

TOUR006-C01 Statistical Analysis Plan

Version 2.0, dated 12-Feb-2026

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**A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate
Quarterly and Monthly TOUR006 in Participants with Chronic Kidney
Disease and Elevated High-Sensitivity C-Reactive Protein**

TOURMALINE

STATISTICAL ANALYSIS PLAN

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Quarterly and Monthly TOUR006 in Participants with Chronic Kidney Disease and Elevated High-Sensitivity C-Reactive Protein

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Protocol Version and Date: Version 4.0: April 7, 2025
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Sponsor: Tourmaline Bio, Inc.
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New York, NY 10010
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LIST OF ABBREVIATIONS

Abbreviation	Description
ADA	Anti-drug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of Covariance
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
CBC	Complete Blood Count
CI	Confidence Interval
CKD	Chronic kidney disease
CL	Clearance
CSR	Clinical Study Report
CR	Complete Response
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram

Abbreviation	Description
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
hs-CRP	High sensitivity C-reactive protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IV	Intravenous
LLQ	Lower limit of quantification
MCMC	Markov Chain Monte Carlo
MH	Mantel Haenzel
MI	Multiple Imputation
MMRM	Mixed model for repeated measures
MTD	Maximum Tolerated Dose
NE	Not Evaluable
PK	Pharmacokinetics
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
TEAE	Treatment Emergent Adverse Events
TFL	Table, Figure, and Listing
ULQ	Upper limit of quantification

1. OVERVIEW

The purpose of the Statistical Analysis Plan (SAP) for this study is to provide a framework for statistically rigorous study data analysis in support of the protocol objectives, without bias or analytical deficiencies.

Mock Table, Figure and Listing (TFL) shells are included in a separate document.

Specifically, this Plan has the following purpose:

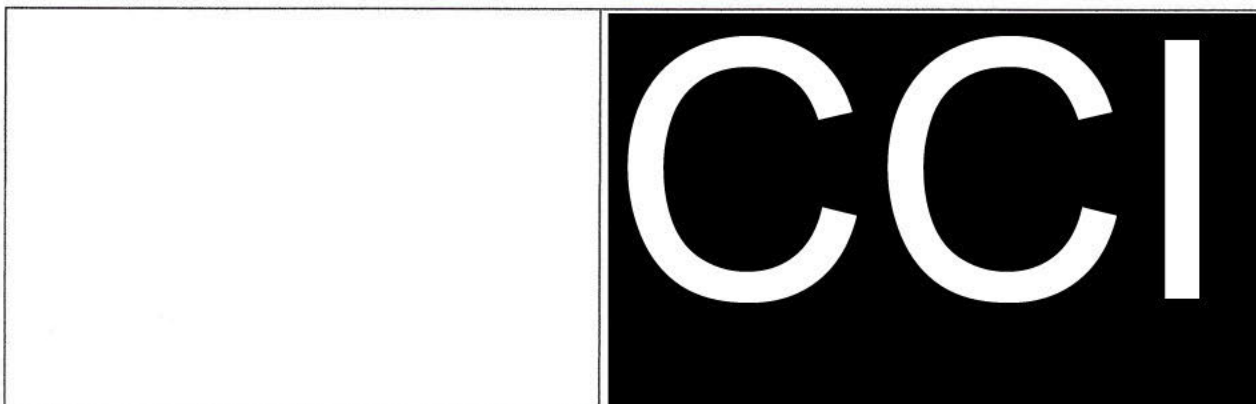
To prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the protocol and to explain in detail how the data will be handled and analyzed, adhering to commonly-accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

2. STUDY OBJECTIVES

The objective of this study is to evaluate the pharmacodynamics, pharmacokinetics, safety, and tolerability of pacibekitug compared to placebo in the treatment of participants with elevated cardiovascular risk (identified as an elevated hs-CRP and a diagnosis of CKD). A list of the specific protocol objectives along with their respective endpoints are listed in the table below; treatment group differences will be estimated for each pacibekitug group relative to placebo:

Objective	Endpoint
Primary	
Evaluate the effects of pacibekitug compared with placebo on hs-CRP	Time-averaged percent change from baseline in hs-CRP through Day 90
Key Secondary	
Evaluate the effects of pacibekitug compared with placebo on hs-CRP	Proportion of participants with time-averaged hs-CRP < 2 mg/L through Day 90
Additional Secondary	
Evaluate the effects of pacibekitug compared with placebo on hs-CRP	- Time-averaged percent change from baseline in hs-CRP through Day 180 - Proportion of participants with time-averaged hs-CRP < 2 mg/L through Day 180 - Proportion of participants with time-averaged hs-CRP < 1 mg/L (1) through Day 90 and (2) through Day 180 - Proportion of participants with time-averaged hs-CRP decrease $\geq$ 50% (1) through Day 90 and (2) through Day 180

	• Proportion of participants with hs-CRP < 2 mg/dL (1) at Days 30, 60, and 90, and (2) at Days 30, 60, 90, 120, 150, and 180 • Proportion of participants with hs-CRP < 1 mg/dL (1) at Days 30, 60, and 90, and (2) at Days 30, 60, 90, 120, 150, and 180 • Proportion of participants with hs-CRP decrease $\geq 50\%$ from baseline (1) at Days 30, 60, and 90, and (2) at Days 30, 60, 90, 120, 150, and 180 • Maximum percent reduction in hs-CRP from baseline (1) through Day 90 (Days 30, Day 60, Day 90) and (2) through Day 180 (Days 30, 60, 90, 120, 150, 180) • Absolute change and percent change in hs-CRP from baseline to Day 30, 60, 90, 120, 150, and 180 • Time-averaged absolute change in hs-CRP from baseline (1) through Day 90, and (2) through Day 180
To evaluate the pharmacokinetics of pacibekitug	• Serum drug concentrations of pacibekitug at baseline and on Day 30, 60, 90, 120, 150, and 180 • Serum drug concentrations of pacibekitug on Day 240, 300, and 365
Safety	
To evaluate the safety and tolerability of pacibekitug in participants with elevated cardiovascular risk and CKD	• Proportion of participants with AEs, SAEs, severe AEs, and AEs leading to discontinuation CCI • Absolute change from baseline in vital signs parameters • Absolute change from baseline in ECG parameters • Absolute change from baseline in laboratory parameters
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AE=adverse event; CKD=chronic kidney disease; hs-CRP=high sensitivity C-reactive protein; CCI

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CCI SAE=serious adverse event

3. STUDY METHODS

3.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled study to evaluate the PD, PK, and safety (including immunogenicity) of 3 dosing regimens of subcutaneous (SC)-administered pacibekitug (50 mg once every 90 days [q90d], 25 mg q90d, and 15 mg q30d) versus placebo in participants with elevated cardiovascular risk (identified as an elevated hs-CRP and a diagnosis of CKD). The study aims to determine whether various dose levels and dosing regimens of pacibekitug can decrease hs-CRP levels following administration every 30 or 90 days. The study will consist of a 180-day treatment period and a 185-day follow-up period.

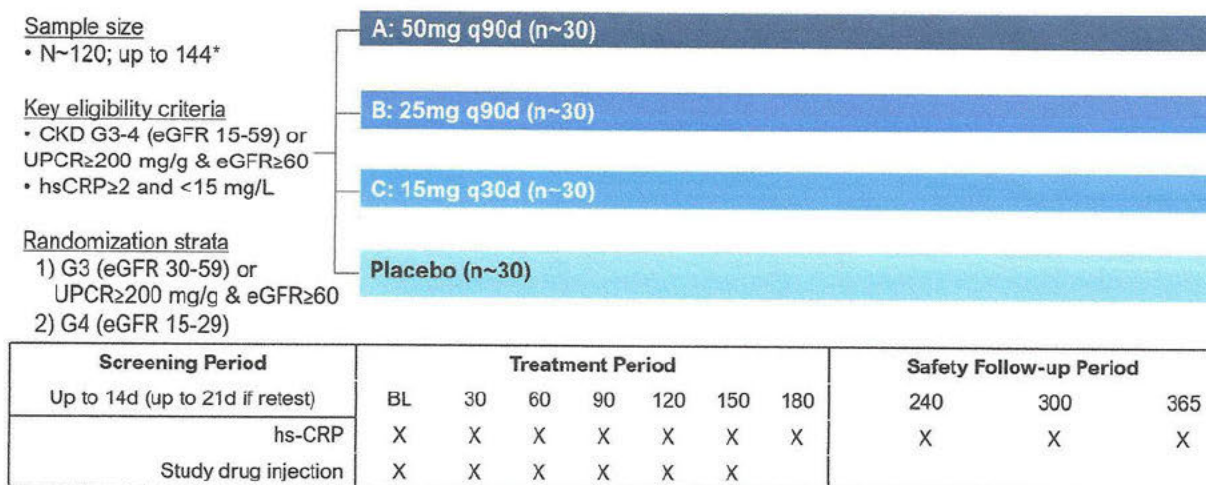
Participants will undergo a Screening Period of up to 14 days to determine eligibility and those who meet all inclusion criteria and no exclusion criteria will be randomized 1:1:1:1 to 1 of 3 dosing regimens of pacibekitug or placebo (see treatment arms below). To mitigate against imbalances in background safety risk from CKD, participants will be stratified by CKD status to ensure balanced randomization. The treatment arms are as follows:

- Placebo: administered subcutaneously every 30 days
- Pacibekitug 25 mg administered subcutaneously every 90 days
- Pacibekitug 50 mg administered subcutaneously every 90 days
- Pacibekitug 15 mg administered subcutaneously every 30 days

Approximately 120 participants (30 per treatment arm) will be randomized 1:1:1:1 to one of 4 treatment arms. After the Screening Period, randomized participants will be dosed with pacibekitug at 50 mg q90d (Arm A), 25 mg q90d (Arm B), 15 mg q30d (Arm C), or placebo q30d. Participants in Arms A and B will receive pacibekitug on Baseline and Day 90 visits and placebo on Study Days 30, 60, 120, and 150 to maintain a q30d dosing schedule as for the Arm C and placebo groups. Participants will be followed until Study Day 365. The primary endpoint evaluation will be through Study Day 90.

Please see Figure 1 below for a detailed study schema. All participants will receive an injection at each dosing visit for a total of 6 injections. Please see Figure 2 below for dosing regimen for Pacibekitug and placebo.

Figure 1: Study Schema

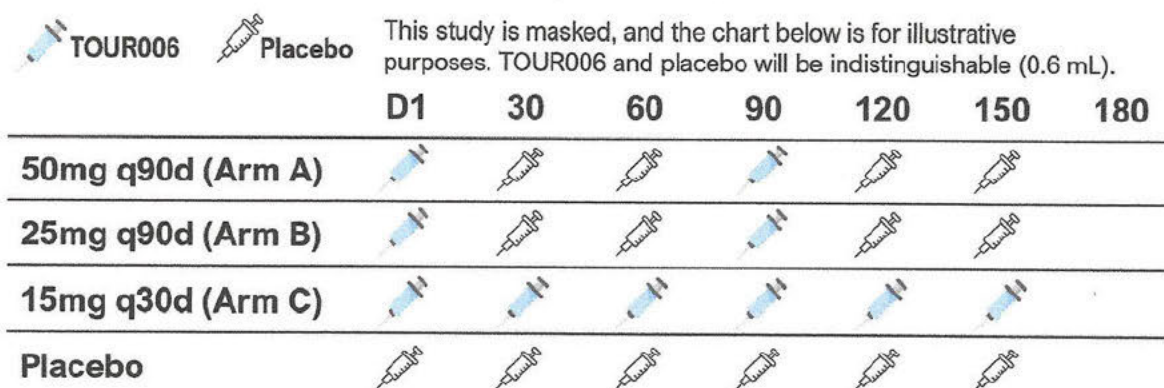


*See Protocol Section 9.9 Sample Size Determination

Abbreviations: BL = Baseline; CKD = chronic kidney disease; D/d = day; eGFR = estimated glomerular filtration rate; hs-CRP = high sensitivity C-reactive protein; q30d = every 30 days; q90d = every 90 days; UPCR = urine protein-to-creatinine ratio

Figure 2: Dosing Regimen for Pacibekitug

All participants will receive an injection at each dosing visit (total 6 injections)



Abbreviations: D = day; q30d = every 30 days; q90d = every 90 days

4. DATA CAPTURE AND PROCESSING

Clinical study data will be captured on electronic case report forms (eCRF) and maintained in a Medidata Rave clinical database. Additionally, pharmacodynamic and pharmacokinetic data are captured and analyzed using central laboratories. The study data will be mapped using Study Data

Tabulation Model (SDTM). Data points used for summaries and analyses will be mapped from SDTM to Analysis Data Model (ADaM).

5. ANALYSIS AND REPORTING

5.1 Through Day 90 and Final Analyses

An analysis of pharmacodynamic effect and safety will be performed after all randomized participants have completed at least their Day 90 visit or terminated early. After the completion of the safety follow-up period, a subsequent final analysis will be performed, following final database lock. The study database will be monitored, cleaned, and frozen through the data cut time point for each analysis (through Day 90 and final). The study team, except the unblinded team members, should remain blinded to individual participant treatment assignment for the duration of the study until after final database lock. Details regarding the unblinding process, including the roles and responsibilities of unblinded personnel, data access procedures, and documentation requirements, are fully described in Tourmaline Day 90 Primary Analysis Unblinding Plan.

5.2 Interim Analysis

No formal interim analysis is planned.

6. SAMPLE SIZE DETERMINATION

Approximately 30 participants will be randomized per treatment group or placebo for a total of 120 participants. Additional participants may be enrolled (up to 20%, or an additional 24 participants beyond the 120 planned) to account for participants whose Baseline hs-CRP is <2.0 mg/L, ≥ 15 mg/L, or decreased by 50% or more from the Screening (or optional Pre-screening) hs-CRP value. No formal power calculation was performed for determination of the sample size.

7. RANDOMIZATION AND BLINDING

Using a centralized Interactive Web Response System (IWRS) eligible participants will be randomly assigned in a 1:1:1:1 ratio to receive pacibekitug (50 mg q90d, 25 mg q90d, or 15 mg q30d) SC or placebo. Randomization will be stratified by CKD status to one of two strata:

- Stage 3 [eGFR 30-59 mL/min/1.73m²] or UPCR $\geq$ 200 mg/g and eGFR $\geq$ 60 mL/min/1.73m² vs
- Stage 4 [eGFR 15-29 mL/min/1.73m²]

Tourmaline personnel, participants, caregivers, investigators, and site personnel, with the exception of the unblinded, qualified staff member, will be blinded to treatment assignments. The site unblinded, qualified staff member will remain unblinded throughout the duration of the trial.

Blinding of the participant and the investigator will remain in place throughout the duration of the study.

To further mitigate the risk of inadvertent unblinding, the following parameters will be blinded in the data transfers provided by the central laboratory: hs-CRP, CCI [REDACTED] CCI [REDACTED]. All results for these parameters will be masked and withheld from the clinical team and any blinded personnel. Only the unblinded personnel will have access to the hs-CRP data at the time of the Through Day 90 data freeze and final analysis database lock.

Blinding will be maintained throughout the duration of the study and will only be lifted following final database lock, unless subject safety requires individual unblinding per protocol.

8. ANALYTIC DEFINITIONS

8.1 Analysis Day

Analysis day will be calculated relative to the date of the first administration of study drug (Pacibekitug or placebo). The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

For an assessment that occurred on or after the first administration of study drug:

$$\text{Analysis Day} = \text{Date of assessment} - \text{date of first study treatment} + 1.$$

For an assessment that occurred prior to the first administration of study drug:

$$\text{Analysis Day} = \text{Date of assessment} - \text{date of first study treatment in treatment phase}$$

8.2 Analysis Visit

Data from scheduled visits will be assigned to analysis visits according to the following analysis visit windows. If data from a scheduled visit is not available, data from unscheduled and early termination visits will be assigned per the following analysis visit windows based on the actual date the assessment took place. When multiple measurements for a particular parameter appear within an analysis window, the scheduled visit will be used. If no scheduled visit appears in the analysis window, the result closest to the target day will be used. If equidistant and both are unscheduled and/or early termination visits, the later result will be used for the summary measure.

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1	1	1	1
Day 30	30	2	45
Day 60	60	46	75
Day 90	90	76	105
Day 120	120	106	135
Day 150	150	136	165
Day 180	180	166	210

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 240	240	211	270
Day 300	300	271	332
Day 365+	365	333	9999

All data, including that not falling within the above windows, will be included in the listings.

8.3 Baseline Measurements

To reduce variation in baseline values and mitigate misclassification, the baseline hs-CRP value is defined as the average of the hs-CRP measurements on Day 1 and the measurement at the preceding visit. If hs-CRP was measured at multiple visits prior to Day 1, the preceding visit is defined as the later (or latest) of these visits, as illustrated in the table below. If a hs-CRP measurement at the Day 1 visit is unavailable, the hs-CRP measurement at the preceding visit will be used as the baseline hs-CRP value.

Visit				Baseline hs-CRP Value
Pre-Screening	Screening	Retest	Day 1	
P	—	—	B	Average of P and B
P	S	—	B	Average of S and B
P	S	UR	B	Average of UR and B
—	S	—	B	Average of S and B
—	S	UR	B	Average of UR and B

Similarly, the baseline for eGFR is defined in a manner similar to hs-CRP, as the average of two values, the eGFR at the Day 1 visit and the eGFR at the visit closest in time before the Day 1 visit.

As specified in Section 9.1.2, for laboratory values below the lower limit of quantification (LLQ), a value equal to half the LLQ (i.e., LLQ/2) will be used in the statistical analyses.

Specifically:

- For hs-CRP, the LLQ is set at 0.2 mg/L; therefore, any baseline values below this threshold will be imputed as 0.1 mg/L.

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For all other evaluations (e.g., labs, vital signs, electrocardiograms, etc.), the last recorded value prior to the first study treatment will serve as the baseline measurement, unless otherwise specified. If

there are multiple results collected on the same day, the collection done at later time and prior to first dose administration, with the repeat status, or with a later sequence number will be used.

8.4 Change from Baseline

Absolute change from baseline at any given visit will be calculated as the non-missing post-baseline value at that visit minus the baseline value. In other words,

$$\text{Change from Baseline} = \text{Post Baseline Measurement} - \text{Baseline Measurement}.$$

The percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100. In other words,

$$\text{Percent Change from Baseline} = 100 \times (\text{Change from Baseline} / \text{Baseline Measurement}).$$

If either the baseline or post-baseline value is missing, then absolute change from baseline and percent change from baseline will be set to missing.

8.5 Duration

A duration between any two dates (*e.g.*, treatment duration, AE duration) expressed in days will be calculated using the following conventions:

$$\text{Duration (in days)} = \text{later date} - \text{earlier date} + 1.$$

8.6 Prior Medication

Prior medication is defined as those medications that started prior to the study treatment. If medications started prior to the study treatment and were ongoing after the study treatment, they will be considered as both prior and concomitant medications.

8.7 Concomitant Medication

Concomitant medication is defined as those taken on or after the study treatment. If medications started prior to the study treatment and were ongoing after the study treatment, those medication will be considered as concomitant medication as well.

8.8 Treatment Exposure

Exposure to study treatment (in days) will be calculated as:

$$\text{date of last dose of study drug} - \text{date of first dose of study drug} + 1.$$

This calculation does not take study treatment interruptions into account and is intended to describe the length of time a participant was exposed to study treatment. Days of exposure to study drug will be summarized by treatment using the safety population.

8.9 Treatment Compliance

Treatment compliance will be calculated as follows:

$$100 \times (\text{Number of injections received} \div \text{Number injections expected}).$$

In this study, the expected injections is 3 for Through Day 90 analysis and 6 for the final analysis.

Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by treatment based on the Safety analysis population with descriptive statistics. Study drug is planned to be administered every 30 days for a total of 3 treatments for the Through Day 90 analysis on Days 1, 30, 60 and a total of 6 treatments for the final analysis on Days 1, 30, 60, 90, 120 and 150.

Counts and percentages of number of injections received (1 to 3 or 1 to 6) along with summary statistics will be summarized by treatment based on the Safety analysis population



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8.11 Derived Data Based on Laboratory Values

The following laboratory parameters will be derived according to the equations below:

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Non-HDL cholesterol is defined as
$$\text{Total cholesterol} - \text{HDL-cholesterol}.$$

Total cholesterol-to-HDL cholesterol ratio is defined as
$$\text{Total cholesterol} \div \text{HDL cholesterol}.$$

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9. GENERAL CONSIDERATIONS FOR STATISTICAL ANALYSIS

9.1 General Principles for Data Analysis

9.1.1 *Summary Statistics*

Categorical data will be summarized by the population size (N), number of participants in each category (n), and the proportion of participants in each category. A missing category will be added as the last category if appropriate.

Continuous data will generally be summarized with descriptive statistics including number of non-missing values (n), mean, standard deviation, median, first quartile, third quartile, minimum, and maximum.

Selected outcomes will also be summarized by graphical displays, e.g., waterfall plots of time-averaged hs-CRP from baseline to Day 90.

9.1.2 *Multicenter Study*

The summaries and analyses will be conducted by pooling data from all study centers.

9.1.3 *Multiplicity Adjustments*

No adjustments will be made to account for multiple comparisons.

9.1.4 Handling of Dropouts and Missing Data

In general, missing data will not be imputed and only observed values will be analyzed except for the data mentioned below or noted otherwise in this SAP.

If the relationship of an AE record is missing the AE will be considered "Related" to the study treatment for reporting purpose. If the intensity of an AE is missing every effort should be made to acquire the information from the investigator. AEs with intensity grade missing will not be imputed. For analyses of other pharmacodynamic and safety data, no imputation will be made for missing values.

In general, missing or partial dates will not be imputed except for AE or medication start and end date. The general imputation rules of partial missing date for both AE and concomitant medication are detailed below:

AE or Medication Start Date Values

If the year portion is missing no imputation will be performed.

If the day portion is missing, the following rules will be implemented:

- Impute with first day of the month if the year and month of the start date is not equal to the year and month of the first study treatment
- Impute with date of first study treatment if the year and month of the start date is the same as the date of the first study treatment

If the month portion is missing, the following rules will be implemented:

- Impute with first day of the year if the year of the start date is not equal to the year of the first study treatment
- Impute with date of first study treatment if the year of the start date is the same as the date of the first study treatment

AE or Medication End Date Values

If the year portion is missing no imputation will be performed.

If the day or month portion is missing:

Impute with the last day of the month (or of the year). If the imputed date is later than the date of death, the death date will be used to impute the end date.

9.1.5 Laboratory Values Above or Below Limits of Quantification

For laboratory values less than the lower limit of quantification (LLQ), half the lower limit value (i.e., LLQ/2) will be used in the analysis. Likewise, for values greater than the upper limit of quantification (ULQ), the upper limit value (i.e., ULQ) will be used in the analysis.

9.1.6 Data Displays for Reporting

For all statistical outputs (tables, listings and figures) the data will be displayed as shown below. Any abbreviation used in the column text will be displayed in full description text in the footnote of the output.

The default ordering of the listings is by site ID, participant ID, test or parameter name (if applicable), date of event or date of collection (if applicable).

The treatment arms are as follows:

- Placebo
- Pacibekitug 25 mg Q90D
- Pacibekitug 15 mg Q30D
- Pacibekitug 50 mg Q90D

9.1.7 Reporting Conventions

The general programming considerations for tables, listings, and figures (TLFs) are provided in the TFL mock shells document. Actual formats and layouts may be altered slightly to accommodate actual data or statistics. Minor format changes will not require updates to the SAP. The TLF numbering and general content follow the ICH E3 guidelines.

The data analyses will be conducted using the SAS® System (SAS Institute Inc., Cary, NC) version 9.4 or above.

9.2 Analysis Populations

9.2.1 Screened Population

The screened population will include all participants who give informed consent and are screened. For this set, treatment arm (or screen failure status), participant disposition, and reasons for premature study termination or screening failure will be described.

9.2.2 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all randomized participants. Participants will be categorized according to randomized treatment.

Unless otherwise specified, the ITT Set will be used for all participant listings with exception of the listing presenting screening failures and the respective reason(s) for screen failure.

9.2.3 Modified Intent-to-treat Population

Includes all randomized participants who:

- received any amount of investigational intervention,
- have at least one post-baseline hs-CRP measurement,

- have baseline hs-CRP ≥ 1.9 mg/L, a threshold within the coefficient of variation for repeated hs-CRP measurements of 2.0 mg/L according to the assay technical specifications,
- did not miss more than one post-baseline hs-CRP assessment in the first 90 days of the study (Days 30, 60, and 90).

Participants will be categorized according to randomized treatment.

The modified intent-to-treat population will be used for the pharmacodynamic analyses.

9.2.4 Safety Population

The safety population will include all participants who received any amount of study treatment. Participants will be classified according to the actual treatment received.

The Safety Set will be used for the analysis of safety data.

9.3 Participant Data and Study Conduct

9.3.1 Participant Disposition

All participants who provide informed consent will be included in disposition summaries. The number of participants screened, screen failed, randomized, completed and discontinued study treatment (with reason for treatment discontinuation), completed and discontinued from the study, as well as reason for discontinuation, will be summarized by treatment group and overall. The number of participants in each analysis set will also be summarized, including reasons for exclusion from the mITT population. All disposition data will be listed by participant.

9.3.2 Protocol Deviations

CSR reportable major protocol deviations will be reported by category for each treatment group. Major protocol deviations will be summarized by site and by deviation categories. All major protocol deviations will be listed.

Major protocol deviations criteria will be finalized before the final database lock.

9.3.3 Demographic and Key Baseline Disease Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be provided by treatment group and overall using the mITT, ITT, and Safety populations. The following demographic characteristics will be summarized:

- Age (years)
- Sex (male, female)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Race (eCRF collected race. If more than one race was checked it will be reported as "Other")
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI, kg/m^2 ; < 30 , and ≥ 30 kg/m^2)

The following key baseline disease characteristics will be summarized:

- Baseline Diseases
 - Years since diagnosis of CKD
 - CKD Stage (defined as eGFR: ≥ 90 [Stage 1], 60 to <90 [Stage 2], 45 to <60 [Stage 3a], 30 to <45 [Stage 3b], 15 to <30 [Stage 4], and <15 [Stage 5] ml/min/1.73m²)
 - Diabetes status (defined as diabetes reported in medical history)
- Baseline Medications
 - Any GLP-1 or GLP-1/GIP Agonist
 - Semaglutide or tirzepatide use
 - Incretin use
 - Any LDL-Lowering Therapy:
 - Statin (yes), and by drug and by intensity (low, medium, high) using the ACC/AHA classification (see Table 1 below)
 - Non-statin, LDL-lowering therapy (yes) and by drug
- Baseline Laboratory Tests:
 - Baseline hs-CRP (mg/L)
 - Baseline Hemoglobin (g/dL)
 - Baseline albumin (g/dL)
 - Baseline LDL cholesterol (mg/dL) (< 100 , and ≥ 100 mg/dL)
 - Baseline urine protein-to-creatinine ratio (UPCR, mg/g)
 - Baseline eGFR (mL/min/1.73 m²)

Table 1: Statin Dosing and ACC/AHA Classification of Intensity

Statin	Intensity Dosage		
	Low	Moderate	High
Atorvastatin	NA	10 to <40 mg	40 to 80 mg
Fluvastatin	20 to <40 mg	40 mg 2x/day; XL 80 mg	NA
Lovastatin	20 to <40 mg	40 to 80 mg	NA
Pitavastatin	NA	1 to 4 mg	NA
Pravastatin	10 to <40 mg	40 to 80 mg	NA
Rosuvastatin	NA	5 to <20 mg	20 to 40 mg
Simvastatin	10 to <20 mg	20 to <80 mg	NA

Adapted from ACC/AHA, 2018. Dosages shown are total daily dosages; exceptions are noted.

Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; LDL-C=low-density lipoprotein cholesterol; NA=not applicable; Low-Intensity Dosage: LDL-C Reduction $<30\%$; Moderate-Intensity Dosage: LDL-C Reduction 30% to $<50\%$; High-Intensity Dosage: LDL-C Reduction $\geq 50\%$.

9.3.4 Medical History

Medical history will be coded using a MedDRA dictionary and will be summarized by SOC and PT. Details of each medical history will be listed for all randomized participants. Furthermore, the number and percentage of participants with a reported history of atherosclerotic cardiovascular disease (ASCVD) will also be summarized.

9.3.5 Prior and Concomitant Medications

All medications will be coded using the World Health Organization (WHO) Drug B3 dictionary. Prior and concomitant medications will be summarized for the safety population.

If a medication's start date is completely missing, it will be counted in both prior and concomitant summaries.

The number and percentage of participants taking prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Levels 2 and preferred terms (standardized drug name) by descending frequency based on all the participants. Patients will be counted only once by medication class or name.

9.3.6 Study Treatment Exposure and Compliance

Exposure to study treatment, number of injections received, and study treatment compliance will be summarized by treatment group using the safety population.

A listing of exposure to the study drugs will be provided.

9.3.7 Pharmacodynamic Assessment

The mITT population will be the primary set for pharmacodynamic analysis. Primary, secondary, CCI CCI endpoints will be presented in listings.

9.3.8 Primary Pharmacodynamic Endpoint

Through Day 90 Analysis

Primary Analysis

The primary pharmacodynamic endpoint is the mean time-averaged percent change from baseline in hs-CRP through Day 90.

The time-averaged percent change from baseline in hs-CRP through Day 90 is defined as follows:

- The analysis should be guided by the treatment-regimen estimand (i.e., pharmacodynamics analysis is performed regardless of treatment discontinuation) and will be conducted using the mITT population.

- Only hs-CRP at derived visit Days 30, 60 and 90 will contribute to the calculations. Unscheduled visits, if any, will not contribute to the analysis.
- Missing hs-CRP measurements at derived visit Days 30, 60, or 90 will be estimated using multiple imputation (MI) under the assumption of missing at random (MAR). Should MI is deemed less than ideal to implement, last observation carried forward will be used.
- For each participant, the time-averaged percent change from baseline in hs-CRP through Day 90 will be calculated using the observed and imputed hs-CRP measurements at derived visit Days 30, 60, and 90. Specifically,
 - The time-averaged percent change from baseline in hs-CRP is the area under the curve for percent change from baseline in hs-CRP divided by the number of days from the observed Day 30 to Day 90 visits (approximately 60 days if visits occur according to the protocol).
 - The area under the curve for the percent change from baseline from Day 30 to Day 90 will be calculated using the linear trapezoidal rule according to the observed visit days.

Suppose p_i denotes the percent change from baseline in hs-CRP at the i -th scheduled visit and t_i denotes the number of days from first dose to the i -th scheduled visit, where $i = 30, 60, 90$. The time-averaged percent change from baseline in hs-CRP at Day 90 is

$$\frac{(\frac{p_{60} + p_{30}}{2})(t_{60} - t_{30}) + (\frac{p_{90} + p_{60}}{2})(t_{90} - t_{60})}{(t_{90} - t_{30})}.$$

Distribution of the hs-CRP are known to have long tails. Given that the authoring biostatistician is blinded to the distribution of post-baseline hs-CRP, median time-averaged percent change from baseline in hs-CRP through Day 90 will also be considered as a more robust alternative should the distribution of the hs-CRP measurements turn out to be severely skewed after unblinding.

Primary Estimand

To assess the primary pharmacodynamic endpoint, the primary estimand is defined by the following key attributes:

- Treatment: Pacibekitug 50 mg SC quarterly, Pacibekitug 25 mg SC quarterly, Pacibekitug 15 mg SC monthly, or placebo SC.
- Analysis Population: mITT population
- Variable(s): Mean/median time-averaged percent change from baseline in hs-CRP.

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- Population-level summary: Median difference between each Pacibekitug group and the placebo group in time-averaged percent change from baseline in hs-CRP through Day 90, 95% CIs and p-value using quantile regression.

Comparisons of each pacibekitug group with the placebo group in mean time-averaged percent change from baseline in hs-CRP through Day 90 will be performed using quantile regression at the 50th percentile ($\tau = 0.5$) implemented in SAS PROC QUANTREG, including treatment, randomization stratum, and baseline hs-CRP as fixed effects

Additionally, an analysis of covariance model (ANCOVA) with baseline hs-CRP, treatment, randomization stratification factor (CKD Stage) as effects.

Missing data will be imputed with Multiple Imputation Markov Chain Monte Carlo (MCMC) method. CCI Individual Pacibekitug treatment groups will be compared against placebo. All statistical analyses will be evaluated on nominal p-value without adjustment of multiple comparison.

Normality assessments will be performed using the Shapiro-Wilk test, with testing performed on the ANOVA model residuals. If substantial deviation from assumption of normality is encountered (Shapiro-Wilk p-value < 0.01), a nonparametric analysis will be performed. Median and quartiles of the time-averaged percent change from baseline in hs-CRP through Day 90 will be presented.

Assessments beyond Day 90 will also be summarized with descriptive statistics only.

Final Analysis

At the time of the final analysis, the primary analysis performed at the Through Day 90 analysis will be repeated and the difference in mean/median time-averaged percent change from baseline in hs-CRP through Day 180 between each Pacibekitug group and the placebo group will be assessed using the same statistical methods.

Time averaged calculations through Day 180 will follow the conventions for the primary pharmacodynamic endpoint at Through Day 90 Analysis, with the additional time intervals of Day 90 to Day 120, Day 120 to Day 150, and Day 150 to Day 180.

Assessments beyond Day 180 in the follow-up period will also be summarized with descriptive statistics only.

9.3.9 Key Secondary Pharmacodynamic Endpoint

Through Day 90 Analysis

The key secondary pharmacodynamic endpoint is the proportion of participants with time-averaged hs-CRP < 2 mg/L through Day 90.

The estimated CMH treatment group difference in proportions will be summarized along with the standard error of the estimate, the 2-sided 95% CI using CMH stratum weights, and the Sato variance estimator. Example SAS code is provided in Section 11.

Missing data imputation rules apply to all hs-CRP-related endpoints and not all other endpoints related to other PD endpoints.

9.3.10 Additional Secondary Pharmacodynamic Endpoints

Through Day 90 Analysis

Analyses of secondary pharmacodynamic endpoints involving proportions will be analyzed using CMH test of the difference in the two proportions stratified by the randomization stratification factor (CKD stage) and baseline hs-CRP strata (1 = Above or equal sample median; 0 = Otherwise) using a type 1 error rate of 5%, 2-sided. This includes the analysis of the following secondary pharmacodynamic endpoints:

- Proportion of participants with time-averaged hs-CRP < 1 mg/L through Day 90
- Proportion of participants with time-averaged hs-CRP decrease $\geq 50\%$ from baseline to Day 90
- Proportion of participants with hs-CRP < 2 mg/dL at Days 30, 60, and 90
- Proportion of participants with hs-CRP < 1 mg/dL at Days 30, 60, and 90
- Proportion of participants with hs-CRP decrease $\geq 50\%$ from baseline at Days 30, 60, and 90

The estimated CMH treatment group difference in proportions will be summarized along with the standard error of the estimate, the 2-sided 95% CI using CMH stratum weights, and the Sato variance estimator. Example SAS code is provided in Section 11.

Analyses of secondary pharmacodynamic endpoints involving continuous outcomes will be analyzed using the same methods as the primary endpoint,

- Change from baseline in hs-CRP at Days 30, 60, 90
- Percent change from baseline in hs-CRP at Days 30, 60, 90.

Medians and quartiles of the change and percent change from baseline will be presented. Between-group differences in the median response will be evaluated using quantile regression at the 50th percentile ($\tau = 0.5$) implemented in SAS PROC QUANTREG, including treatment, randomization stratum, and baseline hs-CRP as fixed effects.

Parameter estimates, confidence intervals and p-value will be obtained using the sparsity method.

Additionally, continuous endpoints will be analyzed by mixed effect models for repeated measures (MMRM). The MMRM model will include the randomization stratification factor (CKD Stage), treatment group, visit, and treatment group-by-visit interaction as categorical fixed effects, baseline hs-CRP and baseline hs-CRP-by-visit interaction will be included as covariates. The least squares means for each dose, the least squares mean differences from placebo along with the associated 95% CIs and p-values will be presented.

An unstructured covariance matrix will be used to model the within-subject correlation. The Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. The analysis will be performed based on all observed post-baseline scores without any imputation of missing data. In the case when the MMRM fails to converge using an unstructured covariance matrix,

the following structures will be investigated: heterogeneous First-Order Autoregressive [AR (1)] and compound symmetry (CS.).

Normality assessments will be performed using the Shapiro-Wilk test, with testing performed on the MMRM model residuals. If substantial deviation from assumption of normality is encountered (Shapiro-Wilk p-value < 0.01), a nonparametric analysis will be performed. Median and quartiles will be presented for hs-CRP values at baseline, Day 90, and percent change in hs-CRP from baseline to Day 90.

Assessments beyond Day 90 will also be summarized with descriptive statistics only.

Final Analysis

At the time of the final analysis, the analyses of the following secondary endpoints will use the same statistical methods as used for the Through Day 90 analysis.

Additionally, assessments beyond Day 180 in the follow-up period will also be summarized with descriptive statistics only.

- Proportion of participants with time-averaged hs-CRP < 2 mg/L through Day 180
- Proportion of participants with time-averaged hs-CRP < 1 mg/L through Day 180
- Proportion of participants with time-averaged hs-CRP decrease $\geq 50\%$ from baseline through Day 180
- Proportion of participants with hs-CRP < 2 mg/dL at Days 120, 150, and 180
- Proportion of participants with hs-CRP < 1 mg/dL at Days 120, 150, and 180
- Proportion of participants with hs-CRP decrease $\geq 50\%$ from baseline to Days 120, 150, and 180
- Absolute change and percent change in hs-CRP from baseline to Day 120, 150, and 180

Assessments beyond Day 180 in the follow-up period will also be summarized with descriptive statistics only.

The logo for CCI (Centers for Disease Control and Prevention) is displayed in large, white, sans-serif capital letters on a black rectangular background.

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All endpoints will be summarized through Day 180. Assessments beyond Day 180 in the follow-up period will also be summarized with descriptive statistics only.

Missing data imputation rules apply to all hs-CRP-related endpoints and not all other endpoints related to other PD endpoints.

9.3.12 Examination of Subgroups

Pharmacodynamic analyses based on subgroups may be performed for primary and secondary endpoints, if necessary. The following subgroups will be defined:

- baseline hs-CRP (<median, ≥median)
- Sex (female, male)
- baseline eGFR (<45 ml/min/1.73m², ≥45 ml/min/1.73m².)
- baseline body mass index (<30, ≥30 kg/m²)
- baseline ASCVD (yes, no)
- baseline diabetes status (yes, no)
- baseline statin status (yes, no)

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- baseline incretin use (yes, no)
- baseline LDL-C (<100, ≥100 mg/dL).

Additional subgroups may be added if identified during the trial.

9.3.14 Pharmacokinetics

Pacibekitug concentrations will be summarized by analysis visit and treatment group. Planned PK analysis is covered in a separate document.

9.4 Safety Assessment

All safety analyses will be based on the safety population. Descriptive statistics will be used to summarize safety data by treatment groups. No formal statistical inference is planned for safety endpoints.

Unless otherwise specified, two analyses are planned for the data captured under this protocol:

1. Through Day 90 Analysis: This analysis will include all data captured up to and including the Day 90 data cutoff date
2. Final Analysis: This analysis will include all data captured for this study.

9.4.1 Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events (TEAEs) are defined as AEs that initiated or worsened on or after the administration of the first dose of study drug. For AEs occurring on the first dosing day, if the start time cannot be ascertained, the event will be considered as treatment-emergent. Also, events with missing start dates will be considered as treatment-emergent.

Adverse events will be presented during the treatment period and for the entire study. During the treatment period presentation will include all treatment-emergent adverse events with an onset date on or before the Day 180 visit. The entire study presentation will include all treatment-emergent adverse events reported.

The incidence of TEAEs will be presented using counts and percentages of participants with TEAEs and tabulated by SOC and PT. SOC will be sorted in descending frequency and PT within SOC will be sorted by descending frequency based on the incidence of all participants in the safety population. If a participant has multiple occurrences (start and stop) of an event associated with a specific SOC or PT within a SOC, a participant will only be counted once in the incidence count for the SOC or PT within SOC respectively.

An overall summary table of AEs will be presented detailing the number and percentage of participants for the following categories:

- Any TEAE
- Any study drug related TEAE
- Any serious TEAE
- Any severe TEAE (CTCAE Grade 3 or higher)
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to death

If a participant experiences more than one TEAE meeting the criteria of interest, the occurrence with the greatest severity and the closest relationship with study drug will be used in the corresponding summary tables.

For each of the above categories, TEAEs will be summarized by SOC and PT.

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Listings will be provided for all adverse events and specifically for SAEs, TEAEs leading to discontinuation of study drug, TEAEs leading to discontinuation of study, CCI

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9.4.2 Safety Laboratory Evaluations

All continuous safety laboratory parameters in chemistry and hematology panels analyzed in the central laboratory will be summarized descriptively by treatment group at each scheduled visit. Analyses will include:

- Laboratory abnormalities.
- Observed, change and percent change from baseline
- Worst post-baseline values
- Last post-baseline values
- CTCAE-based shifts from baseline to worst post-baseline grade

Laboratory results will be graded using NCI CTCAE v5.0. An abnormality is defined as any value meeting Grade 1 or higher criteria. The highest post-baseline CTCAE grade will be summarized for each subject and parameter. For laboratory tests not graded by CTCAE v5.0, clinical significance thresholds will be defined by the Medical Monitor in collaboration with Pharmacovigilance Lead.

Local laboratory results will not contribute to the safety tables and will be included in listings only.

9.4.3 Vital Signs

Vital signs parameters (including systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and weight) will be summarized by scheduled visit and treatment group. Analyses will include:

- Potentially abnormal vital signs
- Observed, change, and percent change from baseline
- Extreme post-baseline values
- Last post-baseline values.

Potentially abnormal vital signs are defined as:

- Systolic BP <90 mmHg
- Systolic BP >160 mmHg
- Heart rate < 50 bpm
- Heart rate >110 bpm.

The highest post-baseline abnormality grade will be summarized by treatment group.

9.4.4 Electrocardiograms (ECGs)

Electrocardiogram interpretation (normal; abnormal, not clinically significant; abnormal, clinically significant) will be summarized using frequency and percentage at each visit by treatment group. ECG intervals (HR, RR, PR, QRS, QT, and QTcF) will be summarized descriptively at each visit. QTcF will be calculated using the Fridericia formula: $QTcF = QT / (RR)^{1/3}$.

The number and percentage of participants with potentially abnormal values that exceed the following pre-defined thresholds will be summarized:

Absolute QTcF interval:

- QTcF interval > 450 ms
- QTcF interval > 480 ms
- QTcF interval > 500 ms

Change from baseline in QTc interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

9.4.5 *Physical Examination and Pregnancy Data*

Physical examination will be performed at Screening and will include assessments of the skin, oropharynx, lungs, heart, abdomen, and extremities. Subsequent physical examination is only carried out as symptom directed.

Pregnancy testing will be conducted for women of childbearing potential as indicated in the protocol.

Physical examination results and pregnancy data will be listed.

10. CHANGES FROM ANALYSES PLANNED IN THE PROTOCOL

Not applicable.

This Statistical Analysis Plan (SAP) Version 2.0 (dated 15 December 2025) reflects updates made following the Day 90 primary analysis. For the Day 90 primary analysis designated Tourmaline personnel were unblinded in accordance with the Tourmaline Day 90 Primary Analysis Unblinding Plan.

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