Official Title: An Open-Label, Randomized, Phase 2, Umbrella Study of Various Neoadjuvant Therapies for Participants With Muscle-Invasive Urothelial Carcinoma of the Bladder Who Are Cisplatin-Ineligible or Refuse Cisplatin Therapy and Undergoing Radical Cystectomy (Optimus)

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Statistical Analysis Plan

INCB 24360-901

An Open-Label, Randomized, Phase 2, Umbrella Study of Various Neoadjuvant Therapies for Participants With Muscle-Invasive Urothelial Carcinoma of the Bladder Who Are Cisplatin-Ineligible or Refuse Cisplatin Therapy and Undergoing Radical Cystectomy (Optimus)

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Protocol Version:	**Protocol Amendment 4 dated 01 MAR 2022**
CRF Approval Date:	**14 DEC 2023**
SAP Version:	**Original**
SAP Author:	[redacted]
Date of Plan:	**27 MAR 2024**

This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BID	twice daily
CI	confidence interval
COVID-19	coronavirus disease 2019
CPS	combined positive score
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FAS	Full Analysis Set
HIV	human immunodeficiency virus
IRT	interactive response technology
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	muscle-invasive bladder cancer
miUBC	muscle-invasive urothelial bladder cancer
NCI	National Cancer Institute
pCR	pathological complete response
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PS	performance status
PT	preferred term
Q2W	every 2 weeks
[redacted]	[redacted]
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
SAP	Statistical Analysis Plan

Abbreviations and Special Terms	Definition
TEAE	treatment-emergent adverse event
TNM	tumor, node, metastasis
TURBT	transurethral resection of bladder tumor
ULN	upper limit of normal
ypT0/1/a/isN0M0	pathologic partial responses post therapy
ypT0N0	complete pathologic response post therapy

1. INTRODUCTION

This is an open-label, randomized, umbrella study to investigate the biological rationale and outcomes for selected monotherapy and combination therapies in order to inform of potential neoadjuvant treatment combinations to be further tested in miUBC in participants who are cisplatin-ineligible or those refusing cisplatin therapy and awaiting radical cystectomy.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCB 24360-901 Protocol.

[redacted]

The details of the analysis methodology of [redacted] pharmacodynamics and results will appear in a separate report.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 24360-901 Protocol Amendment 4 dated 01 MAR 2022 and CRFs approved 14 DEC 2023. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine biologic response in participants with muscle-invasive cisplatin-ineligible or those refusing cisplatin therapy, urothelial carcinoma of the bladder.	For each treatment group, the primary endpoint is the change from baseline in CD8+ lymphocytes within resected tumor.
Secondary	
To evaluate the safety and tolerability of each of the treatment groups.	Safety and tolerability assessed by monitoring the frequency and severity of AEs, including delay in cystectomy due to AEs.
To evaluate the preliminary efficacy of each of the treatment groups.	• pCR rate, defined as percentage of participants with ypT0N0 in each treatment group. • Major pathological response, defined as residual ypT0/1/a/isN0M0.

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

3. STUDY DESIGN

This is an open-label, randomized, Phase 2, umbrella study of various neoadjuvant therapies for miUBC (ie, Galsky et al 2011) undergoing radical cystectomy.

This study will test the biological rationale for the use of targeted and immuno-oncology agents for neoadjuvant treatment of cisplatin-ineligible, or participants refusing cisplatin therapy for, miUBC and the potential for subsequent efficacy benefit, as shown with other anti–PD-1 inhibitors, and at doses shown to add minimal/acceptable risk from side effects (ie, positive benefit/risk). The translational endpoints will inform which therapies are viable candidates for further investigation in miUBC. This study is an umbrella design in which future treatment arms may be added or removed at the discretion of the sponsor.

Participants will be randomized into 1 of the following treatment groups:

- Treatment Group A: Epacadostat plus retifanlimab
- Treatment Group B: Retifanlimab monotherapy
- Treatment Group C: Epacadostat monotherapy
- Treatment Group D: Retifanlimab plus INCAGN02385
- Treatment Group E: Retifanlimab plus INCAGN02385 plus INCAGN02390

Tumor tissue will be tested centrally to determine PD-L1 CPS score before enrollment.

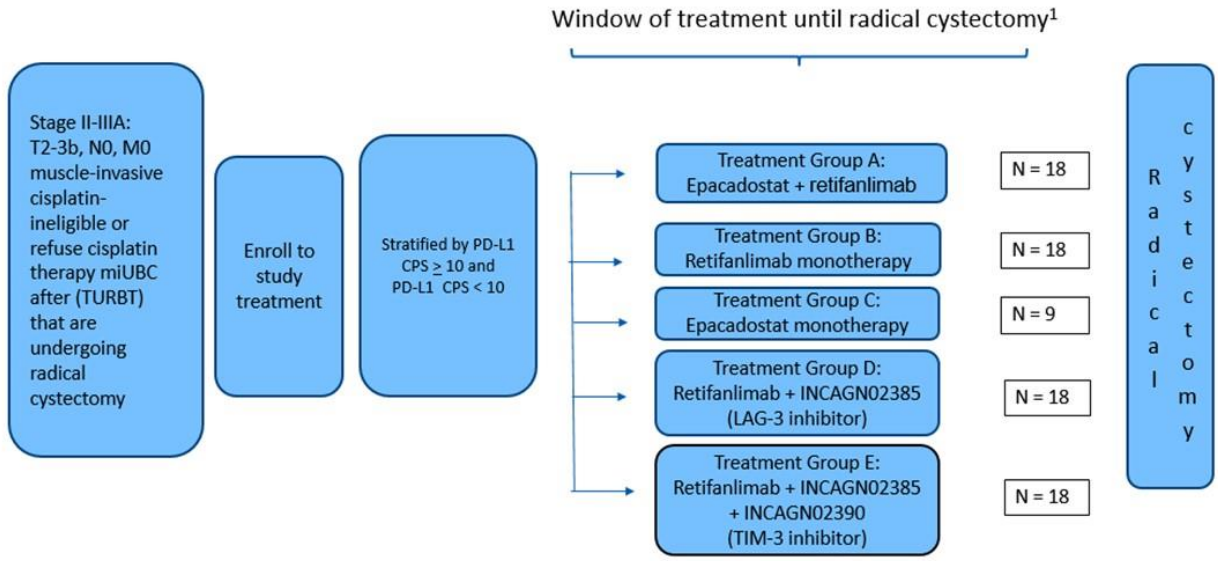
Participants will be randomized into treatment groups according to the schema in Figure 1. Participants with PD-L1 CPS < 10 or PD-L1 CPS ≥ 10 will be randomized at a 2:2:1:2:2 ratio into Groups A, B, C, D, and E, respectively. Participants who pass screening for PD-L1 CPS < 10 will not be randomized into a group once that group has reached the allowed number of participants with PD-L1 CPS < 10. Similarly, participants with PD-L1 CPS ≥ 10 will not be randomized into a group once that group has reached the allowed number of participants with PD-L1 CPS ≥ 10. This will ensure that the desired proportion of participants who have PD-L1 CPS < 10 and PD-L1 CPS ≥ 10 within each group will be enrolled.

For Treatment Group C, the subgroup of participants with PD-L1 CPS < 10 or PD-L1 CPS ≥ 10 that reaches 5 participants will hold enrolling participants to that particular subgroup and will continue to enroll until 4 participants in the other subgroup are enrolled.

Screening assessments may be completed over a period of up to 28 days. Treatment cycles are 28 days unless otherwise noted. Each participant enrolled in the study will receive a minimum of 1 treatment cycle if, in the judgment of the investigator, the participant has not met any criteria for study withdrawal. The treatment duration will be approximately 4 to 10 weeks. Radical cystectomy is typically scheduled for approximately 8 to 10 weeks with an average of 8 weeks from the TURBT (ie, approximately Day 56; Poletajew et al 2014).

Precystectomy assessments will be performed within 2 weeks before surgery. Participants will be followed for safety as well as radiographic imaging for 90 days after cystectomy or the last dose of study treatment in the event cystectomy is not performed.

Figure 1: Study Design Schema



[1] Treatment duration is based on date of radical cystectomy. Participants should receive a minimum of 4 weeks and maximum of 10 weeks of treatment.

The current sample size represents an estimated number of participants per treatment group in order to attain the necessary evaluable paired biopsies. Additional participants will be enrolled in treatment groups to ensure the number of evaluable paired biopsies are obtained. This is a platform design, and additional treatment arms may be added or prematurely stopped for enrollment.

3.1. Randomization

This is an open-label, stratified, randomized study with a translational primary endpoint of change in CD8+ cells within the resected tumor tissue. If eligible for Treatments D and E based on exclusionary criteria, participants will be randomized to Treatment Group A, B, C, D, or E based on PD-L1 CPS values (see Figure 1) at a 2:2:1:2:2 ratio, respectively. If ineligible for Treatments D and E based on exclusionary criteria, participants will be randomized to Treatment Group A, B, or C based on PD-L1 CPS values (see Figure 1) at a 2:2:1 ratio. This will ensure that the planned number of participants will be enrolled into each treatment group with PD-L1 CPS balanced within each treatment group.

3.2. Control of Type I Error

For the primary endpoint, the overall 2-sided Type I error is 0.10.

No adjustment for alpha spending is considered as there are no plans to stop the study early for overwhelming efficacy. A DSMB will be assembled to monitor safety data and study conduct on a regular and ongoing basis during the study. No multiplicity control will be applied to the assessments.

3.3. Sample Size Considerations

Approximately 81 participants will be enrolled in this study. Per treatment group, the evaluable paired biopsies in Table 2 are needed.

Table 2: Sample Size Determination

Treatment Group	Number of Participants	Estimated Number of Paired Biopsies
A: Epacadostat plus retifanlimab	18	16
B: Retifanlimab monotherapy	18	16
C: Epacadostat monotherapy	9	8
D: Retifanlimab plus INCAGN02385	18	16
E: Retifanlimab plus INCAGN02385 plus INCAGN02390	18	16
Total	81	72

For each group, the power consideration is based on the fold change from baseline in CD8+ T effector cells. Eight evaluable paired biopsies in Treatment Group C will provide 80% power to detect a mean fold change from baseline in the degree of 1 standard deviation of the change variable at 2-sided alpha = 0.10 level.

For Treatment Groups A and B, the 16 evaluable paired biopsies will provide > 95% power to detect the same degree of the mean change for the entire group and 80% power at 2-sided alpha = 0.10 level for both PD-L1 subgroups combined (PD-L1 CPS < 10 and PD-L1 CPS ≥ 10).

3.4. Schedule of Assessments

Refer to Protocol Amendment 4 dated 01 MAR 2022 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of any study treatment is administered to the participants.

For randomized participants not treated with any study treatment, Day 1 is defined as the date of randomization.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of any study treatment, unless otherwise defined.

For randomized participants not treated with any study treatment, baseline is defined as the last nonmissing assessment before randomization for all parameters.

When scheduled assessments and unscheduled assessments occur on the same day and the time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Dates

In general, values for missing dates will not be handled unless methods for handling missing dates are specified in this section or relevant sections. The original reported dates collected on the eCRF should be used in all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

When calculating the time since diagnosis of cancer, a partial cancer diagnosis date will be handled as follows in the calculation:

- If only the day is missing, then the first day of the month will be used.
- If both the month and day are missing, then 01 JAN of the year will be used.
- If the diagnosis date is completely missing, then the time since diagnosis will not be calculated.

For AEs, an unsolved missing onset date will be imputed by the date of Day 1, which will force the AE to be treatment emergent, with the following exceptions:

- If the stop/resolution date is prior to the Day 1 date, then the AE will be considered as non–treatment emergent.
- If both the month and day are missing, and the last day of the year is prior to the Day 1 date, then the AE will be considered as non–treatment emergent.
- If only the day is missing, and the last day of the month is prior the Day 1 date, then the AE will be considered as non–treatment emergent.

Imputation of start dates for AEs will be handled as follows:

- If only the day is missing, and the first day of the month is after the Day 1 date, then the AE will be considered as treatment emergent, and the incomplete date will be imputed by the first of the month.
- If both the month and day are missing, and the year is after the Day 1 date, then the AE will be considered as treatment emergent, and the incomplete date will be set to 01 JAN.

Imputation of end dates for AEs will be handled as follows:

- If only the day is missing for the AE stop date, the incomplete date will be imputed as the last day of the month.
- If the participant discontinued treatment or died before the last day of that month, the end of treatment or death date should be used for imputation.

When the date of the last dose is used in deriving variables such as duration of treatment or TEAE flag, a missing or partial date of the last dose will be handled as follows:

- If only the day is missing, then the earlier date of the last day of the month or the date that the participant discontinued treatment will be used.
- If both the month and day are missing, then the earlier date of 31 DEC of the year or the date that the participant discontinued treatment will be used.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

4.1.5. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of study treatment is administered. The scheduled cycle length is 28 days. The actual Day 1 of subsequent cycles will correspond with the first day of administration of epacadostat, retifanlimab, INCAGN02385, INCAGN02390 in that cycle; thus, treatment cycles may become out of sync with the originally planned schedule, and the cycle length may be different from 28 days. The date of the Day 1 of subsequent cycles recorded on the eCRF will be used as the Day 1 of the subsequent cycles.

Treatment Group A will receive retifanlimab 500 mg (25 mg/mL liquid formulation) IV over 30 (+ 15) minutes on Day 1 of each 28-day cycle and epacadostat 600 or 400 mg BID. Treatment Group B will receive retifanlimab 500 mg (25 mg/mL liquid formulation) IV over 30 (+ 15) minutes on Day 1 of each 28-day cycle. Treatment Group C will receive epacadostat 600 or 400 mg BID. Treatment Group D will receive retifanlimab 500 mg (25 mg/mL liquid formulation) IV over 30 (+ 15) minutes on Day 1 of each 28-day cycle followed by a 10-minute flush and INCAGN02385 350 mg Q2W IV over 30 (−5/+10) minutes followed by a 10-minute flush. Treatment Group E will receive retifanlimab 500 mg (25 mg/mL liquid formulation) IV over 30 (+ 15) minutes on Day 1 of each 28-day cycle followed by a 10-minute flush, INCAGN02385 350 mg Q2W IV over 30 (−5/+10) minutes followed by a 10-minute flush, and INCAGN02390 400 mg Q2W IV over 30 (−5/+10) minutes followed by a 10-minute flush.

4.2. Variable Definitions

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

Body mass index (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of study treatment.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of epacadostat, retifanlimab, INCAGN02385, or INCAGN02390 and is ongoing or ends on/after the date of first study treatment administration.
- On/after the date of first administration of epacadostat, retifanlimab, INCAGN02385, or INCAGN02390 and is ongoing or ends during the course of study.

A prior medication could also be classified as "both prior and concomitant medication" if the start date is prior the first dose of study treatment and the end date is on or after first dose of study treatment. In the listing, it will be indicated whether a medication is only prior, only concomitant, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS software (SAS Institute Inc, Cary, NC; v9.4 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include but not be limited to the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

5.2. Treatment Groups

This a randomized, open-label, umbrella study with 5 treatment groups. Participants will be randomized to receive retifanlimab monotherapy, retifanlimab plus epacadostat, epacadostat monotherapy, retifanlimab plus INCAGN02385, or retifanlimab plus INCAGN02385 plus INCAGN02390. Participant data will be summarized by treatment group.

5.3. Analysis Populations

5.3.1. All-Screened Population

The All-Screened Population will include all participants who signed the informed consent form. The All-Screened Population will be used for summarizing the analysis populations.

5.3.2. Full Analysis Set

The FAS will include all participants who were randomized. Participants will be analyzed according to the treatment to which they were assigned at the time of randomization regardless of the actual study treatment that the participant might take during the study.

The FAS will be used to summarize participant disposition, demographics, baseline characteristics, Protocol deviations, prior and concomitant medications, general medical history, disease history, prior systemic therapy, and prior radiotherapy.

5.3.3. Per-Protocol Population

Not applicable.

5.3.4. Enrolled Population

The Enrolled Population will include all participants who were defined as "Completed" on the Screening Disposition eCRF.

5.3.5. Translational-Evaluable Population

The Translational-Evaluable Population will include all participants enrolled in the study who meet the following criteria:

- Completed a baseline scan and has a minimal residual disease.
- Received at least 4 weeks of neoadjuvant study treatment.
  - Treatment Groups A and C: last dose of epacadostat should be within 2 days prior to day of surgery.
  - Treatment Groups A, B, D, and E: last dose of retifanlimab and/or INCAGN02385 and/or INCAGN02390 should be within the 2 weeks prior to day of surgery.
- Provided evaluable paired biopsies (pretreatment core biopsy and surgical resection biopsy).

The Translational-Evaluable Population will be used for the primary efficacy endpoint analysis.

5.3.6. Safety Population

The Safety Population will include all participants who received at least 1 dose of study treatment. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study treatment.

All safety analyses will be conducted using the Safety Population.

5.3.7. Efficacy Population

The Efficacy Population will include all participants with secondary efficacy endpoint data available for both baseline and postbaseline measurements, and this will be used for the analysis of all secondary efficacy endpoints.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

6.1. Demographics, Baseline Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized for the FAS: age, sex, race, ethnicity. Categorical parameters (sex, race, ethnicity) will be summarized by number and percentage. Continuous parameters (age) will be summarized by descriptive statistics (N, mean, standard deviation, median, minimum, and maximum). Age will also be summarized in categories < 65 years and ≥ 65 years by number and percentage.

All demographic and baseline characteristic data will be listed.

6.1.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by number and percentage for the FAS: ECOG performance status.

6.1.3. Disease History

The type of urothelial cancer, stage at diagnosis, current stage, disease histology at diagnosis, current disease histology, TNM staging at diagnosis, current TNM staging, time since MIBC diagnosis, cisplatin therapy use, smoking status, history of hydronephrosis, and history of BCG-intravesical installations will be summarized. Categorical parameters will be summarized by number and percentage. Continuous parameters will be summarized by descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) for the FAS.

The TURBT procedure for diagnosis will be summarized using number and percentage for all categorical values including if a radical TURBT procedure was performed and the PD-L1 CPS score category.

Time since diagnosis will be calculated as follows:

Time since diagnosis (years) = (date of randomization – date of diagnosis + 1) / 365.25.

All disease history data will be listed.

6.1.4. Prior Therapy

The number of prior systemic cancer therapy regimens will be summarized for all participants in the FAS. The component drugs of prior systemic therapy regimens will be coded using the WHO Drug Dictionary. The number and percentage of participants who received each drug will be summarized by WHO drug class and WHO drug PT. The regimen name, component drugs, start and stop dates, route, purpose of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed.

The number of participants who received prior radiation will be summarized for the FAS. The radiotherapy type, body site, start and stop dates, reason for the regimen, number of fractions received, total dose, and best response will be listed.

The number of participants who had prior surgery or surgical procedure for the malignancies under study will be summarized for the FAS. The date and description of the surgery/procedure will be listed.

6.1.5. Medical History

For participants in the FAS, medical history will be summarized by assigned treatment group. This summation will include the number and percentage of participants with a medical history event for each body system/organ class as documented on the eCRF and coded using MedDRA. All available medical history data will be listed.

6.2. Disposition of Participant

The number and percentage of participants who were randomized, who were treated, who were ongoing with study treatment, who completed study treatment, who discontinued study treatment with a primary reason for discontinuation, who underwent radical cystectomy, who were still in the study, who completed the study, and who withdrew from the study with a primary reason for withdrawal will be summarized for the FAS. The number of participants randomized by country and site will also be provided by treatment group. All disposition information will be listed.

6.3. Protocol Deviations

Protocol deviations and adjudications will be summarized and listed.

6.4. Exposure

For participants in the safety population, exposure to epacadostat, retifanlimab, INCAGN02385, and INCAGN02390 will be summarized descriptively as the following:

- **Number of cycles of epacadostat**: number of cycles with a nonzero dose of epacadostat.
- **Number of cycles of retifanlimab**: number of cycles with a nonzero dose of retifanlimab.
- **Number of cycles of INCAGN02385**: number of cycles with a nonzero dose of INCAGN02385.
- **Number of cycles of INCAGN02390**: number of cycles with a nonzero dose of INCAGN02390.
- **Duration of treatment with epacadostat (days)**: date of last dose of epacadostat – date of first dose of epacadostat + 1 – days of interruption.
- **Duration of treatment with retifanlimab (days)**: date of last dose of retifanlimab – date of first dose of retifanlimab + 1.
- **Duration of treatment with INCAGN02385 (days)**: date of last dose of INCAGN02385 – date of first dose of INCAGN02385 + 1.
- **Duration of treatment with INCAGN02390 (days)**: date of last dose of INCAGN02390 – date of first dose of INCAGN02390 + 1.

- **Average daily dose of epacadostat (mg/day)**: total actual epacadostat dose taken (mg) / duration of treatment with epacadostat (days).

  Total actual dose taken will be calculated based on the information entered in the Drug Accountability Epacadostat eCRF.

- **Average dose of retifanlimab (mg)**: total actual retifanlimab dose taken (mg) / number of treatments with retifanlimab.

  Total actual dose taken will be calculated based on the information entered in the Dose Retifanlimab eCRF.

- **Average dose of INCAGN02385 (mg)**: total actual INCAGN02385 dose taken (mg) / number of treatments with INCAGN02385.

  Total actual dose taken will be calculated based on the information entered in the Dose INCAGN02385 eCRF.

- **Average dose of INCAGN02390 (mg)**: total actual INCAGN02390 dose taken (mg) / number of treatments with INCAGN02390.

  Total actual dose taken will be calculated based on the information entered in the Dose INCAGN02390 eCRF.

- **Epacadostat dose modifications**: number of participants who had epacadostat dose reduction and interruption.
- **Dose delays and dose interruptions**: number of participants with dose delays and dose interruptions.

All exposure data will be listed.

6.5. Study Treatment Compliance

For participants in the safety population, overall compliance (%) for epacadostat will be calculated for all participants as follows:

Compliance (%) = 100 × [total dose actually taken] / [total prescribed dose].

The total prescribed dose is defined as the sum of the doses prescribed by the investigator accounting for dose modifications.

The total actual dose taken will be calculated based on information entered on the Drug Accountability Epacadostat eCRF. If there are dispensed drugs that have not been returned yet, the actual dose taken starting from the dispense date of the unreturned drugs will be imputed by the dose taken as reported on the Dose Epacadostat eCRF.

For participants treated with retifanlimab, INCAGN02385, or INCAGN02390, compliance will be calculated based on infusion records documented by the site staff and monitored by the sponsor/designee.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of participants in the FAS for each prior and concomitant medication will be summarized by WHO drug class and WHO drug PT. All medications will be listed.

7. EFFICACY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

7.1. Efficacy Hypotheses

The primary hypothesis is that each study treatment assigned in each treatment group given prior to a cystectomy will change the amount of immune cells (CD8+ lymphocytes) within the resected tumor in participants with bladder cancer. Assuming $S_i(t)$ is the log 2 of fold change from baseline function in regard to CD8+ lymphocyte counts, the testing hypothesis is as follows:

- H_0 (null hypothesis): $S_i(t) = 0$
- H_A (alternative hypothesis): $S_i(t) \neq 0$

7.2. Analysis of the Primary Efficacy Parameter

7.2.1. Primary Efficacy Analysis

The primary efficacy variable is the fold change from baseline in number of CD8+ lymphocytes in the resected tumor tissue. This will be derived as follows:

> Fold change from baseline = number of CD8+ lymphocytes at cystectomy / number of CD8+ lymphocytes at screening

Values of fold change from baseline of CD8+ lymphocytes are transformed to log 2 of fold change and will be summarized by descriptive statistics (N, mean, standard deviation, standard error, median, minimum, and maximum). For each treatment group, a paired t-test will be provided using n – 1 degrees of freedom, where n is the number of evaluable paired samples. An 80% CI with a 2-sided alpha of 0.10 will be included with the test statistic and p-value. Participants in the Translational-Evaluable Population who had tumor samples both at baseline and at the time of cystectomy will be included.

7.2.2. Subgroup Analyses for Primary Endpoint

Not applicable.

7.2.3. Sensitivity and Supportive Analyses for Primary Endpoint

Not applicable.

7.3. Analysis of the Secondary Efficacy Parameters

7.3.1. Pathological Complete Response Rate

Pathological CR rates at the time of radical cystectomy will be assessed as a secondary endpoint. Pathological CR is defined as ypT0N0 and in situ cancer on the basis of histology evaluation of the TURBT and cystectomy samples by local institutional analysis. The number and percentage of participants with ypT0N0 in each treatment group will be calculated, and 80% CIs will be

estimated using the Clopper-Pearson method. The Efficacy Population will be used for this analysis. All response data will be listed.

7.3.2. Major Pathological Response Rate

Major pathological response rates at the time of radical cystectomy will be assessed as a secondary endpoint. The number and percentage of participants with ypT0/1/a/isN0M0 in each treatment group will be calculated, and 80% CIs will be estimated using the Clopper-Pearson method. The Efficacy Population will be used for this analysis. All response data will be listed.

8. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

8.1. General Considerations

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE, either reported for the first time or the worsening of a pre-existing event, occurring after the first dose of study treatment. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study treatment administration. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Adverse events will be tabulated by MedDRA SOC and PT. Severity of AEs will be graded using the NCI CTCAE v5. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to study treatment will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study treatment, the AE will be considered to be treatment-related. The incidence of TEAEs and treatment-related TEAEs will be tabulated. In addition, serious TEAEs will also be tabulated.

All AE data will be listed.

8.2.2. Adverse Events of Special Interest

Adverse events reported as post–radical cystectomy complications as well as those assessed as immune-related will be coded according to the MedDRA 26.0. Postsurgery complications will be further classified according to the Clavien-Dindo Grading System (Dindo et al 2004).

8.2.3. Adverse Event Summaries

An overall summary of AEs by treatment group will include the following:

- Number (%) of participants who had any TEAEs
- Number (%) of participants who had any serious TEAEs
- Number (%) of participants who had any Grade 3 or higher TEAEs
- Number (%) of participants who had any TEAEs related to study treatment
- Number (%) of participants who had any immune-related TEAEs
- Number (%) of participants who had any immune-related TEAEs of Grade 3 or higher
- Number (%) of participants who permanently discontinued study treatment because of a TEAE
- Number (%) of participants who temporarily interrupted study treatment because of a TEAE
- Number (%) of participants who had any fatal TEAEs
- Number (%) of participants who had a delay in radical cystectomy due to a TEAE
- Number (%) of participants who had a TEAE leading to hospitalization

The following summaries will be produced by MedDRA term:

- Summary of TEAEs by MedDRA SOC and PT
- Summary of TEAEs by MedDRA PT in decreasing order of frequency
- Summary of TEAEs by MedDRA SOC, PT, and maximum severity
- Summary of Grade 3 or higher TEAEs by MedDRA SOC and PT
- Summary of Grade 3 or higher TEAEs by MedDRA PT in decreasing order of frequency
- Summary of serious TEAEs by MedDRA SOC and PT
- Summary of serious TEAEs by MedDRA PT in decreasing order of frequency
- Summary of treatment-related TEAEs by MedDRA SOC and PT
- Summary of treatment-related TEAEs by MedDRA PT in decreasing order of frequency
- Summary of immune-related TEAEs by MedDRA SOC and PT
- Summary of immune-related TEAEs of Grade 3 or higher by MedDRA SOC and PT
- Summary of treatment-related serious TEAEs by MedDRA SOC and PT
- Summary of treatment-related serious TEAEs by MedDRA PT in decreasing order of frequency

- Summary of nonserious TEAEs by MedDRA SOC and PT
- Summary of TEAEs leading to dose interruption by MedDRA SOC and PT
- Summary of TEAEs leading to discontinuation of study treatment by MedDRA SOC and PT
- Summary of TEAEs with a fatal outcome by MedDRA SOC and PT
- Summary of TEAEs by MedDRA SOC and PT leading to delay in radical cystectomy
- Summary of TEAEs considered as post–radical cystectomy complications by MedDRA SOC and PT

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values, change from baseline values, and percent change from baseline values will be summarized descriptively by visit. Change from baseline will be defined as:

Change from baseline = observed value at timepoint – baseline value

Percent change from baseline will defined as:

Percent change from baseline = 100 × (observed value at timepoint – baseline value) / baseline value

Baseline will be determined according to Section 4.1.3.

The baseline value will be determined using the nonmissing values collected before the first dose, prioritizing scheduled assessments for baseline identification over unscheduled visits. The last record before administration in the highest priority will be considered the baseline record.

Laboratory test values will be assessed for severity based on the numerical component of CTCAE v5.

8.3.2. Laboratory Value Summaries

Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units, if needed.

When there are multiple nonmissing laboratory values for a participant's particular test within a visit window, the convention described in Table 3 will be used to determine the record used for by-visit tabulations and summaries.

Table 3: Identification of Records for Postbaseline By-Visit Summaries

Priority	Laboratory Visit	Proximity to Visit Window	Tiebreaker
1	Scheduled	In-window	Use smallest laboratory sequence number
2	Unscheduled	In-window	
3	Scheduled	Out-of-window	

Shift tables based on the worst postbaseline value recorded will use all postbaseline values. The denominator for the percentage calculation will use the number of participants in the baseline category as the denominator for the percentage in each of the categories during the study.

Numeric laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary.

Severity grades will be assigned to laboratory test values based on the numerical component of CTCAE v5. Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category. The number of participants who had worsening of laboratory abnormalities will be summarized by maximum severity.

All clinical laboratory data will be listed.

8.3.3. Potential Hy's Law Events

Participants with elevated ALT or AST > 3 × ULN range and alkaline phosphatase < 2 × ULN range accompanied by total bilirubin > 2 × ULN range will be listed by treatment group.

8.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including pulse, respiratory rate, and temperature, will be summarized descriptively. Change from baseline will be defined as:

Change from baseline = observed value at timepoint – baseline value

Percent change from baseline will defined as:

Percent change from baseline = 100 × (observed value at timepoint – baseline value) / baseline value

For vital signs including systolic blood pressure, diastolic blood pressure, and body weight, shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Severity grades will be assigned to these values based on the numerical component of CTCAE v5.

For participants exhibiting vital sign abnormalities, the abnormal values will be listed along with their assigned treatment group.

8.5. Electrocardiograms

Twelve-lead ECGs including heart rate and PR, RR, QT, QRS, QT, QTcB, and QTcF intervals will be obtained for each participant during the study. Values at each scheduled visit, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be the last value collected before the first dose of study treatment. Change from baseline will be defined as:

Change from baseline = observed value at timepoint – baseline value

Percent change from baseline will defined as:

> Percent change from baseline = 100 × (observed value at timepoint – baseline value) / baseline value

Normal ranges for ECG values are defined in Table 4. ECG values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Participants exhibiting ECG abnormalities will be listed with study visit and assigned treatment group. Abnormal values for participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed. Outliers of QT, QTcB, and QTcF values, defined as absolute values > 450 milliseconds, > 470 milliseconds, > 500 milliseconds, respectively, or change from baseline > 30 milliseconds, will be summarized.

Table 4: Normal Ranges for Electrocardiogram Intervals

Parameter	High Threshold	Low Threshold
PR	≤ 200 ms	≥ 120 ms
RR	≤ 1200 ms	≥ 600 ms
QT (male)	≤ 450 ms	≥ 350 ms
QT (female)	≤ 460 ms	≥ 360 ms
QRS	≤ 100 ms	≥ 60 ms
QTcB, QTcF	≤ 450 ms	≥ 295 ms

Interpretation of ECGs will be summarized by number and percentage. Clinically significant abnormalities will be summarized by count and percentage by visit. Specific abnormalities will be listed.

9. INTERIM ANALYSES

There are no planned, formal interim analyses for this study. Periodic review of accrued clinical data will be conducted in accordance with the DSMB charter.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 5.

Table 5: Statistical Analysis Plan Versions

SAP Version	Date
Original	27 MAR 2024

10.1. Changes to Protocol-Defined Analyses

The following differ from those described in the Protocol:

- The primary efficacy endpoint will be fold change from baseline instead of change from baseline in the number of CD8+ lymphocytes.
- The SAP changed CD8+ T effector cells to CD8+ lymphocytes for consistency.
- [redacted]
- The definitions of the Translational-Evaluable and Efficacy Populations were updated.

10.2. Changes to the Statistical Analysis Plan

Not applicable.

11. REFERENCES

Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.

Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J Clin Oncol 2011;29:2432-2438.

Poletajew S, Lisiński J, Moskal K, et al. The time from diagnosis of bladder cancer to radical cystectomy in Polish urological centres - results of CysTiming Poland study. Cent European J Urol 2014;67:329-332.

Voskuilen CS, Oo HZ, Genitsch V, et al. Multicenter validation of histopathologic tumor regression grade after neoadjuvant chemotherapy in muscle-invasive bladder cancer. Am J Surg Pathol 2019;43:1600-1610.

APPENDIX A. PLANNED TABLES AND LISTINGS

This appendix provides a list of the planned tables and listings for the Clinical Study Report. Shells are provided in a separate document.

The lists of tables and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population
Baseline and Demographic Characteristics		
1.1.1	Analysis Populations	All-Screened
1.1.2	Summary of Participant Disposition	FAS
1.1.3	Summary of Number of Participants Enrolled by Country and Site	FAS
1.1.4	Summary of Protocol Deviations	FAS
1.2.1	Summary of Demographics and Baseline Characteristics	FAS
1.3.1	Summary of Cancer History and Baseline Disease Characteristics	FAS
1.4.1	Summary of Prior Medications	FAS
1.4.2	Summary of Concomitant Medications	FAS
1.5.1	Summary of General Medical History	FAS
1.5.2	Summary of Prior Systemic Cancer Therapy	FAS
1.5.3	Summary of Prior Radiotherapy and Procedures	FAS
Efficacy		
2.1	Summary of Fold Change From Baseline in the Number of CD8+ Lymphocytes	Translational-Evaluable
2.2	Summary of Pathological Complete Response Rate	Efficacy
2.3	Summary of Major Pathological Response	Efficacy
Safety		
3.1.1.1	Summary of Exposure and Duration of Exposure to Epacadostat	Safety
3.1.1.2	Summary of Exposure and Duration of Exposure to Retifanlimab	Safety
3.1.1.3	Summary of Exposure and Duration of Exposure to INCAGN02385	Safety
3.1.1.4	Summary of Exposure and Duration of Exposure to INCAGN02390	Safety
3.1.2	Summary of Epacadostat Compliance	Safety
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety
3.2.5	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.6	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.7	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.8	Summary of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety

Table No.	Title	Population
3.2.9	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.10	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.11	Summary of Investigator Assessed Immune-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.12	Summary of Investigator Assessed Immune-Related Treatment-Emergent Adverse Events of Grade 3 or Higher by MedDRA System Organ Class and Preferred Term	Safety
3.2.13	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.14	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.15	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety
3.2.16	Summary of Nonserious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.17	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety
3.2.18	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment by MedDRA System Organ Class and Preferred Term	Safety
3.2.19	Summary of Treatment-Emergent Adverse Events That Caused Delay in Radical Cystectomy by MedDRA System Organ Class and Preferred Term	Safety
3.2.20	Summary of Treatment-Emergent Adverse Events Considered as Post-Radical Cystectomy Complications by MedDRA System Organ Class and Preferred Term	Safety
3.3.1.1	Summary of Laboratory Values - Hematology	Safety
3.3.1.2	Summary of Laboratory Values - Chemistry	Safety
3.3.1.3	Summary of Laboratory Values - Coagulation	Safety
3.3.1.4	Summary of Laboratory Values - Thyroid Panel	Safety
3.3.1.5	Summary of Laboratory Values - Lipids	Safety
3.3.2.1	Shift Summary of Hematology Laboratory Values in CTCAE Grade - To the Worst Abnormal Value	Safety
3.3.2.2	Shift Summary of Chemistry Laboratory Values in CTCAE Grade - To the Worst Abnormal Value	Safety
3.4.1	Shift Summary of Systolic Blood Pressure in CTCAE Grade - To the Worst Abnormal Value	Safety
3.4.2	Shift Summary of Diastolic Blood Pressure in CTCAE Grade - To the Worst Abnormal Value	Safety
3.4.3	Summary of Pulse	Safety
3.4.4	Summary of Respiratory Rate	Safety
3.4.5	Summary of Body Temperature	Safety
3.4.6	Shift Summary of Body Weight in CTCAE Grade - To the Worst Abnormal Value	Safety
3.5.1	Summary of PR Interval (ms) From 12-Lead ECG	Safety
3.5.2	Summary of RR Interval (ms) From 12-Lead ECG	Safety
3.5.3	Summary of QRS Interval (ms) From 12-Lead ECG	Safety
3.5.4	Summary of QT Interval (ms) From 12-Lead ECG	Safety
3.5.5	Summary of QTcB Interval (ms) From 12-Lead ECG	Safety

Table No.	Title	Population
3.5.6	Summary of QTcF Interval (ms) From 12-Lead ECG	Safety
3.5.7	Summary of Heart Rate (bpm) From 12-Lead ECG	Safety
3.5.8	Summary of Outliers of QT, QTcB, and QTcF Interval Values (ms) From 12-Lead ECG	Safety
3.5.8	Summary of Clinically Significant ECG Abnormality	Safety
3.5.9	Summary of ECG Interpretation	Safety
3.6.1	Summary of Delay Time in Planned Radical Cystectomy	Safety
3.6.2	Summary of Reasons for Delay in Planned Radical Cystectomy	Safety

Listings

Listing No.	Title
2.1.1	Informed Consent
2.1.2	Disposition
2.1.3	Radical Cystectomy
2.1.4	Delay in Cystectomy
2.1.5	Last Dose Administration and Radical Cystectomy Delay
2.1.6	Staging of Bladder Cancer Pre- and Post-Radical Cystectomy
2.1.7	End of Study Details
2.1.8	Post-Therapy
2.2.1	Inclusion/Exclusion Criteria
2.2.2	Protocol Deviations
2.3.1	Analysis Populations
2.4.1	Demographics and Baseline Characteristics
2.4.2.1	Urothelial Cancer History: Previous Urothelial Cancer History
2.4.2.2	Urothelial Cancer History: MIBC Current Diagnosis
2.4.2.3	Urothelial Cancer History: TURBT Diagnosis Method
2.4.3	Prior Radiation Treatment
2.4.4	Prior Systemic Therapy
2.4.5	Prior Surgery or Surgical Procedure for Disease Under Study
2.4.6	Procedures and Nondrug Therapy
2.4.7	Medical History
2.4.8	Prior and Concomitant Medications
2.5.1	Study Drug Compliance
2.5.2	Study Drug Administration - Epacadostat
2.5.3	Study Drug Administration - Retifanlimab
2.5.4	Study Drug Administration - INCAGN02385
2.5.5	Study Drug Administration - INCAGN02390
2.6.1	Deaths
2.6.2	Overall Response Assessment by Visit
2.6.3	Response Assessment
2.6.4	Pathological Complete Response
2.6.5	Major Pathological Response
2.6.6	ECOG Status
2.7.1	Adverse Events
2.7.2	Serious Adverse Events

Listing No.	Title
2.7.3	Grade 3 and Higher Adverse Events
2.7.4	Fatal Adverse Events
2.7.5.1	Adverse Events Leading to Study Treatment Discontinuation
2.7.5.2	Adverse Events Leading to Delay of Radical Cystectomy
2.7.5.3	Adverse Events Leading to Hospitalization
2.7.6	Adverse Events Related to Post-Radical Cystectomy
2.7.7.1	Epacadostat-Related Adverse Events
2.7.7.2	Retifanlimab-Related Adverse Events
2.7.7.3	INCAGN02385-Related Adverse Events
2.7.7.4	INCAGN02390-Related Adverse Events
2.7.8	Infusion-Related Reactions
2.7.9	Postsurgical Complications Associated With Bladder Surgery
2.8.1	Clinical Laboratory Values - Hematology
2.8.2	Clinical Laboratory Values - Chemistry
2.8.3	Clinical Laboratory Values - Urinalysis
2.8.4	Clinical Laboratory Values - Coagulation
2.8.5	Clinical Laboratory Values - Thyroid Panel
2.8.6	Clinical Laboratory Values - Lipids
2.8.7	Clinical Laboratory Values - Serology
2.8.8	Abnormal Clinical Laboratory Values
2.8.9	Potential Hy's Law Events
2.8.10	Pregnancy Test
2.9.1	Vital Signs
2.9.2	Abnormal Vital Signs Values
2.10.1	12-Lead ECG Values
2.10.2	Abnormal 12-Lead ECG Values
2.11	Physical Examinations
2.12.1	Translational Assessments
2.12.2	RBC/Platelet Transfusions
2.12.3	Tissue Biopsies
2.12.4	HIV Management
2.12.5	COVID-19 Comments
2.12.6	Imaging