Cover Page for Statistical Analysis Plan

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NCT number	NCT04626505
Sponsor trial ID:	NN6018-4776
Official title of study:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Reduction in Inflammation in Patients With Advanced Chronic Renal Disease Utilizing Antibody-Mediated Interleukin-6 Inhibition in Japan (RESCUE-2)
Document date*:	20 January 2021

*Document date refers to the date on which the document was most recently updated.

[redacted]

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate REduction in Inflammation in PatientS With Advanced Chronic Renal Disease Utilizing Antibody-MEdiated Interleukin-6 Inhibition in Japan (RESCUE-2)
Protocol Number:	COR-001-02-Japan
Protocol Version/Date:	1.2, 13 August 2020
Investigational Product:	Ziltivekimab (human monoclonal antibody to interleukin [IL]-6)
Sponsor:	Corvidia Therapeutics Inc. 35 Gatehouse Drive Waltham, MA 02451 United States Telephone: +1 781-205-4755
SAP Version/Date:	Version 1.0, 20 January 2021

[redacted]

Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
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[redacted]	[redacted]

VERSION HISTORY

Version	Version Date	Description
1.0	20JAN2021	Original signed version

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
ADA	Anti-Drug Antibodies
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BUN	Blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CHr	Reticulocyte Hemoglobin Content
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
EDC	Electronic Data Capture
GFR	Glomerular Filtration Rate
hs-CRP	high-sensitivity C-Reactive Protein
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not at Random
NDD-CKD	Non-dialysis-dependent Chronic Kidney Disease
NT-pro-BNP	N-terminal prohormone-B-type natriuretic peptide
IWRS	Interactive Web-Response System
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIMI	Thrombolysis in Myocardial Infarction
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number COR-001-02-Japan. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to evaluate the effects of 2 dose levels of Ziltivekimab compared to placebo on high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation and cardiac risk, in patients with non-dialysis-dependent chronic kidney disease (NDD-CKD).

2.1.2 Secondary Objectives

The secondary objective is to evaluate the safety of 2 dose levels of Ziltivekimab compared to placebo in patients with NDD-CKD.

2.1.3 Pharmacokinetic (PK) objective

The pharmacokinetic (PK) objective is to evaluate the PK and PK-Pharmacodynamic (PK-PD) modeling of Ziltivekimab following multiple doses at 2 different levels.

2.1.4 Exploratory Objectives

The exploratory objectives are the following:

- To evaluate the effects of 2 dose levels of Ziltivekimab compared to placebo on additional markers of inflammation and cardiac risk, i.e., fibrinogen, serum amyloid A (SAA), N-terminal prohormone-B-type natriuretic peptide (NT-pro-BNP), hemoglobin and albumin; and
- To evaluate the effects of 2 dose levels of Ziltivekimab compared to placebo on markers of atherosclerosis risk (total cholesterol [TC], low density lipoprotein-cholesterol [LDL-C], high density lipoprotein-cholesterol [HDL-C], and triglycerides [TG]).

2.2 Study Design

2.2.1 Overview

This is a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and PK of Ziltivekimab at 2 dose levels (15 mg or 30 mg) compared to placebo in Japanese patients with Stage 3 to 5 NDD-CKD and evidence of inflammation.

The study will consist of 3 periods: a Screening Period, a Treatment Period, and a Safety Follow-Up Period. The total study duration for each patient will be approximately 6 months.

- Screening Period: up to 2 weeks (Days -14 through -1)
  The Screening Period starts on the date of informed consent, and this date will also be the date of the Initial Screening Visit.

- Treatment Period: 12 weeks (Baseline [Day 1] through Week 12)
  The Treatment Period starts with the administration of study drug/randomization (Day 1).
- Safety Follow-Up Period: 8 weeks (Weeks 12 through 20)
  The Safety Follow-Up Period starts 12 weeks after randomization

Patients will undergo a Screening Period of up to 14 days, during which the inclusion and exclusion criteria will be evaluated. Patients who meet all inclusion criteria and no exclusion criteria will be randomized 1:1:1 to Ziltivekimab 15 mg, Ziltivekimab 30 mg, or placebo (12 patients per group) for a 12-week Treatment Period. Approximately 36 patients will be randomized. Patient randomization will be stratified by CKD stage (3, 4 and 5). There will be approximately 10 sites in Japan.

After the Screening Period, patients will be randomized on Day 1. Randomized patients will receive multiple doses of study drug, and the initial dose of study drug will be administered after all assessments are conducted. Patients will then be followed for efficacy and safety through Week 12 and followed for safety in the Safety Follow-Up Period from Weeks 12 through 20. The primary endpoint evaluation will take place at the End of Treatment (using the average of Week 10 and Week 12 assessments).

Patients will be carefully monitored for 1 to 2 hours at the site post every dosing.

The schedule of procedures can be found in Appendix A of the protocol version 1.3.

2.2.2 Randomization and Blinding

Patients who meet all inclusion criteria and no exclusion criteria will be randomized 1:1:1 to Ziltivekimab 15 mg, Ziltivekimab 30 mg, or matching placebo (12 patients per group) for a 12-week Treatment Period. Approximately 36 patients will be randomized. Patient randomization will be stratified by CKD stage. CKD stage is stratified into two categories: (1) stage 3 and (2) stages 4 and 5.

This study is double-blind. The patients, Investigators, site personnel, site monitors, Sponsor, and contract research organization (CRO) clinical operational personnel will be blinded to the treatment assignment. Ziltivekimab and matching placebo will be provided as a liquid for subcutaneous injection.

The randomization list will be generated by an independent CRO statistician not otherwise involved in the study.

In case of a medical emergency or medical situation in which the treatment assignment is necessary for proper patient management, the Investigator may obtain the treatment assignment from the IWRS. The Investigator should make every reasonable attempt to contact the Medical Monitor before unblinding a patient. In all cases, the Investigator must submit a written report, including all pertinent details, to the Medical Monitor within 24 hours of the unblinding.

2.2.3 Study Drug

Ziltivekimab is supplied as a liquid for injection. Drug product is presented as a single use vial and any unused portion must be discarded.

The Ziltivekimab doses to be tested in this study are 15 and 30 mg per injection. Patients will receive subcutaneous injections of either their assigned dose of Ziltivekimab or matching placebo during the study.

Study drug is planned to be administered every 28 days for a total of 3 treatments on Day1, Weeks 4 and 8. The total cumulative dosage will be 45 mg for those patients randomized to 15 mg per injection, and 90 mg for those patients randomized to 30 mg.

2.2.4 Sample Size Determination

The primary efficacy endpoint is the difference in the mean percent change in hs-CRP from Baseline to the End of Treatment (average of Week 10 and Week 12) between each active group and placebo. Based on the observed treatment difference of -60.74% between combined COR-001-01 active and placebo and the associated pooled SD of 16.893% in hs-CRP at Week 4 from the final analysis of study COR001-SC1, a sample size of 6 patients per group provides 90% power with 2-sided $\alpha = 0.05$. Therefore, the planned sample size of 12 patients per group (total of 36 patients) will provide sufficient power for the study.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoints

The primary PD endpoint is the difference in the percent change in hs-CRP levels from Baseline (average of all hs-CRP values prior to the administration of study drug) to the End of Treatment (average of Week 10 and Week 12) between each active group and placebo.

2.3.2 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Difference in the proportion of patients achieving hs-CRP response, defined as hs-CRP<2.0 mg/L, at End of Treatment (average of Week 10 and Week 12) between each active group and placebo.
- Difference in the percent change in fibrinogen, SAA, NT-pro-BNP, change in hemoglobin and change in albumin from Baseline to End of Treatment (average of Week 10 and Week 12) between each active group and placebo.
- Difference in the percent change in TC, LDL-C, HDL-C, and TG from Baseline to End of Treatment (average of Week 10 and Week 12) between each active group and placebo.

2.3.3 Pharmacokinetic and Pharmacokinetic-pharmacodynamic Endpoints

The serum trough levels of Ziltivekimab will be measured at all visits, beginning with Visit 1.

The area under the curve for total IL-6 will be described.

The relationship between trough Ziltivekimab levels and PD parameters, specifically total plasma IL-6 and hs-CRP, will be described.

2.3.4 Safety Endpoints

The safety endpoints include the following:

- Description of safety assessments by treatment group and dose including adverse events (AEs), serious AEs (SAEs), vital signs, electrocardiogram (ECG) results, and clinical laboratory evaluations;
- Proportion of patients with AEs leading to discontinuation;
- Description and frequency of AEs of special interest (AESIs) by treatment group. AESIs include:
    - Serious infections
    - Common Terminology Criteria for Adverse Events (CTCAE) Grade >= 3 injection-related reactions
    - Gastrointestinal perforations
    - CTCAE Grade >= 3 anaphylaxis occurring at any time, even if considered unrelated to the study drug.
    - Neutrophil <500/mm^3 (CTCAE Grade 4) or neutrophil <1000/mm^3 (CTCAE Grade 3) with evidence of concurrent infection. These events will be separately summarized by treatment group and dose.
    - Thrombocytopenia (platelet count < 50,000/mm^3 [CTCAE Grade 3]) or platelet count < 75,000/mm^3 (CTCAE Grade 2) with evidence of concurrent major bleeding as defined by the Thrombolysis in Myocardial Infarction (TIMI) bleeding classification. These events will be separately summarized by treatment group and dose
    - Malignancies
- Description of anti-drug antibodies (ADAs) (binding and neutralizing).

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. 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.

3.1.2 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded in the electronic data capture (EDC) system. If a scheduled visit is not available, unscheduled and early termination visits will be assigned to analysis visits using analysis visit windows based on the actual date the assessment took place. The low analysis day of the analysis window will be calculated as the midpoint between the scheduled assessment and previously scheduled assessment for that parameter. The high analysis day of the analysis window will be calculated as the midpoint between the scheduled assessment and the next scheduled assessment for that parameter. Where 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. For applicable efficacy parameters, "End of Treatment" visit will be derived where the average of assessments at Week 10 and Week 12 visits from the EDC will be calculated. Otherwise Week 12 visit will be used as the derived "End of Treatment" visit.

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Baseline	1		1
Week 1	8	2	12
Week 2	15	13	19
Week 3	22	20	26
Week 4	29	27	36
Week 6	43	37	50
Week 8	57	51	64
Week 10	71	65	78
Week 12	85	79	92
End of Treatment	78	65	92
Week 16	113	93	133
Week 20	141	134	148

The observational period for the study will start from informed consent and end with study completion. Any event occurring after the defined observational period, even if collected on the case report form (CRF), may not be included in the planned statistical analyses. However, all data, including that reported after the defined observational period, will be included in the patient data listings.

3.1.3 Definition of Baseline

The Baseline value for hs-CRP level will be the average of all hs-CRP values prior to the administration of study drug. The Baseline value of other measures is defined as the last measurement collected prior to the administration of study drug, unless otherwise specified.

3.1.4 Summary Statistics

All study-collected data will be summarized by treatment group for the appropriate analysis population using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include number of patients (with non-missing values), mean, standard deviation (SD), median, first and third quartiles, minimum and maximum values for the observed value, and change from Baseline. Analysis of categorical variables will include frequency and percentage. The denominator used for the percentage calculation will be clearly defined.

3.1.5 Handling of Dropouts and Missing Data

Missing data will be imputed only in the context of sensitivity analysis as described in section 3.4.1.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The ITT Population is defined as all randomized subjects and will be the primary population for analysis of efficacy data.

3.2.2 Per-Protocol (PP) Population

The PP population will be the secondary population for analyses of disposition, baseline data, and efficacy data. For PP population, treatment classification will be based on the randomized treatment. The PP Population is defined as all subjects in the ITT Population who completed the study and did not incur a significant protocol violation that may impact the primary efficacy assessment. Significant protocol violations may include but are not limited to:

- Failed to meet eligibility criteria
- Took the wrong study drug (i.e., did not take the randomized study drug)
- Took a restricted concomitant medication
- Failed to complete the primary efficacy assessment

A list of subjects with significant protocol violations leading to exclusion from the PP Population will be finalized prior to unblinding the randomized treatment assignments.

3.2.3 Pharmacokinetics (PK) Population

The PK Population is defined as all randomized subjects who receive at least one dose of study drug and have at least 1 post-dose PK serum concentration. For the PK population, treatment classification will be based on the actual treatment received.

3.2.4 Safety Population

The Safety Population is defined as all randomized subjects who receive at least one dose of study drug. All safety data will be analyzed using the Safety Population. For the Safety population, treatment classification will be based on the actual treatment received.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of subjects who were randomized, discontinued early from the study, and completed the study will be summarized by treatment and in total based on all randomized subjects (ITT population). Reasons for early discontinuation will also be summarized.

3.3.2 Protocol Deviations

Protocol deviations are defined in the Protocol Deviation Plan and classified as CSR reportable or non-CSR reportable. All protocol deviations will be listed by deviation categories.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized by treatment and in total based on all randomized subjects.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Sex
- Race

- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- CKD Stage (Stage 3, Stage 4 or Stage 5) as per randomization strata

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total for the ITT, per-protocol, and safety populations.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment and in total based on the ITT population.

3.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary. For summary purposes, medications will be considered prior medications if they were given before the first dose of study drug and concomitant medications if they were taken before and were continuing after the first dose of study drug or initiated after the first dose of study drug.

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment and in total based on the Safety Population. Patients will be counted only once by medication class or name.

3.3.7 Study Drug Exposure

Weeks of exposure to study drug will be calculated as: (date of last dose of study drug - date of first dose of study drug + 29)/7. 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. Weeks of exposure to study drug will be summarized by treatment based on the Safety population with descriptive statistics.

Study drug is planned to be administered every 28 days for a total of 3 treatments on Day1, Weeks 4 and 8.

Counts and percentages of number of injections received (1 to 3) with summary statistics will be summarized by treatment based on the Safety population. Number of subjects with injections at each visit will also be summarized along with the primary reason for injection not administered.

3.4 Efficacy (Pharmacodynamic) Assessment

For all continuous efficacy variables, the number of patients (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min) and maximum (max) values for the observed value, change from baseline, and percent change from baseline will be reported on the ITT population. The difference (Ziltivekimab - Placebo) in percent changes will be presented. For categorical efficacy variables, the number of patients and percentage will be reported on the ITT population.

Due to the known distribution of the primary and secondary efficacy endpoints, normality assumption is usually difficult to satisfy; therefore, a non-parametric approach will be used for the primary and secondary efficacy analysis. Efficacy analysis will be carried out using the Hodges-Lehmann method to estimate median differences and its corresponding 95% confidence intervals for percent change from baseline to end of treatment between each treatment arm vs. Placebo, where end of treatment is the average of assessments at Week 10 and Week 12. The p-value from the Wilcoxon test will also be presented. The nonparametric analysis will account for the covariate CKD Stage (3 vs. 4 and 5) by aligning responses within the strata defined by the covariate prior to analysis.

Sensitivity analyses will be conducted to explore the robustness of the result for primary efficacy endpoint based on mixed models for repeated measures (MMRM) analysis using log of ratio to baseline, and multiple imputation analysis on a log scale. Sensitivity analysis will also be performed based on the PP population using the non-parametric approach. Efficacy data will be summarized by randomized treatment group based on the ITT and PP populations.

The differences in proportions and 95% CIs will be based on the normal approximation to binomials.

Missing data will be imputed only in the context of sensitivity analysis as described in section 3.4.1.

The pharmacodynamic efficacy of two Ziltivekimab doses compared to placebo will be assessed by evaluating the following:

3.4.1 Primary Efficacy Endpoints

Primary Analysis

The primary PD endpoint is the difference in the percent change in hs-CRP levels from Baseline (average of all hs-CRP values prior to the administration of study drug) to the End of Treatment (average of Week 10 and Week 12) between each active group and placebo.

The Hodges-Lehmann estimate for median of differences for each active group vs. placebo along with the 95% confidence intervals will be presented. P-value from the Wilcoxon test will also be presented. The nonparametric analysis will account for the covariate CKD Stage (3 vs. 4 and 5) by aligning responses within the strata defined by the covariate prior to analysis. Median and quartiles will also be presented for hs-CRP values at baseline, end of treatment, and percent change in hs-CRP from baseline to End of Treatment.

The sample SAS code for Hodges-Lehmann estimates for each treatment arm vs. Placebo can be found below:

```
*Note: PCHG = Percent change in hs-CRP from baseline to End of
Treatment(average of values at Week 10 and Week 12).
* CKD = CKD Stage (stage 3 vs. stage 4 and 5)
* TRT = Treatment group
* VISIT = Study Visit
*****************************************************************;
proc npar1way data=efficacy(where=(TRT in (1, #) & VISIT = "End of Treatment"
     wilcoxon hl(refclass="1") alpha=.05 align=strata(hl);
     class TRT;
     strata CKD;
     var PCHG;
     ods output WilcoxonScores=WilcoxonScores HodgesLehmann=HodgesLehmann;
     output out=pvalue;

run;
```

The overall familywise error rate will be controlled at α = 0.05 using the sequential testing procedure for the primary efficacy endpoint comparing the 2 dose levels of Ziltivekimab vs placebo. The high dose (30 mg) will be compared with placebo first. If the high dose is significant, then the low dose (15 mg) will be compared with placebo. The procedure will stop whenever a nonsignificant test occurs.

Sensitivity Analyses

Sensitivity analyses will be performed as follows:

(1) The nonparametric analysis method used to analyze the primary efficacy endpoint will be performed on the PP population.

(2) Analysis of hs-CRP on a log scale will be performed using MMRM on the ITT population. MMRM analysis will be carried out which includes log of ratio to baseline as the response variable, variable for CKD stage (3 vs. 4 and 5), treatment group, visit and treatment group-by-visit interaction as categorical fixed effects, and log of baseline-by-visit interaction as a covariate. The mixed model will include analysis visits at Week 2, Week 4, Week 10, and Week 12. This model will be analyzed to present estimates for ratio to baseline (with 95% confidence intervals), treatment ratio estimates (with 95% confidence intervals) for each active group to placebo with p-values. Estimates and 95% confidence intervals will also be presented on a percentage scale.
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 visits without any imputation of missing data. In the case when the mixed model for repeated measures (MMRM) fails to converge using an unstructured covariance matrix in any stage, a less stringent covariance matrix (e.g., autoregressive 1) will be used. The mean values from Week 10 and Week 12 as well as the treatment difference of average will be estimated using the LMSESTIMATE statement within PROC MIXED for mixed models. The sample SAS code is provided below:

```
*************************************************************
*Note: PCHG = Percent change in hs-CRP from baseline at each visit
* CKD = CKD Stage (stage 3 vs. stage 4 and 5)
* TRT = Treatment group
* VISIT = Study Visit
```

```
      * LOG_R2BASE = Log of ratio to Baseline
      * LOG_BASE= Log of baseline
      ************************************************************;

      proc mixed data=crp (where=(LOG_R2BASE ne . and
           VISIT in ("VISIT 2 (WEEK 1)", "VISIT 3 (WEEK 2)",
           "VISIT 5 (WEEK 4)", "VISIT 8 (WEEK 10)", "VISIT 9 (WEEK 12)"))
           method=reml covtest ;
           class USUBJID CKD TRT VISIT;
           model LOG_R2BASE = CKD TRT VISIT TRT*VISIT LOG_BASE*VISIT /
           ddfm=KR residual;
           repeated  VISIT / type=un subject=USUBJID ;
           lsmeans TRT*VISIT  / cl;
           lsmestimate TRT*VISIT
      /*average estimates*/
      "Placebo avg week 10, 12" [0.5 1 4] [0.5 1 5],
      "15 mg avg week 10, 12"   [0.5 2 4] [0.5 2 5],
      "30 mg avg week 10, 12"   [0.5 3 4] [0.5 3 5],
      /*differences in averages*/
 "15 mg-placebo week 9, 13 avg" [0.5 2 4] [0.5 2 5] [-0.5 1 4] [-0.5 1 5],
 "30 mg-placebo week 9, 13 avg" [0.5 3 4] [0.5 3 5] [-0.5 1 4] [-0.5 1 5]/CL;
           ods output LSMEstimates = LSMEstimates  LSMeans = LSMeans;
      run;
```

(3) Sensitivity analysis will be performed on the ITT population using a pattern-mixture model using sequential modeling with multiple imputation on the log transformed hs-CRP data. Subjects in the active groups who terminated early will be assumed to have no treatment effect. These subjects are assumed to copy the profile of placebo group and missing values are imputed based on the distribution estimated from the placebo group under the missing not at random (MNAR) assumption. The rest of missing values in the placebo group and active groups will be imputed using the observed data under the missing at random (MAR) assumption. The multiple imputation model will include factors such as treatment arm and CKD stage in addition to the data outcomes at each visit. Data will be log transformed prior to imputation, and imputed data will be back-transformed in the final imputed data.

The following steps will be performed:

Step 1: Intermittent (non-monotone) missing data will be generated using the MCMC option of SAS PROC MI (using seed=5414). Only the observed hs-CRP measurements will be used to create non-monotone missing data.

Step 2: Subjects in the active group who discontinue early will be imputed under the MNAR assumption. Data in this step will include all early terminated patients from the active groups and all patients from the Placebo group (where data from the Placebo group will be used to inform the MNAR imputation). Patients in the active group, to be imputed under MNAR, will have their post-baseline history removed prior to imputation (only baseline values will be included). MNAR imputation will then be performed for active subjects based on data from patients in the Placebo group.

Step 3: For all other patients, imputation will be performed under the MAR assumption.

For monotone missing data, the values for each pattern will be imputed via the chained equation method using SAS PROC MI option MONOTONE REG ().

These steps will be carried out sequentially to construct 100 hypothetical complete data sets. The final imputed dataset will contain observed and imputed data for baseline and the end of treatment endpoint. End of Treatment endpoint will be calculated by taking the average of observed and imputed values at Week 10 and Week 12. Estimates for ratio to baseline, treatment ratio estimates, 95% confidence intervals, and p-values will be generated from an ANCOVA model (not repeated measures and with no random effects) with log of ratio to baseline as the response variable, variables for chronic kidney stage (stage 3 vs. 4 and 5) and treatment group as categorical fixed effects, and log of baseline value as a covariate. The SAS MIANALYZE procedure will be used to generate estimates, confidence intervals, and p-values. Log transformed estimates will be back-transformed to the original scale in the analysis results.

3.4.2 Exploratory Efficacy Endpoints

The exploratory analysis variables measuring change or percent change (as applicable) from baseline to end of treatment will be summarized and analyzed in the same manner as the primary analysis variable (section 3.4.1).

For the continuous efficacy variables, the observed values, change from baseline, and percent change from baseline (as applicable) will be summarized by treatment group using descriptive statistics using ITT population.

For binary endpoints (proportions), proportions of patients and 95% CI for proportions will be based on the normal approximation to binomials. The differences in proportions and 95% CIs for differences for each active group will also be presented.

The sample SAS code for normal approximation of binary endpoints and to calculate differences in proportions and 95% CIs can be found below:

```
**************************************************************************;
*Note: ACHIEVE = status of patients achieving endpoint (1 if Yes, 2 if No)
* TRT = Treatment Group
**************************************************************************;
proc freq data=endpoint;
by TRT;
tables ACHIEVE / binomial (Wald exact);
ods output BinomialCLs=CL BinomialProp=Proportion;

run;

proc freq data=endpoint (where=(trtpn in (#,#));
     table trt*RESPONSE / riskdiff;
     output out=proportion_diff  RDIF2 ;
run;
```

The following exploratory efficacy endpoints will be analyzed:

- Difference in the proportion of patients achieving hs-CRP response, defined as hs-CRP<2.0 mg/L, at End of Treatment (average of Week 10 and Week 12) between each active group and placebo.
- Difference in the percent change in fibrinogen, SAA, NT-pro-BNP, change in hemoglobin and change in albumin from Baseline to End of Treatment (average of Week 10 and Week 12) between each active group and placebo.

- Difference in the percent change in TC, LDL-C, HDL-C, and TG from Baseline to End of Treatment (average of Week 10 and Week 12) between each active group and placebo.

3.4.3 Data Plots

Graphical data display for the efficacy parameters will be employed to present observed data and changes from baseline. The Ziltivekimab 15 mg, and Ziltivekimab 30 mg active dose groups as well the placebo group will be superimposed for visual comparison.

A graphical plot for missing data pattern from baseline to end of treatment for the primary efficacy variable (hs-CRP) will also be generated.

3.5 Analysis of Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Modeling

3.5.1 Pharmacokinetic data

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A by-patient listing of all serum concentration-time data for each dose group will be presented. Ziltivekimab serum concentrations will be summarized by dose group and nominal time point using appropriate descriptive statistics (eg, n, arithmetic mean, SD, coefficient of variation [CV], minimum, median, maximum, geometric mean, and geometric CV).

For IL-6, results of PK parameters, such as AUC, will be summarized by dose group.

Individual and mean concentration-time profiles will be presented graphically.

3.5.2 Pharmacokinetic-pharmacodynamic modeling

PK-PD model parameters will be derived using plasma IL-6 levels to describe target engagement, with clinically meaningful PD parameters, such as hs-CRP. The specific model parameters to be estimated will be determined based on review of the observed data. The PD parameters to be included in the PD analysis will be determined following review of the study data.

A listing of PD blood sample collection times as well as derived sampling time deviations will be provided. A by-patient listing of all PD results and their corresponding change from Baseline value for each dose group will be presented. The observed and change from Baseline serum results will be summarized using descriptive statistics by dose group.

Graphical presentations, as appropriate for PD variables, may include the following: individual observed and percent change from Baseline serum concentration-time curves for each patient on linear scale and arithmetic mean serum concentration-time curves by dose group on linear scale.

Analysis of pharmacokinetic data and PK-PD modeling will be described in a separate PK-PD analysis plan.

3.6 Safety Assessment

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the Safety population.

3.6.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

A TEAE is defined as an AE that initiated or worsened on or after the date of first dose of study drug up to the end of the Safety Follow-Up Period. For AEs occurring on the first dosing day, if the start time cannot be ascertained, the event will be counted as treatment emergent. These events will be identified in the data by coded terms.

Adverse events of special interest (Section 2.3.4) will be summarized by treatment group and dose.

An overview of AEs will be provided for the following categories including counts and percentages of subjects along with number of events:

- Any TEAEs (overall, by maximum severity, and relationship to study drug)
- Any study drug related TEAEs (overall and by maximum severity)
- Any TEAEs of special interest (overall and by maximum severity)
- Any serious AEs (SAEs) (overall, by maximum severity, and relationship to study drug)
- Any study drug related serious adverse events
- Non-serious adverse events (by maximum severity, and relationship to study drug)
- Any treatment-emergent serious AEs (TESEAEs)
- Any TEAEs leading to study drug interruption
- Any TEAEs leading to study drug discontinuation
- Any AEs leading to death

The number of adverse events and number (percentage) of patients reporting treatment-emergent AEs and SAEs for each preferred term (PT) will be tabulated by System Organ Class (SOC), by SOC and severity, and by SOC and relationship to study drug. If more than one event occurs with the same PT for the same patient, the patient will be counted only once for that PT using the most severe or related occurrence for the summary by severity or relationship to study drug, respectively. The number of events will be presented for overall category of TEAE and for each SOC and PT. The number of events will not be presented for each category of maximum severity and maximum relationship to the study drug.

The number and percentage of patients with TEAEs by occurrence time (0-2, 2-4, 4-6, 6-8, 8-10, 10-12 and >12 weeks) will also be summarized for each preferred term, system organ class, and treatment. The number of patients that completed each time period and the proportion of patients presenting TEAEs in proportion to the number of patients that completed the given time period will also be summarized.

Listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study drug.

3.6.2 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected and processed by a central laboratory.

Values and changes from baseline for lab parameters (excluding efficacy lab parameters) will be presented at each scheduled visit and baseline by laboratory test. The incidence of abnormalities (as defined by normal ranges) prior to the first dose of study drug and after the first dose of study drug will be summarized with counts and percentages of subjects.

All laboratory measurements will be listed.

3.6.3 Vital Signs

Vital signs and change from Baseline in vital signs will be summarized descriptively at each visit by treatment group. The number and percentage of patients with exceeding pre-defined absolute and relative threshold values will be summarized. These threshold values are presented in Table 1.

When calculating the percentages for the criterion related to a threshold, the numerator will be the number of subjects with normal baseline with respect to the specific criterion and at least one post-baseline outlier value within the analysis period; and the denominator will be the number of subjects with a baseline and at least one post-baseline assessment within the analysis period.

Table 1 Pre-defined Threshold Value for Vital Signs

Parameter	Criteria
Systolic Blood Pressure (SBP)	>25% mmHg Increased or decreased from Baseline
SBP	>160 mmHg
Heart Rate (HR)	>100 beats per minute
Respiration Rate	>24 breaths per minute
BMI	>10% increased or decreased from Baseline

All vital signs measurements will be listed.

3.6.4 Electrocardiograms

ECG interpretation (normal vs abnormal) will be summarized using frequency and percentage at each visit by treatment group. ECG intervals (ie, PR interval, QT interval, heart rate, and QTcF) will be summarized descriptively at each visit. The number and percentage of patients with exceeding pre-defined absolute and relative threshold values (PR interval >200 msec; QTcF >450 msec, >480 msec, and >500 msec; and QTcF increase from Baseline >30 msec and >60 msec) will be summarized. These threshold values are presented in Table 2.

When calculating the percentages for the criterion related to a threshold, the numerator will be the number of subjects with normal baseline with respect to the specific criterion and at least one post-baseline outlier value within the analysis period; and the denominator will be the number of subjects with a baseline and at least one post-baseline assessment within the *analysis period.*

Table 2 Pre-defined Threshold Value for ECG

PR interval	Criteria

QTcF	>200 msec
QTcF	>450 msec
QTcF	>480 msec
QTcF	>500 msec
QTcF	Increase from Baseline >30 msec
QTcF	increase from Baseline >60 msec

3.6.5 Physical Examinations

Clinically significant new or worsening physical examination findings will be reported as AEs and will therefore be summarized as described for AEs.

3.6.6 Antibodies to Ziltivekimab

The immunogenic potential of Ziltivekimab will be assessed by summarizing the number and percentage of patients who develop detectable ADAs. ADA titers will be summarized descriptively for ADA positive samples, and the impact of ADA on PK will be assessed if data allows.

3.6.7 Bleeding Events

Bleeding events will be classified using the Thrombolysis in Myocardial Infarction (TIMI) Bleeding Classification.

Table 1 TIMI Bleeding Classification

Parameter	Criteria
Major	Intracranial hemorrhage or a ≥5 g/dL decrease in the hemoglobin concentration or a ≥15% absolute decrease in the hematocrit
Minor	Observed blood loss: ≥3 g/dL decrease in the hemoglobin concentration or ≥10% decrease in the hematocrit. No observed blood loss: ≥4 g/dL decrease in the hemoglobin concentration or ≥12% decrease in the hematocrit
Minimal	Any clinically overt sign of hemorrhage (including imaging) that is associated with a <3 g/dL decrease in the hemoglobin concentration or <9% decrease in the hematocrit
All TIMI definitions take into account blood transfusions, so that hemoglobin and hematocrit values are adjusted by 1 g/dL or 3%, respectively, for each unit of blood transfused. Therefore, the true change in hemoglobin or hematocrit if there has been an intervening transfusion between 2 blood measurements is calculated as follows: ΔHemoglobin = [baseline Hgb – post-transfusion Hgb] + [number of transfused units]; Δ Hematocrit = [baseline Hct − post-transfusion Hct] + [numberof transfused units × 3].	

Tables will be generated for each of the TIMI Bleeding Classification parameters by treatment and in total. Bleeding events will also be listed.

4 ANALYSIS TIMING

4.1 Draft Analysis/Blinded Data Reviews

All investigators and patients will remain blinded throughout the study. Additionally, members of the study team including operations team, data management, and statistical team will also remain blinded until the final database lock.

After the last subject completes the last visit, the final database will be cleaned, locked and analysis will be performed. At this time, members of the study team will become unblinded to the subject treatment assignments.

Prior to database lock, the blinded team may perform a blinded data review using tables, figures, and listings.

4.2 Interim Analysis

No interim analysis is planned for the study.

4.3 Pre-Final Analysis

After the final database is locked and exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated. Pre-final TFLs will be provided approximately 4 weeks after final database lock.

4.4 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately 1 week after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, Study Data Tabulation Model (SDTM) data and Analysis Data Model (ADaM) data along with associated files will be provided. Associated files may include annotated CRFs, SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and Clinical Data Interchange Standards Consortium (CDISC) Define packages for both SDTM and ADaM data.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

None.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

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