuals 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.
- Individuals who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Individuals who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Individuals 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 individual ***is eligible*** for this protocol. If the HBV DNA test is **positive**, the individual ***is NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the individual ***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.

10.13. Appendix 13: Anticipated Events (US only)

Purpose (US only)

This appendix applies only to the reporting of anticipated events by the Sponsor to the US FDA, and US-based Investigators and IECs/IRBs, in accordance with the FDA's guidance. The intent is to minimize the submission of a multitude of uninformative IND safety reports to these recipients.

Definition of an Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs, independent of exposure to study treatment, 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.

Background

The FDA acknowledges that certain SAEs can be anticipated to occur commonly in the study population regardless of drug exposure. Although these anticipated SAEs may meet the definition of unexpected (ie, SUSARs), because they are 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.

Reporting of Anticipated Events

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 8.12. Any anticipated event that meets serious criteria will be reported to the Sponsor as described in Section 8.12.1.

To meet US safety reporting, the Sponsor's Safety Assessment Committee (SAC) will periodically perform aggregate analysis of anticipated events per the Anticipated Events Safety Monitoring Plan (ASMP) (see below). 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.

Sponsor's Safety Assessment Committee

The Sponsor's SAC is an established safety committee, independent of the study team, that performs reviews of prespecified anticipated events at an aggregate level. The SAC will meet to aid in the recommendation to the Sponsor's study team as to 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.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate ASMP.

Anticipated Events for the Study 17000139BLC2001

The below list includes adverse events that are commonly anticipated for the disease stage, study population and background treatment, for which the Sponsor does not plan to report individual cases, regardless of the assessment of causality. This list is limited to those events for which an individual occurrence, or even an aggregate incidence consistent with the background rate in the study population, is inconsequential in the developing safety profile of the study treatment.

For the purposes of this study, the following events will be considered anticipated events:

[redacted]

10.14. Appendix 14: Cockcroft-Gault Formula and the CKD-EPI Creatinine Equation (2021)

The Cockcroft-Gault formula calculator can be found at:

https://www.kidney.org/professionals/kdoqi/gfr_calculatorcoc

The CKD-EPI Creatinine Equation (2021) can be found at:

https://www.kidney.org/professionals/kdoqi/gfr_calculator/formula

10.15. Appendix 15: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 4: (12 June 2023)

Overall Rationale for the Amendment: The primary focus of the protocol amendment was to include an additional cohort (Cohort 4) to evaluate the safety and efficacy of TAR-200 monotherapy in patients with papillary disease without CIS (ie, high-grade Ta or any T1).

Further updates include harmonization of shared protocol elements within the protocol and across protocols for the TAR-200/cetrelimab program. In the following table, new text that was added to the protocol is shown in **bold**. Text that was deleted is shown in ~~strike through~~ text.

Section Number and Name	Description of Change	Brief Rationale
Throughout the protocol; 1.1 Synopsis; 4.1 Overall Design; Treatment; 8.2 Treatment Phase	Study design modified to include an additional Cohort 4 of ~50 participants with papillary disease only (high-grade Ta or any T1) receiving TAR-200 alone. Removed language on stratification based on concomitant papillary disease.	Evaluate the safety and efficacy of TAR-200 monotherapy in patients with papillary disease only (high-grade Ta or any T1).
Throughout the protocol	Updates were made to specify the closure of Cohorts 1 and 3 and expansion of Cohort 2 following the interim analysis, in accordance with Amendment 3.	Reflect Sponsor's decisions on cohort modifications in accordance with Amendment 3.
Throughout the protocol	Study design modified to include Cohort 4 (TAR-200) alone in participants with papillary disease only (high-grade Ta or any T1 and absence of CIS)	Evaluate TAR-200 in participants with papillary disease only.
1.1 Synopsis; Section 3 Objectives and Endpoints; 9.4.4. Exploratory Objectives	Added Primary Objective and Endpoint for Cohort 4: "To evaluate disease-free survival (DFS) in participants treated with TAR-200 alone with papillary disease only (Cohort 4)."	
	Cohort 4 added to secondary and exploratory objectives as applicable.	
	Modified definitions of DFS (primary objective – Cohort 4 only), OS, and TTC to be measured from "the date of first dose" instead of "randomization"	Align with study design updates
2.1 Study Rationale	Existing references were updated and new information was added.	Support inclusion of papillary only participants on study.
2.3 Benefit-Risk Assessment	Added interim data from the study to describe the clinical activity and safety of TAR-200 alone	Additional information to support the benefit-risk assessment of TAR-200 monotherapy in treatment of HR-NMIBC.
1.3 Schedule of Activities, Table 1; 8.1 Screening	Statement added: For participants who require repeat biopsy/TURBT and/or repeat imaging during the standard 42-day Screening Phase, the Screening Phase may be extended from CCI .	Provide flexibility during Screening in case of repeat biopsy/TURBT and/or repeat imaging.
1.3 Schedule of Activities, Table 1; 8.10.1.4 CT/MRI Scan with Contrast	Note added: 'CT/MRI (Chest, Abdomen, and Pelvis) performed within 90 days prior to the date of ICF may be considered for eligibility review'	Improve clarity.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.3 Schedule of Activities, Table 5; Section 4.1 Study Design; Section 8.10.1.3 TURBT (Bladder Biopsies); Section 9.4.3 Secondary Endpoints	Specified that Scheduled Week 24 and Week 48 TURBT (Bladder Biopsies) are only required for participants in Cohorts 1, 2, and 3. Unscheduled TURBT (Bladder Biopsy) may be performed as clinically indicated for all participants.	Improve clarity.
1.1 Synopsis; 1.3 Schedule of Activities, Table 11; 8.13.1.1 Sparse Urine PK Samples for Gemcitabine and dfdU Analysis (Cohort 1, Cohort 2, and Cohort 4)	Included Cohort 4 for sparse urine pharmacokinetics.	To reflect the addition of Cohort 4 to sparse urine PK.
1.1 Synopsis; 1.3 Schedule of Activities, Table 16, Table 17, Table 18, Section 8.14 Biomarkers	Specified that biomarker collections are only applicable for participants in Cohort 1, 2, and 3 only.	Improve clarity.
1.3 Schedule of Activities, Table 1, Table 2, Table 3 Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10 6.1.1 TAR-200 Insertion 6.5.1.1 – Management of Adverse Events Related to TAR-200 and Procedures 6.8 Concomitant Therapy 8.10.1.1 Cystoscopy 8.10.1.3 TURBT (Bladder Biopsies)	Updated statements regarding use of prophylactic antibiotics from all intravesical procedures to TAR-200 insertion or removal procedures only.	Clarify use of prophylactic antibiotics associated only with the investigational product. All other intravesical procedures should follow standard of care.
4.4 End of Study Definition; 8.3 End of Treatment Vist	Included Cohort 4 in the Participant Completion of Treatment and End of Treatment definitions.	Reflect the addition of Cohort 4 in the Participant Completion of Treatment and End of Treatment definitions.
5.1 Inclusion Criteria; 1.1 Synopsis; 4.1 Study Design; 1.3 Schedule of Activities, Table 1; 8.10.1.2 Urine Cytology	Inclusion Criterion 2 modified to include diagnosis of **papillary disease only** (high-grade Ta, any 1 and absence of CIS).	Improve clarity and incorporate diagnostic eligibility requirements for Cohort 4
	Inclusion Criterion 3 modified to clarify that residual CIS is acceptable **for participants eligible for Cohorts 1, 2, and 3 only** and that **for patients with papillary disease only (Cohort 4), local urine cytology at screening must be negative or atypical (for HGUC).**	Improve clarity
	Inclusion Criterion 10 removed.	Enrollment into Cohorts 1 and 3 is closed, this criterion is no longer applicable for study eligibility.
	Inclusion Criterion 11 modified to include reference to the Cockroft-Gault Formula.	Improve clarity.
5.2 Exclusion Criteria	Removed Criteria 9, 17, 19, 24, and 25.	As enrollment into Cohorts 1 and 3 is closed, these

Section Number and Name	Description of Change	Brief Rationale
		criteria are no longer applicable for study eligibility.
5.4 Screen Failure	Modified statement on the assignment of a new participant number: "If re-screened a new participant number must be assigned."	Correction
6.1 TAR-200 and Cetrelimab Study Drug Dosing; 6.3 Measure to Minimize Bias: Randomization and Blinding	Clarified that treatment assignment will only occur for Cohorts 2 and 4.	Improve clarity
8.13.1.1 Sparse Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1, Cohort 2, and Cohort 4); 8.13.1.2 Serial Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 and Cohort 2)	Removed: "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 urine samples will be stored at -20°C or colder." Removed: "Labeled urine collection containers will be stored in the refrigerator during each 24-hour collection interval."	Prevent contradiction or redundancy with the information on urine collection, storage, and transfer provided in the Laboratory Manual.
8.3 EOT Visit	Modified the End of Treatment Visit (EOT) definition to include criteria for Cohort 4. Clarified EOT definitions for Cohorts 2 and 3.	Incorporate Cohort 4 in the EOT definition and improve clarity for existing cohorts.
8.11.3 Vital Signs; 9.4.5 Safety Analyses	Removed "respiration rate"	Correction to the scope of vital sign collection
9.1 Statistical Hypotheses; 9.2 Sample Size Determination; 9.3 Populations for Analysis Set; 9.4.1 General Considerations; 9.4.2 Primary Endpoints; 9.5 Interim Analysis	Clarifications were made to indicate which statistical hypothesis, general considerations, primary and secondary endpoints are applicable to Cohorts 1, 2, and 3 only.	Clarify statistical methods for Cohorts 1, 2, and 3 and add methods for Cohort 4.
	Updates were made to include the statistical hypothesis, sample size determination, general considerations, primary endpoint for Cohort 4.	
	The "enrolled" population and definition was added to the populations for analysis sets.	
	Updates were made to the language on interim analysis to indicate the actions post-futility	
9.4.6 Other Analysis	Details on serial urine PK analyses were added: "For serial urine PK, PK parameters will be listed and summarized using descriptive statistics."	Clarify serial urine PK analyses
Title page	Added: "EU CTR NUMBER: 2023-506146-23-00"	Comply with EU CTR requirements.
10.11 Appendix 10.11: Cytokine Release Syndrome – Severity Grading and Management	Appendix updated using NCI-CTCAE (Version 5.0) grading systems.	Align with NCI-CTCAE Version 5.0
10.14: Appendix 14: Cockcroft-Gault Formula and the CKD-EPI Creatinine Equation (2021)	New appendix. Links to the Cockcroft-Gault Formula and the CKD-EPI Creatinine Equation (2021) provided.	Inclusion criteria for study participants is creatinine clearance ≥30 mL/min based on Cockcroft -Gault formula; and to determine ineligibility to platinum therapy the CKD-EPI equation is used
10.15 Appendix 15: Protocol Amendment History	Summary of Changes Table from Protocol Amendment 3 moved to the Appendix.	Change for Protocol Amendment 4.

Section Number and Name	Description of Change	Brief Rationale
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, and the list of abbreviations and definitions updated (Section 10.1).	Align with updates to the oncology protocol template. Minor errors were noted.
	Language containing potential Company Confidential Information (CCI) and considered not essential for the protocol was deleted.	In accordance with the EU Clinical Trial Regulation (CTR) effective as of 31 January 2022

Amendment 3: (22 February 2023)

Overall Rationale for the Amendment: The primary focus of the protocol amendment was to update the study design to allow the closure of any of the 3 cohorts (intravesical TAR-200 in combination with IV cetrelimab, TAR-200 alone, or IV cetrelimab alone). In addition, updates were made to increase study visit window to [redacted] during Year 1, to revise the end of study definition, and to harmonize shared protocol elements within the protocol and across protocols for the TAR-200/cetrelimab program. In the following table, new text that was added to the protocol is shown in **bold**. Text that was deleted is shown in ~~strike-through~~ text.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.2 Schema; 4.1 Overall Design; 9.2 Sample Size Determination; 9.4.2 Primary Endpoint; 9.5 Interim Analysis	Study design modified to include the possibility of closure of any cohort after the results of the pre-specified futility analysis. In Figure 1, footnote added. In Section 4.1, subsection '**Study Treatment After Futility Analysis**' added to include updates in study design. Updates made in statistical sections.	To provide more flexibility in the study design after the pre-specified futility analysis outcome.
1.1 Synopsis; 3 Objectives; 9.1 Statistical Hypotheses	Study hypothesis was updated to include the 3 cohorts in the hypothesis testing. In Section 9.1, the following language was updated: 'will lead to a higher overall CR rate ~~(regardless of time)~~ than observed in historical studies with chemotherapy'.	
Throughout the protocol	Window of assessments in Year 1 updated from '~~±3 days~~' to [redacted] In Section 1.3, Schedule of Activities, Tables 2, 3, 5, and 8, note added for IV cetrelimab and TAR-200 administration: '**In the event a visit is scheduled that is within [redacted] window, every attempt should be made to maintain the initial Q3W regimen calculated from the date of first dose (W0D1)**'.	To provide more flexibility in the window for disease assessments in Year 1 without expected impact to the integrity of the trial.
	In Section 1.3, Schedule of Activities, in Tables 4, 7, and 10 (Follow-up Phase), visit window in Year 2 updated from '~~±7 days~~' to [redacted]	To improve clarity and for consistency with the study

Section Number and Name	Description of Change	Brief Rationale
		window used in the protocol.
1.1 Synopsis; 1.3 Schedule of Activities; 4.1 Overall Design; 4.4 End of Study Definition; 7.1 Discontinuation of Study Drug; 7.3 Withdrawal of Consent; 8.2 Treatment Phase; 8.6 Follow-up Phase; 8.8 End of Study, 8.10.1 Disease Assessments	End of Study definition was updated to (new text in bold): 'The **end of study**/study **completion** is considered ~~completed with the last follow-up OS assessment for the last participant in the study, or 5~~ **as either 2.5** years after the last participant is randomized **or 6 months after all participants have either completed or discontinued treatment, have withdrawn consent from the study, are lost to follow-up, or died, whichever occurs first**.' In SoA Tables 4, 7, and 10, Surveillance F/U note updated accordingly, and reference to Section 4.4 added. Same update made in Synopsis, Section 4.1, Section 7.1, Section 7.3, Section 8.2, Section 8.6, Section 8.8, and Section 8.10.1.	To increase flexibility for study completion, while allowing adequate safety follow-up for the last participant randomized.
	In Section 4.4, Participant Completion of Study definition updated to include requirement of completion of Follow-up Phases.	To harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
1.3 Schedule of Activities	In Table 1, note added for Eligibility confirmation: '**Must be assessed during screening period and confirmed prior to randomization'.** In Table 1, '**X'** added to screening Bladder PVR assessment.	To improve clarity.
1.3 Schedule of Activities; 10.2 Clinical Laboratory Tests	In Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, and Table 10: removed "TSH" from the following statement: • "T3, ~~TSH~~, and HbA1c at screening, then only as clinically indicated."	To ensure that regular and comprehensive examinations of thyroid function, inclusive of TSH, are performed after screening in accordance with Appendix 2, which lists TSH as a protocol required safety laboratory assessment.
	In Section 10.2 (Appendix 2), note added for T3: '***T3 is required at Screening and then only as clinically indicated**'.	For consistency with T3 assessments described in Schedule of Activities Tables.
1.3 Schedule of Activities; 8.11.5 Clinical Safety Laboratory Assessments	In Table 1 (Screening Assessments) language updated from 'within X days ~~of~~' to 'within X days **prior to'**. Same update in Section 8.11.5.	To improve clarity
1.3 Schedule of Activities	In Tables 2, 5, and 8, ECG assessment added indicating that '**ECG may be conducted at any time on study as clinically indicated'**.	To improve clarity, and for consistency across Schedule of Activities tables.
1.3 Schedule of Activities; 8.5 100-Day Safety Follow-up Visit	In Tables 4, 7, 10, and 19 (Follow-up Phase), window for 100 Day Safety F/U Visit modified from CCI to CCI Same update made in Section 8.5.	To increase flexibility in 100-day F/U visit.
1.3 Schedule of Activities	In Tables 4, 7, 8, and 10, urine cytology assessment updated to: 'Urine Cytology ~~for~~	For consistency within the protocol and across SoA tables.

Section Number and Name	Description of Change	Brief Rationale
	~~participants with CR~~ will be sent for central review'.	
Throughout the protocol	'~~Woman of childbearing potential (WOCBP)~~' updated to '**participant of childbearing potential (POCBP)**'	To use inclusive language and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
1.3 Schedule of Activities; 8.13.1.2 Serial Urine PK Samples for Gemcitabine and dFdU Analysis (Cohort 1 and Cohort 2).	In Table 12, note updated to: 'it is anticipated that ~~the first~~ 40 participants…' Same update made for urine sampling in Section 8.13.1.2.	To improve clarity.
1.1 Synopsis; 1.3 Schedule of Activities; 3 Objectives and Endpoints; 8.14 Biomarkers	In Table 16, redefined tissue biomarker 'RNA Seq' to '**DNA/RNA sequencing**'. Exploratory objective and Section 8.14 updated to include **urine samples** and rationale updated.	Broaden scope to allow for targeted DNA sequencing as well as RNA sequencing, in accordance with the exploratory objectives of the study. Improved clarity for use of urine samples.
	In Table 16, added 'at the time of **persistence**'. Same update made in Section 8.14.	To improve clarity.
	In Table 17, included '**Blood biomarker**' for assessing peripheral immune response. In Section 8.14, removed specific methodologies for peripheral immune cell profiling. Exploratory objective updated to: 'Peripheral immune **cell profiling and characterization** of ~~response by~~ T cell receptor (TCR) ~~sequencing~~ **repertoire**.'	To ensure the evaluation of peripheral immune response is performed in accordance with the exploratory objectives of the study.
	In Table 17 and Table 19, removed collection of blood ctDNA seq biomarker. Description of ctDNA assessments updated in Section 8.14 and reference to blood ctDNA was removed.	Blood for ctDNA removed for futility. To improve clarity.
	In Section 8.14, **DNA mutational profiling** was added.	To align with updated Schedule of Activities and to improve clarity
1.1 Synopsis; 2 Introduction; 6.1 Study Treatment (s) administered	Updated the descriptions of TAR-200 and the Urinary Placement Catheter (UPC).	To improve clarity and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
2.2.3 TAR-200 Clinical Studies; 2.2.5 Combination Therapy; 2.3 Benefit-risk Assessment	Number of participants treated with TAR-200 alone or TAR-200 + IV cetrelimab was included, Phase 1 clinical studies were summarized, and completion date for TAR-200-103 was included. Phase 2 and Phase 3 summaries were updated with enrollment status. Summary of Phase 2 Study 17000139BLC2002 added.	To improve clarity. To provide an updated summary of TAR-200 ongoing studies.
2.2.4 Cetrelimab Clinical Studies	Number of studies and number of participants updated.	To improve clarity.

Section Number and Name	Description of Change	Brief Rationale
	Summary of cetrelimab Study 63723283LUC1001 updated, including updates in PK data and deletion of information related to SC cetrelimab.	To provide an updated summary of cetrelimab studies.
3 Objectives and Endpoints; 4.1 Overall Design	Exploratory objective and endpoint of exploring gemcitabine and dFDU concentrations in biopsied tissue was deleted. PK analysis of biopsied tissue deleted from Section 4.1.	To improve clarity in PK objectives and endpoints, since this was not an exploratory objective of the study.
4.1 Overall Design	Section 4.1.2 was added to include the Diversity and inclusion language (moved from Section 5 in Protocol Amendment 2). Language updated: '~~For further discussion~~ **Details** of diversity metrics and goals ~~refer to the latest version of the Diversity Plan~~ **will be outlined in the Sponsor's Diversity Plan**.	To harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program. To clarify a Diversity Plan will be submitted.
4.2 Scientific Rationale for Study Design	Description of patient-reported outcomes updated.	To improve clarity.
4.3 Justification for Dose	For TAR-200, modification made to better describe dosing during Study Years 1 and 2.	To improve clarity.
5.1 Inclusion Criteria	Inclusion criterion 2 modified: text deleted ~~(eg, <20% variant histologic subtype).~~	To improve clarity.
	Inclusion criterion 11 modified. Language for renal function modified to 'Creatinine clearance ~~> 40~~ **≥30** mL/min using the Cockcroft-Gault formula'	Based on health authority feedback and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
	Inclusion criterion 12 modified to use '**participants**' instead of '~~males or females~~'. Statement for non-breastfeeding participants added: '**including participants temporarily withholding breastfeeding in order to participate in the study**'.	To harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
5.2 Exclusion Criteria	Exclusion criterion 1 modified to: '**Presence or history of** histologically confirmed, muscle invasive, locally advanced, nonresectable, or metastatic urothelial carcinoma', new text in bold.	To provide greater clarity in the definition of histologically confirmed disease (to clarify it can refer to active presence or history of disease).
	Exclusion criteria 3 and 21 updated to specify the indicated time is **prior to randomization**.	To improve clarity.
	Exclusion criterion 10 modified to replace '~~planned start~~' by '**prior to the initiation of study treatment**' and 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.	For consistency throughout the protocol and to improve clarity on types of vaccines allowed.
	Exclusion criterion 11 modified to: 'Active infection requiring systemic IV therapy **within 14 days prior to randomization**'.	For consistency across protocols for the TAR-200/cetrelimab program.
	Exclusion criterion 30 deleted.	This exclusion criterion was not applicable to this study

Section Number and Name	Description of Change	Brief Rationale
		as the investigational products are not expected to impact healing of wounds or ulcers.
5.5 Criteria for Temporarily Delaying Administration of Study Treatment	Language to describe delay in TAR-200 administration was updated for consistency with Section 6.5.1. Language to describe delay in cetrelimab administration was added.	To improve clarity.
6.1 Study Treatment(s) Administered; 6.1.2 TAR-200 Removal; 6.4 Study Treatment Compliance; 8.2 Treatment Phase	Table 20 updated to include Type, Route of administration, Use, IMP, and NIMP/AxMP information.	To improve clarity and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
	In Table 20, dosing instructions updated to specify cystoscope **should be flexible** and to include **that a rigid cystoscope can be utilized for removal when clinically needed**. Same clarification added to Section 6.1.2, TAR-200 Removal, and language about removal updated to 'must be performed by a **trained healthcare provider**~~the Investigator/or a trained, credentialed designee~~'. In Section 6.4, language updated to: 'TAR-200 will be inserted and removed from the bladder by **documented and** trained Investigators or ~~trained and crednetialed~~ designees'. In Section 8.2, language updated to: 'All Investigators **or healthcare provider designees** must have training completed ~~per~~ **and documented in accordance with** TAR-200 training guidance' (new text in bold).	
6.1.1 TAR-200 Insertion	Statement added to indicate **the bladder should not be completely empty when TAR-200 is inserted.** Bladder analgesics corrected: ~~phenopyrazidine~~ replaced by **phenazopyridine**.	To improve clarity and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
6.2 Preparation/Handling/Storage/ Accountability	In the Accountability section, '~~treatment accountability form~~' was 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~~'. IFU was added as guidance information for TAR-200.	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 describe 'Management of adverse events' prior to 'Dose Modification'. Cross-references 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.
	List of cetrelimab-related immune-related AEs (irAEs) requiring delay or discontinuation updated.	To match irAEs reported in the cetrelimab IB

Section Number and Name	Description of Change	Brief Rationale
6.6 Continued Access to Study Treatment After the End of the Study	Section 6.6, added.	To harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
6.7 Treatment of Overdose	Evaluation of participant by the Investigator updated to 'in consultation with the **Study Responsible Physician (SRP)** ~~Sponsor's Medical Monitor~~'.	To improve clarity.
6.8.2 Prohibited Medications	The following was removed from the list of prohibited medications: '~~concurrent traditional or herbal medications intended for general health support~~'. Vaccinations updated to 'Vaccinations with live vaccines should not be administered **within 30 days of the initiation of study treatment (refer to Section 5.2),** during study treatment, and for 90 days following completion of study treatment (**non-live or non-replicating vaccines such as** annual inactivated influenza or COVID-19 vaccine, **or monkeypox are** allowed', new text in bold.	To improve clarity and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
7.1 Discontinuation of Study Drug	For conditions for Sponsor to close the study, added 'the right to close **the enrollment or** the study', and '**in case of poor enrollment**'	To improve clarity.
7.4 Withdrawal From the Future Use of Research Samples and 10.3.5 Long-term Retention of Samples for Additional Future Research	Section 10.3.5 added in Appendix 3. In Section 7.4, duplicated information about long-term retention of samples deleted.	To improve clarity and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
8 Study Assessments and Procedures	Under 'Home Health Care and Telehealth Visits', language updated to: 'Site visits may be replaced with telephone visits during **a major disruption, eg, natural disaster, pandemic, regional crises** ~~national disaster~~.	To provide flexibility for major disruptions other than a national disaster.
	Under 'Sample Collection and Handling', text added: '**The instructions above are applicable for collection of biomarker and PK samples. For collection and handling of other samples, local laboratories should follow local procedures, and for handling of central lab samples, the Laboratory Manual that will be provided should be followed'.** Study-Specific Materials updated to remove ~~PRO Questionnaire(s)~~ and to update **e**PRO completion guidelines (new text in bold).	To improve clarity.
8.3 End of Treatment Visit	End of Treatment Visit description included for each cohort.	To improve clarity.
8.10.2 Participant-Reported Outcomes	Heading updated to '~~Paricipant~~**Patient** Reported Outcomes'. Subheading updated to '**Health-related** Quality of Life Assessments'.	To improve clarity.

Section Number and Name	Description of Change	Brief Rationale
	Cross-references to Appendix 6 (Section 10.6) added.	
8.11.2 Physical Examinations	Text deleted: 'clinically relevant changes ~~occurring during the study~~'.	To improve clarity.
8.11.6 Pregnancy Testing	The following sentence was deleted: '~~The Sponsor will provide home pregnancy testing kits as needed for testing between study visits~~'.	To provide flexibility in the supply of home pregnancy testing kits.
1.3 Schedule of Activities; 8.12 Adverse Events, Serious Adverse Events, and Other Safety Reporting; 9.4.5 Safety Analyses; 10.4.6 Product Quality Complaint Handling; 10.4.7 Contacting Sponsor Regarding Safety, Including Product Quality; 10.10 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	Text regarding PQC updated to 'PQC ~~including~~ **and** Device Deficiencies'. Cross-references to Appendices included or deleted when applicable. Sub-headings in Section 8.12 modified with updated terminology. In Section 8.12.8, text added: 'If a **PQC is reported for TAR-200 or IV cetrelimab**, or a Device Deficiency is reported for the UPC, **the respective product must** ~~should~~ be retained ~~until further instruction~~ **by the site under the appropriate storage conditions until a shipment request is received** from the Sponsor'. Reference to the IPPI was added. Same note added to Schedule of Activities tables 2, 3, 5, 6, 8, and 9 (PQC Assessments). In Section 10.4.6, text added: '**A PQC may have an impact on the safety and efficacy of the product**'. Device deficiency text was deleted from Section 8.12 and Section 10.4.6. A reference to Appendix 10 was added in Section 8.12. Reference to PQC form included in Section 8.12.1. In Section 9.4.5, '~~and product quality complaints~~' was deleted from safety analyses In Section 10.4.6, procedures for PQC reporting were updated.	Per the latest Sponsor template/Standard Operating Procedures (SOPs) and regulatory reporting requirements. To improve clarity.
	Section 10.10 was updated: subsections created; headings modified.	
8.12.5 Pregnancy; 10.5.3 Pregnancy During the Study	Section 10.5.3 was deleted and pregnancy language that was missing in Section 8.12.5 was moved to this section.	To avoid repeated information, to improve clarity.
8.13 Pharmacokinetics; 9.4.6 Other Analyses	Headings updated. Details about blood, plasma and urine samples added to Section 8.13.1.3.	To improve clarity.
	Details about serum immunogenicity were added to Section 8.13.1.4 and Section 8.13.1.5 Serum Immunogenicity for Cetrelimab/Analytical Procedures (Cohort 1 and Cohort 3) was deleted.	
	In Section 9.4.6, Pharmacokinetic Analyses were updated.	
	In Section 8.13.1.1, statement deleted about sparse urine PK sample collection: '~~Labeled urine collection containers will be stored in the refrigerator during each 24-hour collection~~	For consistency with the Laboratory Manual.

Section Number and Name	Description of Change	Brief Rationale
	~~interval and then transferred to the study clinic where the urine samples will be stored at -20°C or colder~~'.	
9.4.5 Safety Analyses	Descriptive statistics of ECG data and QTc intervals updated with the deletion of '~~at each scheduled timepoint~~'.	To improve clarity.
10.2 Appendix 2: Clinical Laboratory Tests	Text added with instructions for laboratory tests, including cross-references to SoA tables. Text in bold added: 'HIV antibody**: if positive, further testing of CD4 count and HIV viral load should be carried out**'.	For consistency 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' (new text in bold).	To improve clarity.
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 for Medicinal Products	In Section 10.4.1 Adverse Event Definitions and Classifications, sentence deleted: '~~If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study treatment and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality~~).	To improve clarity on AE reporting, since reporting will be conducted by the Sponsor and the Investigator does not assess expectedness.
	In Section 10.4.1 Adverse Event Definitions and Classifications, language for combination products was deleted.	
	In Section 10.4.3 Severity Criteria, text on CTCAE V5.0 and reporting of AEs with fatal outcome/Grade 5 deleted.	To align with updates to the Sponsor oncology protocol template and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
	In Section 10.4.5 Procedures, the following statement was added for SAEs: '**In this latter case, these will be reported if they fulfill the SAE definition**', and reference to Appendix 4 included.	To improve clarity and to align with the Sponsor oncology protocol template
10.5 Contraceptive and Barrier Guidance	Language about participant not of childbearing potential updated to include participants with '**congenital abnormalities resulting in sterility'.** Language about user independent and user dependent highly effective contraceptives updated. Footnote '**a**' about failure rates added.	To align with updates to the Sponsor oncology protocol template and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.
10.8 Appendix 8: Study Conduct During a Natural Disaster	Language updated.	To align with updates to the Sponsor oncology protocol template and to harmonize shared protocol elements across protocols for the TAR-200/cetrelimab program.

Section Number and Name	Description of Change	Brief Rationale
10.9 Appendix 9: Guidelines for Management of Immune-related Adverse Events and Adverse Events of Clinical Interest	Appendix updated to align with guidance provided in the cetrelimab IB Edition 7, including the addition of a new section for Cardiovascular Events (10.9.11). Updates made for gastrointestinal adverse events, hepatic adverse events, endocrinopathies, rash, pulmonary adverse events, and uveitis and visual complaints. Cross-references to tables in the Appendix included.	To align with guidance provided in the cetrelimab IB for management of irAEs that may occur with cetrelimab therapy.
8.12.4 Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events; 10.13 Appendix 13: Anticipated Events (US Only)	In Section 8.12.4 the following statement was deleted: '~~For the purposes of this open-label study, there is no anticipated events list~~' and a cross-reference to Appendix 13 was added. Appendix 13 Anticipated Events added to the protocol.	To minimize the submission of anticipated events by the Sponsor to the US FDA, and US based Investigators and IECs/IRBs, in accordance with the FDA's guidance on reporting anticipated events.
10.14 Appendix 14: Protocol Amendment History	Summary of Changes Table from Protocol Amendment 2 moved to the Appendix.	Change for Protocol Amendment 3.
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, and the list of abbreviations and definitions updated (Section 10.1).	To align with updates to the oncology protocol template. Minor errors were noted.
	Language containing potential Company Confidential Information (CCI) and considered not essential for the protocol was deleted.	In accordance with the EU Clinical Trial Regulation (CTR) effective as of 31 January 2022

Amendment 2: (04 March 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
6.5.1.1 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 [redacted] to Week [redacted] as well as for participants who have achieved complete response (CR).	To clarify guidance on the clinical management of TAR-200 related AEs, including drug delays and discontinuations.

Section Number and Name	Description of Change	Brief Rationale
	Streamlined criteria for TAR-200 drug delay or removal.	
10.9.2 Hepatic Adverse Events	Added monitoring for participants who have predominant cholestatic pattern of liver injury to conduct further evaluations and exclude a diagnosis of treatment-emergent sclerosing cholangitis.	To bring awareness of the occurrence of a rare but potentially severe adverse event of programmed-cell death-1 (PD-1) inhibitor-related sclerosing cholangitis (PSC).
6.1.1 TAR-200 Insertion	Added guidance on performing a post-insertion cystoscopy following TAR-200 insertion.	This section was updated to provide more information regarding the post-insertion cystoscopy procedure.
CCI [redacted]	[redacted]	[redacted]
1.1 Synopsis; 1.2 Schema; 1.3 Schedule of Activities 4.1 Overall Design 6.5.1.1 TAR-200 Participant Stopping Safety Criterion; 8.1 Screening 8.10.1.1 Cystoscopy; 8.10.1.2 Urine Cytology; 8.10.1.3 TURBT (Bladder Biopsies)	Updates were applied to the Screening, Treatment Phase, and Follow-Up Phase schedules to align with the main section of the protocol.	To clarify eligibility, Screening requirements and assessments as well as on study disease assessments; to align descriptions across cohorts and with clarifications in the main sections of the protocol, enhance readability, and provide a more consistent presentation
1.3 Schedule of Activities 6.1.1 TAR-200 Insertion 6.5.1.1 TAR-200 Participant Stopping Safety Criterion	TAR-200 should not be administered less than 14 days after any procedure resulting in traumatized urothelium during the biopsy (eg, gross hematuria).	To provide guidance on TAR-200 insertion in case of traumatized urothelium after biopsy and ensure participant safety.
2.2.3 TAR-200 Clinical Studies 2.2.3.1 Development in Muscle Invasive Bladder Cancer 2.2.3.2 Development in Non-Muscle Invasive Bladder Cancer; 2.2.5 Combination Therapy; 2.2.4 Cetrelimab Clinical Studies	Updates were made to reflect the latest information for the clinical program, with corresponding update to references.	To provide the most current information pertaining to completed and ongoing clinical studies.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; Table 1; 5.1 Inclusion Criteria 5.2 Exclusion Criteria	Clarifications were made to Inclusion Criterion #2, #3, #6, #10, #12, #14. Removed Exclusion Criterion #12.	Clarifications to inclusion and exclusion criteria.
6. Study Treatment and Concomitant Therapy; Table 20	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.
8.5 100-Day Safety Follow-Up Visit; 8.11 100-Day Safety Follow-Up Visit;	Revised to clarify that treatment-related adverse events should be collected from the time of signed ICF to 100 day safety follow-up visit for all cohorts.	This change was made to align with the schedule of assessments and ensure that the AE reporting time frame in consistent among cohorts.
9.3 Populations for Analysis Set; 9.4.5 Safety Analyses	Clarified statistical definitions and updated details on listings summarizing laboratory, adverse events, vital signs, and ECG data as specified in the Statistical Analysis Plan	Clarifications.
8.12 Adverse Events, Serious Adverse Events, and Other Safety Reporting; 8.12.8 Product Quality Complaints and Medical Device Deficiencies; 10.4.2 Attribution Definitions; 10.4.6 Product Quality Complaint Handling; 10.4.7 Contacting Sponsor Regarding Safety, Including Product Quality	Added further details 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.	Change made to clarify device safety reporting requirements for TAR-200 and the UPC.
10.5.2 Examples of Contraceptives	Subsection on examples of not highly effective methods of contraception was removed.	To streamline contraceptive examples specific to those allowed on study.
10.13 Appendix 13: 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 2.
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, and the list of abbreviations and definitions updated (Section 10.1).	To align with updates to the oncology protocol template. Minor errors were noted.

Amendment 1: (13 July 2021)

Overall Rationale for the Amendment: The primary focus of the protocol amendment was to incorporate feedback from multiple health authorities thereby integrating multiple country-specific protocols into a single global amendment. In addition, updates were made to harmonize consistent protocol elements across all protocols for the TAR-200/cetrelimab program.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.2 Schema	Changes made to correspond with updates to the main section of the protocol	Consistency between sections.
1.2 Schema	Added Figure 2 and Figure 3 showing a timeline of study dosing and key assessments.	To provide clarity/visual representation of the dose schedule and assessments across all Cohorts.
1.1 Synopsis; 3 Objectives and Endpoints; 4.1 Overall Design	The description of the key secondary endpoint of complete response (CR) was revised, including a change in terminology from "durability of CR" to "duration of CR."	Clarification of the secondary endpoint CR.
3 Objectives and Endpoints; 9.4.3 Secondary Endpoints	Definitions of endpoints were revised for duration of response (DOR) and overall survival (OS). Product Quality Complaint (PQC) assessment was deleted as a secondary endpoint.	Update and clarification of secondary endpoints.
9.4.3 Secondary Endpoints; 9.4.4 Exploratory Endpoints	Time to cystoscopy (TTC) was moved from Section 9.4.3 to note as an Exploratory Endpoint.	Correction and clarification
9.4.5 Safety Analyses	All safety analyses and PQCs will be made on the Treated Analysis Set.	Revision to analyzed set.
1.3 Schedule of Activities	Table format for renumbered Tables 1 through 10 was revised; changes included the addition of a separate table to capture screening and randomization activities, separation of the treatment phase and follow-up phases into separate tables, the addition of a 100-Day Safety Follow-Up (F/U) period to Cohort 2, and the relocation of footnotes to notes for specific activities. Assessments across cohorts were aligned as applicable.	Adoption of new table format/revisions were made to enhance readability and provide a more consistent presentation across SunRISe protocols.
1.3 Schedule of Activities	Hematology timepoints during the Follow-up Phase were aligned across cohorts; this included: • An added collection at the 100-Day Safety F/U period in Cohort 2 (renumbered Table 7), and • The addition of a collection during Disease Assessments Year 4-5 in all cohorts (see renumbered Tables 4, 7, and 10).	Alignment of assessments across cohorts.
1.3 Schedule of Activities	Serum pregnancy testing was deleted from the Follow-up Phase at the 30- and 100-Day Safety F/U period (Cohorts 1 and 3, renumbered Tables 4 and 10, respectively), and at the 30-Day Safety F/U period in Cohort 2 (renumbered Table 7).	Deleted as serum pregnancy testing is only needed at Screening, and as a confirmation of a positive urine pregnancy test.
1.3 Schedule of Activities; 5.4 Screen Failures; 8.1 Screening	The Screening Period was revised from C to C days.	Revised to provide a wider screening window and align with other SunRISe protocols.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities; 8.2 Treatment Phase	The Randomization Phase was revised from 3 to 7 days.	Revised to provide a wider screening window and align with other SunRISe protocols.
1.3 Schedule of Activities; 8.13.1.1 Sparse Urine Sampling (Cohort 1 and 2); 8.13.1.2 Serial Urine Sampling (Cohort 1 and 2)	Updated instructions pertaining to urine collection and sampling (text and renumbered Tables 11 and 12).	This change was made to clarify urine collection requirements for PK analysis.
1.3 Schedule of Activities; 8.5 100-Day Safety Follow-Up Visit	Section updated as shown: 'Reasonable efforts should be made to have the participant return for the safety follow-up visit, to be scheduled 100 days (+7 days) after the EOT visit ~~(or after the last dose of cetrelimab if the EOT visit was not performed)~~ and to report any AEs that occur during that time.' Tables were updated accordingly: For renumbered Table 14, the 'Week C or EOT' timepoint was deleted, a 'Week C timepoint added, and footnotes revised to reflect the change. For renumbered Table 15, the 'EOT' and '30-D Safety F/U' timepoints were deleted, a 'Week C timepoint added, and footnotes revised to reflect the change.	Clarification of timing
1.3 Schedule of Activities; 8.13.1.4 Serum PK Samples for Cetrelimab (Cohort 1 and 3)	Added a Week 3 collection timepoint to renumbered Table 14. Updated text to address end of infusion (EOI) sampling and documentation.	Serum PK timepoints for cetrelimab were updated.
1.3 Schedule of Activities; 3 Objectives and Endpoints; 4.1 Overall Design; 8.14 Biomarkers	Edits (including the addition of Table 18) were made to address the assessment of biomarkers in urine.	Urine samples will be collected for analysis of circulating tumor DNA (ctDNA).
1.3 Schedule of Activities	Note added recommending that urine culture at screening be performed with adequate time for treatment of potential positive urine cuture prior to Week 0.	This change was made to mitigate the risk of active infection at start of treatment.
1.1 Synopsis; 4.1 Study Design; 8.10.1.1 Cystoscopy	Revised treatment windows for cystoscopy and urine cytology for Year 1: ±3 days and Year 2-3: ±7 days.	Alignment of treatment windows with those cited in the Schedule of Activities for Year 1 versus Year 2-3.
6.7 Concomitant Therapy; 8.11.8 Genitourinary and Non-Genitourinary Procedures	Genitourinary events and procedures and all non-genitourinary procedures will be assessed at each visit through the 100-day safety follow-up visit.	Safety follow-up extended from 30- to 100-days.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities; 8.11.2 Physical Examinations; 8.11.7 ECOG Performance Status	Added targeted physical examination and Eastern Cooperative Oncology Group (ECOG) evaluation to coincide with other disease assessments in all cohorts. Corresponding notes were also updated to clarify requirements for these evaluations.	These changes were made to enhance safety monitoring and to meet a request from the Czech and German Health Authorities.
1.3 Schedule of Activities	The Schedule of Activities was updated to ensure that MRU assessment is conducted at visits until disease progression.	Clarification of assessment timing
1.3 Schedule of Activities	Additional clinical laboratory collection timepoints at Weeks CCI were added to renumbered Tables 9 and 10 for Cohort 3.	Laboratory test result were added to ensure safety prior to conducting cystoscopy and CT/MRI procedures.
1.3 Schedule of Activities	Notes for clinical laboratory test result were revised for the following points: • Fasting glucose is required, • Coagulation panels are required every 12 weeks through Year 2 (while on study drug), • Coagulation studies will not be performed during Year 3. and • T3 and HBA1c are only required as clinically indicated.	Changes made based on the safety profile of the study drugs, and to ensure consistency among cohorts for purposes of comparison.
1.3 Schedule of Activities	Renumbered Table 1, Screening Cystoscopy: Deletion of the note stating 'Assessment cystoscopy at the screening visit is only required for participants referred from an outside institution.'	Correction
1.1 Synopsis; 8.10.1.2 Urine Cytology	Text revised to note that voided urine specimens (rather than instrumented urine specimens collected from bladder washings during cystoscopy and TURBT procedures) will be collected and submitted for central cytopathologic review to assess for recurrence and/or progression of disease.	Text added to clarify that voided urine specimens are the preferred cytology samples.
1.1 Synopsis; 1.3 Schedule of Activities; 8.10.1.2 Urine Cytology; 8.10.1.3 TURBT (Bladder Biopsies)	Text and notes in renumbered Tables 2, 5, and 8 (ie, the Year 1 tables for Cohorts 1, 2, and 3) were revised as voided urine cytology will be locally assessed approximately 3 weeks prior to the C and C -week assessments (ie, at Weeks CCI rather than 2 weeks prior.	Change in collection timepoints to align with scheduled study visits.
1.1 Synopsis; 4.1 Overall Design; 8.10.1.4 CT/MRI Scan with Contrast	Text revised to note that new papillary lesions must be resected to completion by TURBT, as is feasible, both prior to screening and during trial participation.	Clarification of TURBT procedures and requirements.
1.3 Schedule of Activities	In renumbered Table 7 (Cohort 2 Years 3-5), an assessment was added for the 30-day follow-up phase for assessment of EORTC-QLQ-C30.	Corrected to align with EORTC-QLQ-NMIBC24 assessment.
1.3 Schedule of Activities	In renumbered Table 10 (Cohort 3 Follow-up), the Week 120 and 144 timepoints for EORTC-QLQ-C30 and EORTC-QLQ-NMIBC24 were deleted.	Corrected to align timepoints across cohorts.
1.1 Synopsis	Statement added: 'Participants who initiate post-protocol alternative therapies will continue to be followed for OS. Additional therapies will be collected where possible.'	Added to clarify follow-up requirements for OS.

Section Number and Name	Description of Change	Brief Rationale
7.3 Withdrawal of Consent; 8.3 End of Treatment Visit	Text added that if a participant withdraws consent, a visit must be scheduled for TAR-200 removal(if required), and a final evaluation.	To ensure all TAR-200 systems are removed prior to study discontinuation.
1.1 Synopsis; 4.1 Study Design	Unscheduled cystoscopy and biopsy may be performed as clinically indicated.	Clarification regarding allowed cystoscopy/biopsy procedures.
1.1 Synopsis; 4.1 Study Design; 8.1 Screening; 8.10.1.3 TURBT (Bladder Biopsies)	Conditions for patient eligibility were updated and/or clarified, and included the following: All enrolled participants will have confirmed CIS within 12 months of completion (last dose) of adequate BCG therapy. Definition of adequate BCG treatment; Update to note that peri-operative intravesical chemotherapy prior to study treatment is allowed per institutional guidelines.	Clarification of diagnosis criteria and qualification of adequate BCG treatment.
5.1 Inclusion Criteria	Modified Inclusion Criterion 2 (to 2.1) to clarify that the diagnosis of high-risk Non-muscle Invasive Bladder Cancer (HR-NMIBC) must be of a persistent or recurrent nature. Adequate BCG treatment (including timing) was also qualfied.	Clarification of diagnosis criteria.
1.3 Schedule of Activities; 5.1 Inclusion Criteria; 8.11.6 Pregnancy Testing; 10.5 Appendix 5: Contraceptive and Barrier Guidance	Added note regarding monthly pregnancy testing for 6 months following the last administration of study drug. Modified Inclusion Criterion 12 (to 12.1) to provide greater clarity in contraceptive requirements (including restrictions on sperm/ova donation and breastfeeding). Information was also added that male and female participants should be advised on the options for banking of sperm and ova for reproductive conservation. Modified Inclusion Criterion 13 (to 13.1) to specify that a negative serum pregnancy test must be obtained within 72 hours of the first dose of study drug. Modified Appendix 5: Contraceptive and Barrier Guidance to provide greater clarity in contraceptive requirements and to remove tubal occlusion as a highly effective method of contraception.	These changes were made to minimize the risk of pregnancy during study participation, to improve safety related to contraception, and to align with guidance from the Clinical Trials Facilitation and Coordination Group (CTFG).
1.3 Schedule of Activities; 8.11.6 Pregnancy Testing	Urine pregnancy timepoints were added to ensure that for women of childbearing potential (WoCBP), pregnancy testing will be conducted monthly (ie, at least every 4 weeks, and between study visits) through 6 months after the last dose of study drug/study drug comparator, and at disease assessments in Year 4 and 5, per institutional guidelines.	Changes to minimize the risk of pregnancy during study participation, and to clarify timing of urine pregnancy testing across cohorts.

Section Number and Name	Description of Change	Brief Rationale
	For test conducted between visits, participants are advised to report any pregnancy test to the Investigator immediately.	
5.2 Exclusion Criteria	Updated Exclusion Criteria as follows: Criterion 2 (to 2.1): Text revised to:'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 nephrouretrectomy more than 24 months prior to initiating study.' Criterion 3 (to 3.1): Potential allowed exceptions for active malignancies updated. Criterion 4 (to 4.1): Text added regarding inability to treat with intravesical BCG. Criterion 7 (to 7.1): Clarified that participants should not have history of uncontrolled cardiovascular disease 3 months prior to screening. Criterion 10 (to 10.1): Updated to allow inactivated vaccines for emergency use (eg, COVID-19 vaccines). Criterion 11 (to 11.1): Added cross-reference to UTI criterion; minor clarification made re: systemic therapy. Criterion 15 (to 15.1): Updated to allow peri-operative intravesical chemotherapy prior to study treatment. Criterion 23 (to 23.1): Updated to note participants must have no culture evidence of $>10^5$ CFUs to be eligible. Criterion 27 (to 27.1): TAR-200 urinary placement catheter description updated.	These changes were made to provide increased clarity for the specific exclusion criteria.
1.3 Schedule of Activities; 5.2 Exclusion Criteria; 10.2 Appendix 2: Clinical Laboratory Tests	Added HIV and Hepatitis B and C testing at screening. Updated Exclusion Criterion 21 (to 21.1) to align with screening testing for HIV. Updated Exclusion Criterion 22 (to 22.1) to align with screening testing for Hepatitis B and C. Updated Appendix 2: Clinical Laboratory Testing to indicate screening testing of HIV and Hepatitis B and C.	This change was made to ensure participants do not enter the study with HIV or Hepatitis B or C.
1.3 Schedule of Activities;	Text indicating that at least one dose of prophylactic periprocedural antibiotics must be administered for	Revisions were made to ensure/clarify administration of

Section Number and Name	Description of Change	Brief Rationale
6.1.1 TAR-200 Insertion; 6.7 Concomitant Therapy; 8.10.1.1 Cystoscopy	intravesical study procedures to mitigate the risk of procedure related UTI was added to or clarified in the aforementioned sections.	prophylactic antibiotics in order to prevent UTI.
1.3.Schedule of Activities; 6.1.1 TAR-200 Insertion; 6.1.3 Cetrelimab Administration	Revised instruction related to timing of TAR-200 and cetrelimab dosing to indicate that for participant comfort insertion of TAR-200 should occur at least CCI before the start of or after the completion of the cetrelimab infusion.	This change was made to clarify the timing of TAR-200 and cetrelimab administration.
6 Dosage and Administration; 6.1.3 Cetrelimab Administration	Added details of cetrelimab dosing consistent with that presented in other areas of the protocol and aligned text with other SunRISe protocols. Additionally, information regarding TAR-200 and cetrelimab (ie, manufacture, provision, excipients, and overdose) was transferred from Section 6.1.3 to Section 6, along with renumbered Table 16.	These changes were made to provide all dosing information in a single location within the protocol amendments, as well as to harmonize information across all SunRISe protocols.
6 Dosage and Administration 6.1.4 Combination Products	Removed reference to Instructions for Use (IFUs) within participant kits.	IFUs will be provided separately to ensure translation to local language(s).
6.1.1 TAR-200 Insertion; 6.1.2 TAR-200 Removal	Added information and reformatted section to provide TAR-200 insertion and removal information. Added Figure 3: Loading and Deployment (Insertion) of TAR-200 using the Urinary Placement Catheter. Added Figure 4 for TAR-200 removal.	These sections were added/updated to provide more information regarding the TAR-200 insertion and removal process, as well as to harmonize information across all SunRISe protocols.
6.1.2 TAR-200 Removal; 6.2 Preparation/ Handling/Storage/ Accountability; 6.4 Study Intervention Compliance	Added wording to indicate investigators and trained designees who were performing insertion or removal of TAR-200 must be credentialed. Exact phrasing was also aligned with other protocols in the program.	This change was made to clarify personnel requirements for insertion and removal of TAR-200.
1.3 Schedule of Activities 8.12. Adverse Events, Serious Adverse Events, And Other Safety Reporting; 8.12.4 Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events	Added “Device Deficiencies” to line regarding PQC reporting in the Schedule of Activities. Text added: ‘Device-related safety reporting (regarding Urinary Placement Catheter) will be done according to local and regional legislation where required, including the MDCG-2020-10/1 and 2 Guidance in line with Regulation (EU) 2017/745 in the EU. See Section 10.4 for additional information regarding SAE attribution and reporting.’ Added Appendix 12: 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 to provide instructions for device-related reporting associated with the urinary placement catheter.	Change made to clarify device-related reporting requirements and comply with European Union (EU) Medical Device Regulations (MDR).

Section Number and Name	Description of Change	Brief Rationale
6.1.2 TAR-200 Removal	Note added to indicate that palliative radiation may only be administered after a 10-day gemcitabine washout after TAR-200 removal.	This addition was made to clarify when palliative radiation may be safely administered.
6.7.2 Prohibited Medications	Updated section to add a statement that live vaccines should not be administered while on study treatment and for 90 days following the completion of study treatment, and to note that the administration of traditional or herbal medications while on study is prohibited.	Changes were made to provide clarification on management of vaccine administration and traditional or herbal medicines in study participants.
6.7. Concomitant Therapy; 6.7.1 Permitted Medications	Text added to state: 'Anticoagulation should be used with caution in this patient population due to procedural interventions.'	Statement added to ensure participant safety related to antithrombotic medications, (including effects potentiated by concomitant use with gemcitabine).
6.7. Concomitant Therapy	Section updated to include the recording of all therapies that differ from study treatment, and any concomitant therapies used in conjunction with any new or worsening serious adverse events (SAEs).	These changes were made to ensure participant safety.
6.4 Study Intervention Compliance	Text edited to indicate that cetrelimab is to be administered in a qualified medical research center.	Administration at an oncology center is not necessary.
1.1 Synopsis (Efficacy Evaluation); 4.1 Overall Design; 8.10.1.4 CT/MRI Scan with Contrast	Clarified that CT/MRI scans with contrast (where applicable) will be performed on the abdomen, pelvis and chest, rather than on the abdomen, pelvis, and thorax.	Clarification/alignment on preferred terminology and use of CT/MRI scans.
1.3 Schedule of Activities; 6.7 Concomitant Therapy; 10.2 Appendix 2: Clinical Laboratory Tests	Coagulation panel testing including Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), and International Normalized Ratio (INR), were added to all Cohorts to coincide with clinical laboratory evaluation. A statement regarding caution with use of anticoagulant concomitant medications was added.	These changes were made for enhanced safety due to preclinical prolongation in prothrombin and to meet a request from the Czech and German Health Authorities.
10.2 Appendix 2: Clinical Laboratory Tests; 10.3.7 Data Quality Assurance	Clinical laboratory testing will be performed by (and data transmitted from) the local laboratory.	Correction; clinical laboratory test result are performed locally, not centrally.
1.1 Synopsis; 1.2 Schema; 1.3 Schedule of activities; 4.1 Overall Design	Year 2 was redefined from Week 96 to Week 99, (except as otherwise noted for Cohort 3).	Timing updated to coincide with exposure to TAR-200 (ie, removal at Week 99).
5.5 Criteria for Temporarily Delaying Administration of Study Intervention; 6.5.1. TAR-200 Missed Dosing Cycles	Definition of skipped dose added, along with clarification of dose modification (ie, early removal, delayed placement, discontinuation).	This change was made to clarify the circumstances for a skipped TAR-200 dose and dose modification.
6.5.2.1 Cetrelimab Dose Delay	Definitions for skipped dose and dose interruption were added.	This change was made to clarify the circumstances for a skipped, interrupted, delayed,

Section Number and Name	Description of Change	Brief Rationale
	Language on discontinuation recommendations was refined, with instruction added regarding the continuation of TAR-200 only dosing. The list of drug-related immune-related adverse events (irAEs) requiring dose delay was corrected.	or discontinued cetrelimab dose.
6.5.2.2 Cetrelimab Dose Discontinuation	Section updated for the following: ALT and AST elevation criteria updated. Edit made to note that a participant must discontinue for a treatment-related AE that doesn't resolve to Grade ≤1 or **baseline** within 12 weeks of the last dose. Removal of the discontinuation criterion of 'Any Grade 4 drug-related toxicity'	ALT and AST values were updated to align with Hy's Law; edits were made for clarification or to remove duplicate or redundant criterion.
6.5.1.1 TAR-200 Participant Stopping Safety Criterion	Modified TAR-200 safety stopping criteria to indicate any Grade ≥2 allergic reactions will require permanent discontinuation of the study drug. Reorganized the section to improve clarity of criteria for dose delay and permanent discontinuation of TAR-200. Added text to note that if TAR-200 dosing is permanently discontinued, the Sponsor may continue treatment with cetrelimab (Cohort 1 only).	To enhance safety of stopping criteria for those experiencing allergic reactions and clarify overall delay and discontinuation criteria.
6.5.1.1 TAR-200 Participant Stopping Safety Criterion; 7.1 Discontinuation of Study Drug; 7.2 Discontinuation of Study	Additional information regarding discontinuation while TAR-200 indwelling. Text added to clarify what should happen if the patient is benefiting from study drug and/or to state that the patient must commit to a clinic visit to have the TAR-200 removed and perform an EOT Visit	This change was made to provide instruction in the event a participant discontinues the study with a TAR-200 system indwelling.
8.3. End Of Treatment Visit	EOT definition added. Text added to state that the patient must commit to a clinic visit to have the TAR-200 removed and perform an EOT Visit and to state how participants will be followed for certain information after discontinuing treatment.	Add clarity regarding definition and procedures for early discontinuation.
9.5 Interim Analysis	Text added to note that if Cohort 1 is terminated for futility, Cohorts 2 and 3 will continue unless the Sponsor decides to stop the entire study.	Clarification
8.5 100-Day Safety Follow-Up Visit; 8.12.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 9.4.5 Safety Analyses	Minor changes to wording of section clarifying that treatment-related adverse events should be collected beyond 100 days after last treatment while participants are in study follow-up.	This change was made to clarify the AE reporting time frame.

Section Number and Name	Description of Change	Brief Rationale
8.2 Treatment Phase	Minor changes to wording of section to clarify the time windows for vital sign monitoring.	This change was made to clarify time period for monitoring post cetrelimab infusion.
1.3 Schedule of Activities; 4.1 Overall Design; 10.4.6 Product Quality Complaint Handling	Clarified text to state that identified PQCs should be reported at any time during the treatment phase. Clarified that the definition of a PQC includes any PQC related to any study intervention; updates included the addition of PQC collection in Cohort 3 (refer to renumbered Tables 8 and 9). Referral to the SIPPM was added to Section 10.4.6.	To clarify that PQCs should be reported for any study intervention during the treatment phase.
6.5.2 Cetrelimab	Table 14 was deleted.	The table is not needed, as there is no retreatment with cetrelimab (only dose delay).
2 Introduction; 2.1 Study Rationale; References	Minor updates to wording of section with corresponding update to references.	Administrative changes to harmonize common content across all SunRISe protocols.
2.2.3 TAR-200 Clinical Studies; 2.2.4 Cetrelimab Clinical Studies; 2.2.5 Combination Therapy; 2.3 Benefit-Risk Assessment; References	Updates were made to reflect the latest information for the clinical program, with corresponding update to references.	To provide the most current information pertaining to completed and ongoing clinical studies.
2.2.4 Cetrelimab Clinical Studies	Added statement that while prolonged prothrombin times were observed in the non-clinical evaluations, a corresponding signal has not been observed in human trials.	These changes were made to clarify the clinical impact of these non-clinical findings.
10.4.2 Attribution Definitions	Adverse Events and Serious Adverse Events relatedness should be specified in the eCRF as related or not related to the TAR-200 + Cetrelimab, TAR-200 Alone or Cetrelimab Alone, or due to the procedure of the insertion (including the Urinary Placement Catheter) or removal of the TAR-200 system.	This change was made to clarify relatedness of AE and SAEs.
9.4.2 Primary Endpoint	Text revised to the following: 'Intercurrent event: subsequent therapy. Hypothetical Strategy: Response after this intercurrent event will not be considered as a response.'	Edit made in response to Health Authority request.
5.3.1 Meals and Dietary Restrictions	Fluid requirements are for non-alcoholic liquids.	Updated instructions regarding liquid consumption.
6.5.2.2 Cetrelimab Dose Discontinuation; 6.6 Treatment of Overdose; 8.12.5 Pregnancy; 10.3.5 Committees Structure; 10.5.2 Examples of Contraceptives;	Revision made to note that the Study Responsible Physician (SRP) and not the medical monitor will assist with safety oversight.	Correction

Section Number and Name	Description of Change	Brief Rationale
10.9.11 Treatment of Anti-PD-1 Infusion-related Reactions		
1.1 Synopsis (Efficacy Evaluation); 1.3 Schedule of Activities; 4.1 Overall Design; 5.2 Exclusion Criteria; 8.1 Screening; 8.1.2 Bladder Post-Void Residual; 8.2 Treatment Phase; 8.6 Follow-up Phase; 8.10.1.1 Cystoscopy; 10.9.3 Endocrinopathies	Replaced the term "Standard of Care (SOC)" with "institutional guidelines."	Text revised as the SOC may differ between countries.
8.1 Screening; 8.10.1.1 Cystoscopy	Text on assessment cystoscopy at screening was moved to Section 8.1 from 8.10.1.1	Text applicable to screening.
Title Page, Headers	Compound information (number and name) for cetrelimab were added.	Information was added as both TAR-200 and cetrelimab are administered in the study.
6.4 Study Intervention Compliance; 6.5 Dose Modification; 8.12.3 Follow-up of Adverse Events and Serious Adverse Events; 8.12.8 Medical Device Deficiencies; 8.13 Pharmacokinetics; 10.3.1 Regulatory and Ethical Considerations; 10.3.6 Publication Policy/Dissemination of Study Data; 10.5 Appendix 5: Contraceptive and Barrier Guidance; 10.8 Appendix 8 Study Conduct During a Natural Disaster	Protocol template-driven updates were made where applicable; changes included the following: • Section 6.4: Updated section title. • Section 6.5: Added text that any dose adjustment should be overseen by medically-qualified study site personnel. • 8.12.3: Text was added that the investigator will arrange for the performance of additional tests to elucidate the nature and causality of an AE, SAE, or PQC. • 8.12.8: Added a note that deficiencies meeting the definition of an AE/SAE will follow the processes outlined in Sections 8.12 and 10.4. • Section 8.13: Added text on the potential use of PK samples to address safety and efficacy concerns, and to note participant confidentiality will be maintained. • Section 10.3.1: Added paragraph on "Protocol Clarification Communications" • Section 10.3.6: Clarified language regarding the disclosure of results. • Section 10.5: Added cross-reference to Section 10.4 to clarify pregnancy reporting standards. • Section 10.8: Title and section updated with the latest guidance.	To align with updates to the oncology protocol template.
Title Page	The short title was revised to the study name, 'SunRISe-1.'	Clarification.
10.10 Appendix 10: 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	Minor grammatical, formatting, or spelling changes were made, and links and cross-references	Minor errors were noted.

Section Number and Name	Description of Change	Brief Rationale
	corrected/updated. Abbreviations were added to tables and noted where applicable within the document, and the list of abbreviations and definitions updated (Section 10.1).	

11. REFERENCES

American Joint Committee on Cancer. AJCC Cancer Staging Handbook Seventh Edition. Springer, 2017.

Babjuk M, Bohle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol. 2017;71:447-461.

Balar AJ, Kulkarni GS, Uchio EM, et al. Keynote 057: phase II trial of pembrolizumab (pembro) for patients (pts) with high-risk (HR) nonmuscle invasive bladder cancer (NMIBC) unresponsive to bacillus calmette-guerin (BCG). J Clin Oncol. 2019;37(7):350.

Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. Lancet Oncol. 2021;22(7):919-930.

Bas WG, Burger M, Lotan Y, et al. Recurrence and progression of disease in non-muscle-invasive bladder cancer: from epidemiology to treatment strategy. Eur Urol. 2009;56(3):430-442.

Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. Lancet Oncol. 2021; 22:107-17.

Bray F, Ferlay J, Soerjiomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

Cattel L, Airoldi M, Delprino L, et al. Pharmacokinetic evaluation of gemcitabine and 29,29-difluorodeoxycytidine-59-triphosphate after prolonged infusion in patients affected by different solid tumors. Ann Oncol. 2006;17(5):142–147.

Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline [manuscript]. 2016. 45 p.

Cozzi PJ, Bajorin DF, Tong W, et al. Toxicology and pharmacokinetics of intravesical gemcitabine: a preclinical study in dogs. Clin Cancer Res. 1999;5(9):2629-2637. PMID: 10499642.

Daneshmand S, Brummelhuis ISG, Pohar KS, et al. The safety, tolerability, and efficacy of a neoadjuvant gemcitabine intravesical drug delivery system (TAR-200) in muscle-invasive bladder cancer patients: a phase I trial. Urol Oncol. 2022 Jul;40(7):344.e1-344.e9.

Daneshman S, van der Heijden MS, Jacob JM, et al. First results from SunRISe-1 in patients with BCG unresponsive high-risk non-muscle-invasive bladder cancer receiving TAR-200 in combination with cetrelimabm TAR-200, or cetrelimab alone. Urol. 2023;209(4).

Eriksson E, Wenthe J, Irenaeus S, Ullenhag G. Gemcitabine reduces MDSCs, tregs and TGFß-1 while restoring the teff/treg ratio in patients with pancreatic cancer. J Transl Med. 2016;14(1):282.

Food and Drug Administration. BCG-unresponsive nonmuscle invasive bladder cancer: developing drugs and biologics for treatment: guidance for industry. Silver Spring, MD. 2018.

Giesing H, Reynolds D, Agarwal V, et al. Significant cytotoxic and immumomodulatory effects of continuous low dose intravesical gemcitabine in rodent bladder tumor models DOI: 10.1158/1538-7445.AM2018-LB-122 Published 2018.

Han RF, Pan JG. Can intravesical bacillus Calmette-Guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized rials. Urol. 2006; 67(6):1216-1223.

Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? J Urol. 2001.166(4):1296-1299.

Ipilimumab US Package Insert. Princeton, NJ: Bristol-Myers Squibb. October 2015.

Jeon HG, Yoon CY, Yu JH, et al. Induction of caspase mediated apoptosis and down-regulation of nuclear factor-κB and Akt signaling are involved in the synergistic antitumor effect of gemcitabine and the histone deacetylase inhibitor trichostatin A in human bladder cancer cells. J Urol. 2011;186(5):2084-2093.

Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group study. J Urol. 2000;163(4):1124-1129.

Lerner SP, Tangen CM, Sucharew H, Wood D, Crawford ED. Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high risk non-muscle invasive bladder cancer. Urol Oncol. 2009;27:155-159.

Lightfoot AJ, Rosevear HM, O'Donnell MA. Recognition and treatment of BCG failure in bladder cancer. Scientific World J. 2011;11:602-613.

Liu WM, Fowler DW, Smith P, Dalgleish AG. Pre-treatment with chemotherapy can enhance the antigenicity and immunogenicity of tumours by promoting adaptive immune responses. Br J Cancer. 2010;102(1):115-123.

Malmstrom PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomized studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle invasive bladder cancer. Eur Urol. 2009;56(2):247-256.

Massacesi C, Burattini L, Marcucci F, Bonsignori M. Short communication: the efficacy of fixed dose rate infusion of gemcitabine combined with IFN-alpha2a in patients with advanced refractory renal cell carcinoma. J Interferon Cytokine Res. 2005;25(3):165-168.

Matera M., Costantino G., Clementi G. al. Experimental study on the toxicity and the local and systemic tolerability of gemcitabine after topical treatment of the rabbit bladder. Oncol. Rep. 2004;11:1145–1151.

National Cancer Institute. Surveillance, Epidemiology, and End Results Program Turning Cancer Data Into Discovery. *Cancer of the Urinary Bladder*. http://seer.cancer.gov/statfacts/html/urinb.html. Accessed March 01, 2022.

Necchi A, Roumiguié M, Esen AA, et al. Pembrolizumab (pembro) monotherapy for patients (pts) with high-risk non–muscle-invasive bladder cancer (HR NMIBC) unresponsive to bacillus Calmette–Guérin (BCG): Results from cohort B of the phase 2 KEYNOTE-057 trial. J Clin Oncol. 2023;41(60):LBA442.

Nivolumab Summary of Product Characteristics. Uxbridge, United Kingdom: Bristol-Myers Squibb Pharma EEIG.

Nivolumab US Package Insert. Princeton, NJ: Bristol-Myers Squibb Company; May 2016.

Nowak AK, Lake RA, Marzo AL, et al. Induction of tumor cell apoptosis in vivo increases tumor antigen cross-presentation, cross-priming rather than cross-tolerizing host tumor-specific CD8 T cells. J Immunol. 2003;170(10):4905-4913.

Nowak AK, Robinson BW, Lake RA. Gemcitabine exerts a selective effect on the humoral immune response: implications for combination chemo-immunotherapy. Cancer Res. 2002;62(8):2353-2358.

Pembrolizumab Summary of Product Characteristics. Hertfordshire, United Kingdom: Merck Sharp & Dohme Limited.

Pembrolizumab US Package Insert. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.; December 2015.

Rizvi N, Hellman MD, Brahner JR, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. Journal of Clin Oncol. 2016;34(25):2969-2979.

Shabsigh A, Korets R, Vora KC, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol. 2009; 55:164-176.

Shelley M, Burgon K, Court JB, Kynaston H, Wilt TJ, Fish R, Mason M. A systemic review of ntravesical bacillus Calmette-Guerin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. BJU Int. 2001;88(3):209-216.

Shelley M, Court JB, Kynaston H, Wilt TJ, Fish R, Mason M. Intravesical Bacillus Calmette-Guerin in Ta and T1 bladder cancer (review). Cochrane Database Syst Rev. 2000;(4):CD001986.

Shelley M, Court JB, Kynaston H, Wilt TJ, Mason M. Intravesical Bacillus Calmette-Guerin superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU Int. 2004;93(4):485-490.

Shelley MD, Jones G, Cleves A, Wilt TJ, Mason MD, Kynaston HG. Intravesical gemcitabine therapy for non-muscle invasive bladder cancer (NMIBC): a systematic review. BJU Init. 2012;109(4):496-505.

Shevchenko I, Karakhanova S, Soltek S, et al. Low-dose gemcitabine depletes regulatory T cells and improves survival in the orthotopic Panc02 model of pancreatic cancer. Int J Cancer. 2013;133(1):98-107.

Skinner EC, Goldman B, Sakr WA, et al. SWOG S0353: Phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette-Guérin. J Urol. 2013;190(4):1200-1204. doi: 10.1016/j.juro.2013.04.031. Epub 2013 Apr 15. PMID: 23597452; PMCID: PMC4113593.

Steinberg G, Bahnson R, Brosman S, Middleton R, Wajsman Z, Wehle M. Efficacy and safety of valrubicin for the treatment of BCG refractory carcinoma in situ of the bladder. J Urol. 2000;163(3):761-767. DOI: https://www.auajournals.org/doi/10.1016/S0022-5347%2805%2967799-3.

Stein JP, Lieskovsky G, Cote R, et. al. Radical cystectomy in the treatment of invasive bladder cancer: long- term results in 1,054 patients. J Clin Oncol. 2001;19:666-667.

Sylvester RJ van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49:466-477; discussion 75-77.

Thomas F, Noon AP, Rubin N, Goepel J, Catto JW. Comparative outcomes of primary, recurrent and progressive high-risk non-muscle invasive bladder cancer. Eur Urol. 2013;63:145-154.

Tyson MD, Morris D, Palou J, et al. Safety, tolerability and efficacy of TAR-200 in patients with muscle-invasive bladder cancer who were unfit for curative intent therapy: A phase 1 trial (presented at the Society of Urologic Oncology, SUO meeting, Dec 1-3, 2021).

Witjes JA, van der Heijden AG, Vriesema JL, Peters GJ, Laan A, Schalken JA. Intravesical gemcitabine: a phase 1 and pharmacokinetic study. Eur Urol. 2004;45(2):182-186.

World Cancer Research Fund. Worldwide cancer data. https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data. Accessed 9 February 2020.

INVESTIGATOR AGREEMENT

JNJ-17000139 (TAR-200) / JNJ-63723283 (Cetrelimab) Clinical Protocol 17000139BLC2001 Amendment 5

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)

Sponsor's Authorized Person:

Name (typed or printed): _____

Institution: Janssen-Cilag International NV

Signature: _____ Date: _____
(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.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 198
Status: Approved, Date: 02 July 2024