Cover Page for Protocol

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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)
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CLINICAL STUDY PROTOCOL

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)

Investigational Product: Ziltivekimab (human monoclonal antibody to interleukin-6)
Protocol Number: COR-001-02-Japan

Sponsor:
Corvidia Therapeutics Inc.
35 Gatehouse Drive
Waltham, MA
02451 United
States
Telephone: +1 781-205-4755

Version Number: 1.4
Date: 17Mar2021

Redacted protocol
Includes redaction of personal identifiable information only.

[redacted]

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Corvidia Therapeutics Inc. (hereinafter, Corvidia) to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study drug and study procedures. I will let them know that this information is confidential and proprietary to Corvidia and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Corvidia, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Pharmaceuticals and Medical Devices Agency Regulations, Institutional Review Board/Ethic Committee Regulations, International Council for Harmonisation Guidelines for Good Clinical Practices, and the Japanese Ministerial Ordinance on Good Clinical Practice for Drugs, where applicable.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

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

INVESTIGATIONAL PRODUCT: Ziltivekimab (human monoclonal antibody to interleukin [IL]-6)

PHASE: 2

TARGET INDICATION: Cardiovascular risk reduction (including myocardial infarction, stroke, urgent revascularization, hospitalization due to heart failure, or death from cardiovascular causes) in CKD patients at high-risk (hs-CRP ≥2.0 mg/L) of developing major cardiovascular events.

OBJECTIVES:

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).

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

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

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, ie, fibrinogen, serum amyloid A (SAA), 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]).

POPULATION:

Inclusion criteria:

After signing an informed consent form (ICF) approved by the Institutional Review Board or Independent Ethics Committee, in order to be eligible, potential patients must meet all of the following criteria:

1. Age ≥20 years at the time of signing the ICF;
2. Stage 3 to 5 NDD-CKD, ie, estimated glomerular filtration rate >10 and <60 mL/min/1.73 m^2 using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation;
3. Serum hs-CRP level ≥2.0 mg/L measured during the Screening Period;

Note: Targeting patients with a history of advanced stage chronic kidney disease (CKD), atherosclerotic cardiovascular disease, anemia, diabetic retinopathy, obesity, or elevated body mass index (BMI), and diabetes for Screening will help increase the chances of identifying patients with hs-CRP ≥2.0 mg/L;

4. The patient agrees to comply with the contraception and reproduction restrictions of the study as follows:
   a. Women of childbearing potential must be using a method of contraception that is "highly effective" (ie, <1% failure rate) for at least 3 months following the last dose of study drug;
   b. Postmenopausal women must have had no menstrual bleeding for at least 1 year before initial dosing and either be over the age of 60 years or have an elevated plasma follicle stimulating hormone level (ie, >40 mIU/mL) at Screening;
   c. Women of childbearing potential must have a documented negative serum pregnancy test result at Screening; and
   d. All male patients, from the day of dosing until the final study visit, unless surgically sterile, must be willing to use a condom with a partner (male patients with partners of childbearing potential must be willing to use 2 effective methods of birth control, 1 should be condom with spermicide) to prevent pregnancy and drug exposure of a partner, and refrain from donating sperm or fathering a child; and
5. The patient must be willing and able to provide informed consent and abide all study requirements and restrictions.

Exclusion criteria:

Patients who meet any of the following criteria will be excluded from participation in the study:

Laboratory values

1. Absolute neutrophil count $<2.0 \times 10^9$/L during Screening;
2. Platelet count $<120 \times 10^9$/L during Screening;
3. Spot urine protein-creatinine ratio >4000 mg/g (4.0 g/g) during Screening;
4. Alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal during Screening;
5. Positive testing for tuberculosis during Screening. Blood testing (eg, QuantiFERON) is preferred, but a purified protein derivative (PPD) skin test read within 48 to 72 hours by a qualified healthcare professional may also be performed. If a patient is PPD positive but QuantiFERON negative, the patient is eligible;
6. Evidence of human immunodeficiency virus (HIV)-1 or HIV-2 infection by serology measured during Screening;
7. Hepatitis B or C by serology (eg, hepatitis B surface antigen or hepatitis C antibody positive) measured during Screening;

Medical conditions or diseases

8. Expected to require blood transfusion within 12 weeks post-randomization;
9. Thromboembolic event within 12 weeks prior to randomization;
10. Clinical evidence or suspicion of active infection;
11. History of peptic ulcer disease or gastrointestinal ulceration in the 12 months prior to randomization;

12. History of active diverticulitis in the 12 months prior to randomization;
13. History of inflammatory bowel disease that has been clinically active during the 12 months prior to randomization;
14. Uncontrolled hypertension (defined as an average systolic blood pressure >160 mmHg or an average diastolic blood pressure >100 mmHg) during Screening. Patients may be re-evaluated within 2 weeks, at the discretion of the Principal Investigator, for this criterion if antihypertensive therapy has been started or increased as a result of initial screening blood pressure being above these limits;
15. Planned coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or any other major surgical procedure during the time frame of the study;
16. Major cardiac surgical, non-cardiac surgical, or major endoscopic procedure within the past 6 months prior to randomization;
17. Prior gastric bypass surgery;
18. History of New York Heart Association Class IV congestive heart failure within 12 weeks prior to randomization;
19. Diagnosis of malignancy within 1 year prior to randomization with the exception of successfully treated nonmetastatic basal cell or squamous cell carcinomas of the skin and/or local carcinoma in situ of the cervix;
20. History of bone marrow or solid organ transplant or anticipated to receive an organ transplant during the time frame of the study;
21. Known allergy to the study drug or any of its ingredients;

Prior or current medications

22. Received an investigational drug within 30 days prior to Screening;
23. Received a live/live attenuated vaccine product within 14 days of study drug administration or expect to receive live/live attenuated vaccine during the Treatment Period;
24. Expected to receive any investigational drug or any of the exclusionary drugs during the Treatment Period or Safety Follow-Up Period;
25. Chronic use of systemic immunosuppressive drugs during the Screening Period or anticipated use of such drugs any time during the study.

    Note: Use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not exclusionary. Oral prednisone up to 5 mg per day (or equivalent) is permitted if the dose has been stable for at least 4 weeks prior to Screening and no dose changes are planned during study participation. Short-term use of oral steroids for treatment of rash or asthma exacerbation is allowed;
26. Use of systemic antibiotics, systemic antivirals, or systemic antifungals during the Screening Period.

    Note: “Systemic” is defined as oral or intravenous drugs that are absorbed into the circulation;
27. Requirement of an indwelling catheter of any type;

General exclusions

28. Currently breastfeeding; or
29. Any condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or interpretation of the study results, or that would in the opinion of the Investigator increase the risk of participating in the study.

STUDY DESIGN AND DURATION:

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 into two categories: (1) Stage 3 and (2) Stages 4 and 5.

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 should 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.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

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.

EFFICACY (PHARMACODYNAMIC) 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.

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

SAFETY ENDPOINTS:

The safety endpoints include the following:

- Description of safety assessments by treatment group and dose. Safety assessments include 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; and
- Description of anti-drug antibodies (ADAs) (binding and neutralizing).

PHARMACOKINETICS AND PHARMACOKINETIC-PHARMACODYNAMIC MODELING:

The serum trough levels of Ziltivekimab will be measured at all site 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.

STATISTICAL ANALYSES:

The following analysis populations are defined for the different types of data analysis:

- Intent-to-Treat (ITT) Population: all randomized patients;
- Per-Protocol Population: all randomized patients who complete the study and do not incur a significant protocol violation;
- PK Population: all randomized patients who receive study drug and have at least 1 postdose PK blood sample; and
- Safety Population: all randomized patients who receive study drug.

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, 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 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.

Efficacy:

For efficacy (PD) variables, the median difference between each active group and placebo will be analyzed. Efficacy analysis will be performed using the nonparametric Hodges-Lehmann method to estimate median differences between each active group and placebo, associated 95% confidence intervals, and p-values. Additionally, the nonparametric analysis will adjust for the randomization stratification variable CKD Stage (3 vs. 4 and 5). .

For the efficacy variables, the observed values and changes from Baseline will be summarized by treatment group using descriptive statistics and the ITT Population.

The overall familywise error rate will be controlled at $\alpha = 0.05$ 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.

Pharmacokinetics and pharmacokinetic-pharmacodynamic modeling:

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, number of patients, arithmetic mean, SD, coefficient of variation [CV], minimum, median, maximum, geometric mean, and geometric CV).

For IL-6, results of PK parameters, such as area under the curve, will be summarized by dose group 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.

Safety:

The 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 1 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. AESIs will be summarized by treatment group and dose.

Clinical laboratory values (excluding efficacy laboratory parameters) will be summarized by treatment group, including changes from Baseline at each visit.

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 (systolic blood pressure increase or decrease from Baseline >25% mmHg, >160 mmHg, or <90 mmHg; heart rate >100 beats per minute or <50 beats per minute; and respiration rate >24 breaths per minute) will be summarized.

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.

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

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.

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 COR- 001-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.

SITES: Approximately 10 sites in Japan

SPONSOR:

Corvidia Therapeutics Inc. 35 Gatehouse Drive
Waltham, MA 02451
United States
Telephone: +1 781-205-4755

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ASCVD	Atherosclerotic cardiovascular disease
AUC	Area under the curve
BMI	Body mass index
BNP	B-type natriuretic peptide
CAD	Coronary artery disease
CFR	US Code of Federal Regulations
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRA	Clinical Research Associate
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CTN	Clinical trial notification
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ESA	Erythropoiesis-stimulating agent
ESRD	End stage renal disease
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HDL-C	High density lipoprotein-cholesterol
HFpEF	Heart failure with preserved ejection fraction
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRadj	Adjusted hazard ratio
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IL	Interleukin
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IWRS	Interactive web-response system
KDIGO	Kidney Disease Improving Global Outcomes
LDL-C	Low density lipoprotein-cholesterol
LVH	Left ventricular hypertrophy
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
n	Number of patients
NDD-CKD	Non-dialysis-dependent chronic kidney disease
NOAEL	No observed adverse effect level
NT-pro-BNP	N-terminal-pro hormone B-type natriuretic peptide
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PPD	Purified protein derivative
PT	Preferred term
QTcF	Heart rate-corrected QT interval using Fridericia's formula
SAA	Serum amyloid A
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIMI	Thrombolysis in Myocardial Infarction
vs	Versus

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Background

Ziltivekimab (COR-001), formerly MEDI5117, is an extended half-life human immunoglobulin G (IgG)1κ anti-human interleukin (IL)-6 monoclonal antibody designed with 3 amino acid substitutions ("YTE") in the CH2 region of the Fc domain to decrease clearance and thereby dosing frequency. Ziltivekimab is being developed for the reduction of risk for cardiovascular events in patients with the inflammatory sequelae of advanced chronic kidney disease (CKD). Patients with non-dialysis-dependent CKD (NDD-CKD) are 10 times more likely to die of ASCVD than the general population. [1] However, cardiovascular disease is frequently underdiagnosed and undertreated in patients with CKD. Inflammation is highly prevalent in patients with CKD and is consistently associated with cardiovascular morbidity and mortality. Markers of inflammation, including plasma C-reactive protein (CRP), are associated with an increased risk of cardiovascular disease, and it has been suggested that this association is causal. An abundance of biologic, epidemiologic, and clinical study data have demonstrated that inflammation is a key driver of atherosclerosis. [2] Circulating biomarkers of inflammation, including high-sensitivity CRP (hs- CRP) and IL-6, are associated with increased risk of cardiovascular events independent of cholesterol and other traditional risk factors. Randomized studies have shown that statins reduce hs-CRP, and the magnitude of hs-CRP reduction is proportional to the reduction in cardiovascular risk.[2,3,4]

1.1.1. Study of Heart And Renal Protection (SHARP)

The Study of Heart and Renal Protection (SHARP) assessed the associations between circulating CRP and low density lipoprotein-cholesterol (LDL-C) levels and the risk of vascular and non-vascular outcomes.[5] Higher baseline CRP was associated with an increased risk of major vascular events (hazard ratio [HR] per 3-fold increase 1.28; 95% confidence interval [CI] 1.19-1.38). Higher baseline LDL-C was also associated with an increased risk of major vascular events (HR per 0.6 mmol/L higher LDL-C 1.14; 95% CI 1.06-1.22). Higher baseline CRP was associated with an increased risk of a range of non-vascular events (1.16; 95% CI 1.12-1.21), but there was a weak inverse association between baseline LDL-C and non-vascular events (0.96; 95% CI 0.92-0.99). The efficacy of lowering LDL-C with simvastatin/ezetimibe on major vascular events, in the randomized comparison, was similar irrespective of CRP concentration at Baseline; however, the risk of increased cardiovascular events was significantly greater in patients who had elevated CRP on treatment. This "residual inflammatory risk" has increasingly become a viable pharmacologic target.

1.1.2. Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS)

To further assess the potential benefits of reducing residual inflammation as determined by hs-CRP reduction, the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) was a randomized, double-blind study of 3 subcutaneous (SC) doses of canakinumab (50, 150, and 300 mg) in 10,061 patients with previous myocardial infarction (MI) and an hs-CRP level of ≥2 mg/L. [6] The primary efficacy endpoint of CANTOS was nonfatal MI, nonfatal stroke, or cardiovascular death. At 48 months, the median reductions in hs-CRP levels compared to placebo were 26% (50 mg), 37% (150 mg), and 41% (300 mg), with all comparisons being statistically significant ($p<0.0001$). For the primary objective of CANTOS, the incidence rate of the predefined cardiovascular events was 4.50 events per 100 person years for placebo, 4.11 events per 100 person years for 50 mg, 3.86 events per 100 person years for 150 mg, and 3.90

events per 100 person years for 300 mg. Compared to placebo, the 150 mg dose displayed a significant effect on the primary endpoint outcomes (HR versus [vs] placebo 0.85; p=0.02075; threshold p=0.02115). The 300 mg dose displayed a similar HR vs placebo (0.86) but did not reach significance vs placebo (p=0.03140; threshold p=0.01058). In addition, the 50 mg canakinumab dose did not reach significance compared to placebo for the primary endpoint. Similar results were seen for the key secondary cardiovascular endpoint of the primary endpoint plus hospitalization for unstable angina leading to urgent revascularization. CANTOS showed that directly reducing inflammation with an IL-1β antagonist reduces cardiovascular event rates independent of LDL-C.[2]

1.1.3. CANTOS high-sensitivity C-reactive protein threshold analysis

In the CANTOS study, an additional prespecified secondary analysis of major cardiovascular events, cardiovascular mortality, and all-cause mortality was performed in hs-CRP subgroups <2.0 mg/L and ≥2.0 mg/L.[3] During the CANTOS study, patients who were treated with canakinumab and achieved an on-treatment hs-CRP level <2.0 mg/L had a 25% reduction in major cardiovascular events (adjusted HR [HRadj] 0.75; 95% CI 0.66-0.85; p<0.0001). Patients who had on-treatment hs-CRP levels ≥2.0 mg/L did not display a significant reduction in major cardiovascular events (HRadj 0.90; 95% CI 0.79-1.02; p=0.11). Similar significant reductions (31%) in cardiovascular mortality (HRadj 0.69; 95% CI 0.56-0.85; p=0.0004) and all-cause mortality (HRadj 0.69; 95% CI 0.58-0.81; p<0.0001) were observed in patients who achieved the hs-CRP threshold, and no significant reductions in both cardiovascular and all-cause mortality were observed in patients who did not achieve the hs-CRP threshold. These results suggest that the reduction in hs-CRP levels during initial dosing of canakinumab may provide a method to identify patients who may have the largest benefit from treatment.

1.1.4. CANTOS patients with moderate chronic kidney disease

Patients in the CANTOS study had serial monitoring of estimated glomerular filtration rate (eGFR), the urine albumin-to-creatinine ratio, and renal and urinary adverse event (AE) monitoring.[7] Of the 10,061 CANTOS patients, 18.6% (1875 patients) had a baseline eGFR of <60 mL/min/1.73 m^2 indicative of moderate CKD. Patients in this group had higher incidence rates of major vascular events compared with those patients who had a baseline eGFR ≥60 mL/min/1.73 m^2 (6.92 vs 4.13 per 100 person years; p<0.0001). Among those patients with moderate CKD, treatment with canakinumab reduced the risk of major cardiovascular events by 18% (HR 0.82; 95% CI 0.68- 1.00; p=0.05). However, the largest of these effects occurred in patients with moderate CKD who achieved on treatment hs-CRP levels <2 mg/L after taking an initial dose of canakinumab (HR 0.68; 95% CI 0.53-0.86; p=0.0015). The primary endpoint of nonfatal MI, nonfatal stroke, or cardiovascular death in the placebo-treated CKD patients had an event rate of 7.92 per 100 person years while the event rate in canakinumab-treated CKD patients who achieved an hs-CRP level <2 mg/L was 5.35 per 100 person years, representing a 32% relative risk reduction between placebo and active, which correlated to a number needed to treat of 8.

1.1.4.1. Modulation of the interleukin-6 signaling pathway and incidence rates of atherosclerotic events and all-cause mortality in CANTOS

Based on the results and additional analyses from the hs-CRP/IL-6/IL-1 pathway discussion and the CANTOS study described in the above sections, moving downstream from IL-1β inhibition to IL-6 inhibition may be a more effective target for the reduction of hs-CRP expression and

ultimately improved atheroprotection.[8]

In the CANTOS study, 4833 patients had IL-6 levels measured before randomization and after treatment. [9] Compared with those allocated to placebo, CANTOS participants receiving canakinumab who achieved on-treatment IL-6 levels below the study median value of 1.65 ng/L experienced a 32% reduction in major adverse cardiovascular events (MACE) (multivariable HRadj 0.68; 95% CI 0.56-0.82; p<0.0001), a 30% reduction in MACE plus the additional endpoint of hospitalization for unstable angina requiring urgent revascularization (MACE+, HRadj 0.70; 95% CI 0.59-0.84; p<0.0001), a 52% reduction in cardiovascular mortality (HRadj 0.48; 95% CI 0.34-0.68; p<0.0001), and a 48% reduction in all-cause mortality (HRadj 0.52; 95% CI 0.40-0.68; p<0.0001) with prolonged treatment. In contrast, those with on-treatment IL-6 levels ≥1.65 ng/L after taking the first dose of canakinumab had no significant benefit for any of these endpoints. CANTOS provides proof-of-concept evidence in humans that modulation of the IL-6 signaling pathway, at least with canakinumab, is associated with reduced cardiovascular event rates, independent of lipid lowering.

1.2. Description of Ziltivekimab

Ziltivekimab is an extended half-life anti-IL-6 antibody (human IgG1κ anti-human IL-6 monoclonal antibody) with 3 amino acid substitutions ("YTE") in the CH2 region of the Fc domain designed to decrease clearance, and thereby dosing frequency. Additional information about the mechanism and structure of Ziltivekimab can be found in the Ziltivekimab Investigator's Brochure (IB).

1.3. Summary of Relevant Nonclinical Experience With Ziltivekimab

For information regarding nonclinical pharmacology, pharmacokinetics (PK) in animals, and nonclinical toxicology and safety, please refer to the Ziltivekimab IB.

1.4. Summary of Relevant Clinical Experience With Ziltivekimab

1.4.1. Phase 1 Study in Patients With Rheumatoid Arthritis (D4430C00001)

This study was a Phase 1, double-blind, placebo-controlled, single ascending dose study in rheumatoid arthritis patients (Study D4430C00001) that completed in February 2014. This study was a dose-escalation from 30 mg, with provisional doses of 90, 270, and 600 mg thereafter. After 4 patients were enrolled (3 receiving Ziltivekimab 30 mg IV [single dose] and 1 receiving placebo), the study was terminated due to difficulties with recruitment. Further details surrounding this study can be found in the Ziltivekimab IB.

1.4.2. Phase 1 Study in Patients With Chronic Kidney Disease (COR-001-SC1)

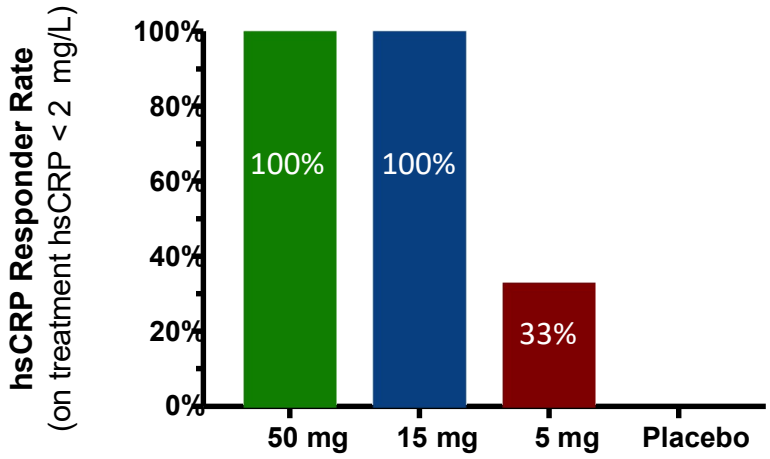
This study was a Phase 1, randomized, double-blind, placebo-controlled, cohort dose-escalation study in patients with CKD to assess the safety, PK, and pharmacodynamics (PD) of a single dose of Ziltivekimab. The study population had moderate-to-severe CKD (ie, eGFR 20 to 60 mL/min/1.73 m^2) who had serum CRP levels >2 mg/L over 2 consecutive measurements. The primary objective evaluated the safety of single SC doses of Ziltivekimab (planned doses of 5, 15, 50, and 100 mg). The main secondary objective evaluated single-dose PK of SC Ziltivekimab and the effects of Ziltivekimab on CRP and serum amyloid A (SAA).

After SC administration, Ziltivekimab concentrations reached peak levels by 7 to 17 days after dosing, on average, and serum Ziltivekimab concentrations remained quantifiable up to 217 days

postdose in all patients. Ziltivekimab concentrations increased in a dose-dependent manner. Terminal slopes (half-life) appeared similar for the 5 and 15 mg doses, suggesting linear PK. High intersubject variability among the 3 patients in the highest dose cohort (50 mg) confounded the interpretation for that dose. One patient in the 50 mg dose cohort had levels 2- to 3-fold higher than the other 2 patients so that it appeared that the latter patients displayed a less than dose proportional increase, while the former showed a greater than dose proportional increase in Ziltivekimab serum levels.

Mean hs-CRP levels were comparable and elevated at Baseline across placebo and the Ziltivekimab treatment groups, suggesting systemic inflammation. Figure 2 presents the percentage of patients who achieved an hs-CRP level of <2.0 mg/L from Baseline to Week 32. A consistent decrease in hs-CRP levels was observed in the Ziltivekimab dose groups throughout the first 8 weeks post randomization, while levels in the placebo group increased over time.

Figure 1 Percentage of Chronic Kidney Disease Patients Treated With Ziltivekimab or Placebo Who Achieved a High-Sensitivity C-Reactive Protein Level of <2.0 mg/L From Baseline to Week 32



hs-CRP = high-sensitivity C-reactive protein.

During the study, 33 AEs were reported by 12 subjects. The only AE reported by more than 1 subject (n=3) was upper respiratory tract infection. Other than 1 report of diarrhea, none of the other AEs were considered related to the study drug. During the study, 1 subject on placebo reported a serious AE (SAE) of acute cardiac failure. There were no deaths, and no subject discontinued the study.

1.4.3. Phase 1/2 Study in Patients With Chronic Kidney Disease on Hemodialysis (COR-001-01)

This study was a Phase 1/2, randomized, double-blind, placebo-controlled, cohort dose-escalation study in hemodialysis patients to assess the safety, PK, and PD of multiple IV doses of Ziltivekimab (COR-001). The target population was composed of hemodialysis patients who had a predefined genetic makeup, and who displayed high serum IL-6 levels and high ESA requirements.

After IV administration, COR-001 concentrations increased in a dose-related manner and appeared to decline in a biphasic manner. The terminal half-life of Ziltivekimab ranged from 38 to 44 days, and there was no evidence of body weight as a covariate. Exposure levels were unaffected by hemodialysis, and there was no pattern of altered PK to suggest neutralizing

antibodies. Further details of this study can be found in the Ziltivekimab IB.

There was a greater incidence of treatment-emergent AEs (TEAEs) in each of the Ziltivekimab groups than in the placebo group; there was not a clear dose response. The 6 mg COR-001 dose group had the greatest incidence of patients with at least 1 TEAE, and the 2 TEAEs that occurred at the highest incidence in the study were reported in this treatment group (congestive cardiac failure and dyspnea which each occurred in 4 patients).

SAEs occurred at a higher rate in the 6 and 20 mg dose groups than in the placebo and 2 mg groups. The 6 mg group had the greatest incidence of SAEs (7 patients reported a total of 14 SAEs), and all 4 of the congestive cardiac failure events in the 6 mg group were considered serious. None of the SAEs in any group were assessed as treatment related. There were 4 patients who had SAEs with a fatal outcome; sepsis (Patient [redacted]) and sudden cardiac death (Patient [redacted]) in the 6 mg group and sepsis (Patient [redacted]) and cardiac arrest (Patient [redacted]) in the 20 mg group. None of the deaths were attributed to study drug. More information on the safety results from study COR-001-01 can be found in the Ziltivekimab IB.

1.4.4. Conclusions on Ziltivekimab Treatment of Anemia in Chronic Kidney Disease

Ziltivekimab is a potent and highly selective fully human anti-IL-6 antibody in development for the treatment of anemia in CKD patients. Ziltivekimab has shown marked reductions in hs-CRP levels (inflammation) within the first weeks of administration and continuing throughout the treatment period. In summary, the clinical evidence presented here supports investigating Ziltivekimab as a product to reduce hs-CRP based inflammation and an ultimate reduction in the risk of MACE in the proposed patient population.

1.5. Rationale

A separate ongoing Phase 2 study (Study Protocol COR-001-02) will determine which dose of Ziltivekimab will have a significant reduction in hs-CRP with acceptable increases in LDL-C or triglycerides (TG) and without clinically meaningful reductions in neutrophils and platelet counts.

The purpose of this study is to collect efficacy (PD), safety, and PK data of multiple administration of Ziltivekimab at 2 dose levels in Japanese patients. Patients with NDD-CKD who have evidence of systemic inflammation with increased cardiovascular risk will be enrolled into this study. The doses that will be tested in this study are 15 mg and 30 mg of Ziltivekimab, administered SC.

1.6. Benefit and Risk Assessment

Despite the fact that the concept of inflammatory risk in renal patients has been in the public domain for decades, with an active basic research and clinical investigational community focused on its remediation, no therapy has been specifically designed for or developed to address it. The advancement of an anti-inflammatory therapy for CKD patients should offer the benefit of myocardial protection and potential treatment of heart failure in this otherwise vulnerable population.

As for the risks associated with administration of Ziltivekimab, nonclinical toxicology studies established the no observed adverse effect level (NOAEL) by the maximal dose administered (see the Ziltivekimab IB). Both in terms of local and systemic effects, Ziltivekimab was well tolerated, with no apparent adverse findings. Of note, the highest Ziltivekimab dose planned for this study allows a greater than 40-fold margin compared to the NOAEL established in the

nonclinical toxicology program.

Available data for anti-IL-6 receptor (tocilizumab) and anti-IL-6 (siltuximab) therapies suggest neutralization of IL-6 has an acceptable safety and tolerability profile for the indications studied. Injection-related and life-threatening hypersensitivity reactions are rare with these agents. Anti-inflammatory therapies in general run the risk of inducing immune suppression and promoting the emergence of infections, sometimes serious in nature. Although anti-IL-6 therapies lower neutrophil counts and may induce frank neutropenia, their rates of infectious complications appear to be similar to other immune-modulatory biologic agents when accounting for patient-specific factors.[10,11] Gastrointestinal perforation has been associated with anti-IL-6 therapy; however, data suggest proper exclusion criteria may mitigate these risks.[12]

On balance then, the Sponsor proposes the potential risks to patients in this study are justifiable and the benefit-to-risk ratio positive. Patients will be consented as to the potential risks and will be required to sign an informed consent form (ICF) documenting their understanding of these risks and willingness to participate in the study

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to evaluate the effects of 2 dose levels of Ziltivekimab compared to placebo on hs-CRP, a marker of inflammation and cardiac risk, in patients with NDD-CKD.

2.2. Secondary Objective

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

2.3. Pharmacokinetic Objective

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

2.4. 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, ie, fibrinogen, SAA, 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], LDL-C, high density lipoprotein-cholesterol [HDL-C], and TG).

3. STUDY DESCRIPTION

3.1. Summary of Study Design

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 which is stratified into two categories: (1) Stage 3 and (2) Stages 4 and 5.

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 should 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.

Study visits will follow the Schedule of Procedures (Appendix A).

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

After signing an ICF approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), in order to be eligible, potential patients must meet all of the following criteria:

1. Age ≥20 years at the time of signing the ICF;
2. Stage 3 to 5 NDD-CKD, ie, eGFR >10 and <60 mL/min/1.73 m^2 using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation;[13]
3. Serum hs-CRP level ≥2.0 mg/L measured during the Screening Period.

   Note: Targeting patients with a history of advanced stage CKD, ASCVD, anemia, diabetic retinopathy, obesity, or elevated body mass index (BMI), and diabetes for Screening will help increase the chances of identifying patients with hs-CRP ≥2.0 mg/L;
4. The patient agrees to comply with the contraception and reproduction restrictions of the study as follows (Appendix C):
   a. Women of childbearing potential must be using a method of contraception that is "highly effective" (ie, <1% failure rate) for at least 3 months following the last dose of study drug;
   b. Postmenopausal women must have had no menstrual bleeding for at least 1 year before initial dosing and either be over the age of 60 years or have an elevated plasma follicle-stimulating hormone (FSH) level (ie, >40 mIU/mL) at Screening;
   c. Women of childbearing potential must have a documented negative serum pregnancy test result at Screening.; and
   d. All male patients, from the day of dosing until the final study visit, unless surgically sterile, must be willing to use a condom with a partner (male patients with partners of childbearing potential must be willing to use 2 effective methods of birth control, 1 should be condom with spermicide) to prevent pregnancy and drug exposure of a partner, and refrain from donating sperm or fathering a child; and
5. The patient must be willing and able to provide informed consent and abide all study requirements and restrictions.

4.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

Laboratory values

1. Absolute neutrophil count <2.0 × 10^9/L during Screening;
2. Platelet count <120 × 10^9/L during Screening;
3. Spot urine protein-creatinine ratio >4000 mg/g (4.0 g/g) during Screening;
4. Alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal during Screening;
5. Positive testing for tuberculosis during Screening. Blood testing (eg, QuantiFERON) is

preferred, but a purified protein derivative (PPD) skin test read within 48 to 72 hours by a qualified healthcare professional may also be performed. If a patient is PPD positive but QuantiFERON negative, the patient is eligible;

6. Evidence of human immunodeficiency virus (HIV)-1 or HIV-2 infection by serology measured during Screening;
7. Hepatitis B or C by serology (eg, hepatitis B surface antigen or hepatitis C antibody positive) measured during Screening;

Medical conditions or diseases

8. Expected to require blood transfusion within 12 weeks post-randomization;
9. Thromboembolic event within 12 weeks prior to randomization;
10. Clinical evidence or suspicion of active infection;
11. History of peptic ulcer disease or gastrointestinal ulceration in the 12 months prior to randomization;
12. History of active diverticulitis in the 12 months prior to randomization;
13. History of inflammatory bowel disease that has been clinically active during the 12 months prior to randomization;
14. Uncontrolled hypertension (defined as an average systolic blood pressure >160 mmHg or an average diastolic blood pressure >100 mmHg) during Screening. Patients may be re-evaluated within 2 weeks, at the discretion of the Principal Investigator, for this criterion if antihypertensive therapy has been started or increased as a result of initial screening blood pressure being above these limits;
15. Planned coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or any other major surgical procedure during the time frame of the study;
16. Major cardiac surgical, non-cardiac surgical, or major endoscopic procedure within the past 6 months prior to randomization;
17. Prior gastric bypass surgery;
18. History of New York Heart Association Class IV congestive heart failure within 12 weeks prior to randomization;
19. Diagnosis of malignancy within 1 year prior to randomization with the exception of successfully treated nonmetastatic basal cell or squamous cell carcinomas of the skin and/or local carcinoma in situ of the cervix;
20. History of bone marrow or solid organ transplant or anticipated to receive an organ transplant during the time frame of the study;
21. Known allergy to the study drug or any of its ingredients;

Prior or current medications

22. Received an investigational drug within 30 days prior to Screening;
23. Received a live/live attenuated vaccine product within 14 days of study drug administration or expect to receive live/live attenuated vaccine during the Treatment Period;
24. Expected to receive any investigational drug or any of the exclusionary drugs listed in Section 5.7.1 during the Treatment Period or Safety Follow-Up Period;

25. Chronic use of systemic immunosuppressive drugs during the Screening Period or anticipated use of such drugs any time during the study.

    Note: Use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not exclusionary. Oral prednisone up to 5 mg per day (or equivalent) is permitted if the dose has been stable for at least 4 weeks prior to Screening and no dose changes are planned during study participation. Short-term use of oral steroids for treatment of rash or asthma exacerbation is allowed;

26. Use of systemic antibiotics, systemic antivirals, or systemic antifungals during the Screening Period.

    Note: "Systemic" is defined as oral or IV drugs that are absorbed into the circulation;

27. Requirement of an indwelling catheter of any type;

General exclusions

28. Currently breastfeeding; or
29. Any condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or interpretation of the study results, or that would in the opinion of the Investigator increase the risk of participating in the study.

4.3. Anaphylaxis Study Stopping Rule

If at any point during the study ≥10% of patients experience an anaphylactic event, the anaphylaxis study stopping rule will be executed. The study stopping rule will halt any additional enrollment into the study for safety purposes. Additionally, any planned study drug administration to randomized patients will be immediately discontinued. The remaining study procedures and visits may be performed if deemed necessary by the Sponsor.

4.4. Temporary Discontinuation of Study Intervention

Participants may have their study drug administration temporarily suspended during the course of the study. Study drug administration should be temporarily withheld if theparticipant experiences one or more of the following:

- ALT >3x ULN (moderate)
- Neutrophils <1000/mm^3 (severe)
- Platelet count <50,000/mm^3 (severe)
- Platelet count <75,000/mm^3 (moderate) with evidence of concurrent TIMI major bleeding.

Laboratory measures should be present on two independent assessments. After a temporary suspension of study drug has been performed, study drug may be restarted provided the participant has met the following criteria:

- Neutrophils ≥1500/mm^3, and
- Platelets ≥100,000/mm^3

No ongoing clinical sequalae attributable to neutropenia or thrombocytopenia, respectively. If,

after restarting study drug, the event causing temporary discontinuation reoccurs study drug should be discontinued permanently.

4.5. Patient Discontinuation/Withdrawal From the Study

The following are descriptions of patient discontinuation and withdrawal from the study. This is not an exhaustive list, and each instance should be evaluated on a case-by-case basis.

- Withdrawal of consent. A patient may elect to withdraw consent to treatment at any time;
- Patients withdrawing their consent for all study procedures must be given the option to continue to give consent for passive follow-up (ie, by means of chart review) for AEs;
- Patients discontinuing study drug treatment after receiving any amount of study drug should undergo all early termination (ET) and safety follow-up study procedures per the Schedule of Procedures (Appendix A) unless the patient also explicitly withdraws consent for these procedures as mentioned above. If patients discontinuing during the Safety Follow-up Period, conduct procedure per the Schedule of Procedures for ET2. The study drug has a long PD effect. Therefore, continued monitoring for PD effects and safety is prudent;
- A patient may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. Participation in the ET and safety follow-up procedures will be evaluated on a case-by-case basis. If possible, patients should take part in the ET and safety follow-up procedures in the Schedule of Procedures (Appendix A);
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent; or
- If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested. The Investigator must document this in the site study records.

4.6. Lost to Follow-Up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return for any required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible. If possible, the site should attempt to reschedule the missed visit within any allowed visit or treatment window;
    - The site should advise the patient that it is important to adhere to the assigned visit schedule; and
    - The site shall attempt to ascertain whether or not the patient wishes to and/or should continue in the study; and
- Prior to a patient being deemed lost-to-follow-up, the Investigator or designee must make every effort to regain contact with the patient. All attempts to regain contact with the patient must be recorded in the patient's medical record. If the patient continues to be unreachable, the patient will be considered to have withdrawn from the study.

4.7. Study Completion

Primary study completion is defined as the completion of the Week 12 visit, even if 1 or more interim visits or procedures was/were missed.

Completion of the Safety Follow-Up Period is defined by the completion of the Week 20 visit, even if 1 of the 2 visits is missed or if procedures were missed.

5. STUDY TREATMENTS

5.1. Treatment Groups

Patients will be randomized in a 1:1:1 ratio to 1 of the following dose cohorts:

- Dose Cohort 1: Ziltivekimab 15 mg
- Dose Cohort 2: Ziltivekimab 30 mg
- Dose Cohort 3: Placebo

5.2. Rationale for Dosing

The doses used in this study will include the dose used in the Cardiovascular Outcomes trial. In accordance with the planned primary analysis. The 15 mg and 30 mg dose used in the ongoing RESCUE study (COR-001-02) is planned for inclusion in this Japanese study.

5.3. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Treatments will be assigned to randomized patients via an interactive web-response system (IWRS). Patients will be randomized in a 1:1:1 ratio to receive Ziltivekimab 15 mg, Ziltivekimab 30 mg, or matching placebo. Patient randomization will be stratified by CKD stage which 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 SC injection.

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

5.4. Breaking the Blind

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.

5.5. Drug Supplies

5.5.1. Formulation and Packaging

The composition of Ziltivekimab for injection is displayed in Table 1.

Table 1 Composition of Ziltivekimab for Injection

Component	Amount per mL (15 mg Vial)	Amount per mL (30 mg Vial)	Amount per mL (Placebo Vial)
Ziltivekimab	15 mg	30 mg	0 mg
Trehalose dihydrate	50.00 mg	50.00 mg	50.00 mg
L-arginine monohydrochloride	14.75 mg	14.75 mg	14.75 mg
L-methionine	1.49 mg	1.49 mg	1.49 mg
L-histidine	1.55 mg	1.55 mg	1.55 mg
L-histidine monohydrochloride monohydrate	2.10 mg	2.10 mg	2.10 mg
Polysorbate 80	0.70 mg	0.70 mg	0.70 mg
Water for injection	qs to 1.0 mL	qs to 1.0 mL	qs to 1.0 mL
qs = quantum satis.			

5.5.2. Study Drug Preparation and Dispensing

The dose of Ziltivekimab for SC injection must be prepared using aseptic techniques. Drug product is presented as a single use vial.

Ziltivekimab is supplied as a liquid for injection.

Personnel responsible for study drug preparation should have an appropriate background (ie, physician, pharmacist, pharmacy technician, nurse, or other personnel approved by the Sponsor) and be appropriately trained. Please see Pharmacy Manual for full details. The final required volume of Ziltivekimab is provided in Table 2.

Please see the Pharmacy Manual for instructions on preparing and administering the study drug and storage of prepared study drug.

Table 2 Planned Study Drug Doses and Administered Volumes

	Dose Cohort 1	Dose Cohort 2	Dose Cohort 3
Study drug name	Ziltivekimab	Ziltivekimab	Placebo
Type	Active drug	Active drug	Comparator
Dose	15 mg	30 mg	Not applicable
Dose administration	15 mg in 1 mL injection	30 mg in 1 mL injection	1 mL placebo injection
Route of administration	SC injection	SC injection	SC injection
SC = subcutaneous.			

5.5.3. Study Drug Administration

One mL of the assigned study drug will be administered SC by trained study site personnel. The date and time of study drug administration must be recorded in the appropriate sections of the electronic case report forms (eCRFs).

5.5.4. Treatment Compliance

To ensure treatment compliance, study drug will be administered under the supervision of site personnel. The date, time, and volume (dose) of study drug administered will be recorded in the appropriate sections of the eCRFs.

5.5.5. Storage and Accountability

Ziltivekimab and placebo must be stored at 2 to 8°C in the original container and must not be frozen.

The dispensing pharmacist or designated qualified individual will write the date dispensed, dose dispensed, and the patient's identification number on the Drug Accountability Source Documents. All medication supplied will be accounted for on the Drug Accountability Record. All partially used or unused drug supplies will be destroyed at the site in accordance with approved written site procedures or returned to Corvidia. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to Corvidia. All records will be retained as noted in Section 11.6.

5.6. Management of Specific Adverse Events

5.6.1. Injection-Related Reactions, Hypersensitivity, and Anaphylaxis

Patients will be carefully monitored for 1 to 2 hours at the site post every dosing. If any safety concerns are observed between the first and second doses, the Investigator/Sponsor will investigate the discontinuation of further doses and/or the entire study.

Signs of a possible injection-related reaction include fever, chills, pruritus, and urticaria.

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, such as an investigational product.

For the purposes of this study, a hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both during injection of the study drug (but does not meet the definition of anaphylaxis described above).

If signs and symptoms of injection-related reactions are observed and the patient's cardiovascular status is stable, treat the patient as follows:

- If the patient continues to show signs and symptoms of hypersensitivity, administer an SC dose of antihistamine, if the Investigator believes this is appropriate.
- In patients who have experienced mild or moderate injection reactions in the past or there is concern that the patient may develop an injection reaction, antihistamines and/or acetaminophen may be administered prophylactically prior to subsequent injections, at the discretion of the Investigator.
- In patients who experience severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥3) injection-related reactions, anaphylaxis, or hypersensitivity, treat the patient as follows:
  - Permanently discontinue the study drug;
  - Treat the patients as for an anaphylactic reaction with IV antihistamines, corticosteroids, epinephrine, inhaled bronchodilators, and other measures as necessary; and
  - Obtain a blood sample to determine the presence of anti-drug antibodies (ADAs).

  Note: The patient should remain in the study for the End of Treatment Visit and safety follow-up.

5.7. Prior and Concomitant Medications and/or Procedures

5.7.1. Excluded and Restricted Medications and/or Procedures

See Section 4.1 and Section 4.2 for restrictions on prior medications and treatments.

Patients with cardiovascular disease should be treated according to published guidelines throughout the study; in addition, patients may receive concomitant medications as clinically indicated with the following restrictions:

- Patients using herbal remedies and supplements must be on a stable dose and brand of product and new treatments may not be started during the study.
- Systemic immunosuppressive drugs (such as cyclosporine, tacrolimus, sirolimus, mycophenolate, and oral and IV glucocorticoids other than prednisone [or equivalent] up to a dose of 5 mg per day) may not be prescribed at any time during the study. Topical use (eg, cyclosporine eye drops) is not restricted.

  Note: Use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not restricted. Short-term systemic glucocorticoid use (ie, <5 consecutive days) for managing acute illnesses is also not restricted.
- Narrow therapeutic window medications that are influenced by cytochrome P450 enzymatic pathways may not be prescribed at any time during study. Such medications include the following:
  - Digoxin;
  - Theophylline;
  - Terfenadine;
  - Tizanidine;
  - Quinidine;
  - Phenytoin and its derivatives (eg, fosphenytoin, mephenytoin, dantrolene, enzalutamide, allantoin, ethotoin, neocitrullamon);
  - Taxane chemotherapeutic agents;
  - Cyclosporine;
  - Mammalian target of rapamycin inhibitors (eg, sirolimus, tacrolimus);
  - Ergot alkaloids;
  - Antipsychotic medications (specifically pimozide, thioridazine); and
  - Fentanyl and derivatives (eg, alfentanil and sufentanil).
- Live/live attenuated vaccine product
- Other investigational drugs
- Warfarin is permitted, but the international normalized ratio (INR) must be monitored closely and, at minimum, according to the protocol Schedule of Procedures (see Appendix A).
- Blood transfusion
- Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or any other major surgical procedure
- Organ transplant
- Indwelling catheter

5.7.2. Documentation of Prior and Concomitant Medication Use

Medications used within 28 days prior to Screening will be recorded. All concomitant medications will be recorded on the eCRF as indicated in Appendix A.

6. STUDY PROCEDURES

Every effort should be made to obtain the blood tests for each visit on the same day of the week (eg, on Wednesdays).

6.1. Informed Consent

Prior to conducting any study procedures, informed consent will be obtained from the patient by the Investigator (or other study staff who are conducting the informed consent interview). The Initial Screening procedures will be conducted after informed consent has been obtained. After signing the ICF, patients should be registered into the electronic data capture (EDC) system to obtain a patient identification number for the study.

6.2. Screening Period

6.2.1. Screening Visit (Visit -1, Day -14 to -4)

If a screening hs-CRP result is outside inclusion criteria parameters, Screening may be extended up to 2 week to allow for retesting of an hs-CRP result that did not meet inclusion criteria. If laboratory test results are delayed, come back unable to perform analysis, come back indeterminate, or require confirmatory testing, the screening window may be extended until central laboratory results are available. Patients who have failed screening can be re-screened based on investigator's evaluation of the subject's eligibility and approval by the sponsor.

The following procedures will be performed at the Screening Visit (Week -1, Day -14 to -4):

- Obtain informed consent;
- Confirm inclusion/exclusion criteria;
- Record demographic information;
- Record medical history;
- Record prior/concomitant medications;
- Perform limited physical examination;
- Obtain vital signs prior to electrocardiogram (ECG) recording;
- Perform infectious disease screen;
- Perform serum pregnancy test for women of childbearing potential only;
- Perform FSH test for postmenopausal women only;
- Perform 12-lead ECG;
- Collect sample for chemistry and hematology assessments;
- Collect sample for urinalysis (including albumin);
- Collect sample for lipids and subfractions assessment;
- Perform spot urine protein-creatine ratio assessment;
- Collect sample for screening IL-6 (central) assessment;
- Collect sample for hs-CRP assessment (may be repeated 1 time prior to Day 1. hs-CRP

values of 1.5 to <2 mg/L should be retested).

- Collect Ziltivekimab PK sample;
- Collect ADA sample; and
- Assess AEs

6.3. Treatment Period (Visits 1 Through 9)

Following Screening, patients will return for visits and procedures within the study day windows specified below and in Appendix A.

For Visit 1, Visit 5 and Visit 7, all sample will be collected within 1 hour ± 30 minutes prior to study drug administration. For other visits, all samples will be collected at approximately the same time (±1 hour) as when the predose sample is collected on Day 1. Visits 2, 4, and 6 can be converted to phone visits, with the following procedures performed: Record prior/concomitant medications; Assess AEs. If there are any safety concerns raised during a phone visit, the patient may be asked to attend an unscheduled site visit.

6.3.1. Visit 1 (Day 1)

The following procedures will be performed at Visit 1 (Day 1):

- Reaffirm inclusion/exclusion criteria;
- Update medical history;
- Record prior/concomitant medications;
- Obtain vital signs;
- Collect sample for chemistry and hematology assessments;
- Collect sample for urinalysis (including albumin);
- Collect sample for lipids and subfractions assessment;
- Collect sample for IL-6 (total) assessment (predose);
- Collect sample for hs-CRP assessment;
- Obtain BMI;
- Collect Ziltivekimab PK sample;
- Randomize patient;
- Collect ADA sample;
- Collect sample for fibrinogen, SAA, NT-pro-BNP, hemoglobin and albumin assessments;
- Collect sample for INR assessment (only for patients currently receiving warfarin);
- Assess AEs; and
- Administer assigned study drug (after all other Day 1 assessments).

6.3.2. Visit 2 (Week 1, Day 8 + 3 days)

The following procedures will be performed:

- Record prior/concomitant medications;
- Collect sample for chemistry and hematology assessments;
- Collect sample for IL-6 (total) assessment;
- Collect sample for hs-CRP assessment;
- Collect Ziltivekimab PK sample;
- Collect ADA sample;
- Collect sample for INR assessment (only for patients currently receiving warfarin); and
- Assess AEs.

6.3.3. Visit 3 (Week 2, Day 15 + 3 days)

The following procedures will be performed:

- Record prior/concomitant medications;
- Obtain vital signs;
- Collect sample for chemistry and hematology assessments;
- Collect sample for IL-6 (total) assessment;
- Collect sample for hs-CRP assessment;
- Collect Ziltivekimab PK;
- Collect ADA sample;
- Collect sample for INR assessment (only for patients currently receiving warfarin); and
- Assess AEs.

6.3.4. Visit 4 (Week 3, Day 22 + 3 days)

The following procedures will be performed

- Record prior/concomitant medications;
- Obtain vital signs;
- Collect sample for chemistry and hematology assessments;
- Collect sample for IL-6 (total) assessment;
- Collect Ziltivekimab PK sample;
- Collect ADA sample;
- Collect sample for INR assessment (only for patients currently receiving warfarin); and
- Assess AEs.

6.3.5. Visit 5 (Week 4, Day 29 + 3 days)

- The following procedures will be performed: Record prior/concomitant medications;
- Obtain vital signs prior to electrocardiogram (ECG) recording;

- Perform 12-lead ECG;
- Collect sample for chemistry and hematology assessments;
- Collect sample for IL-6 (total) assessment (predose);
- Collect sample for hs-CRP assessment;
- Collect Ziltivekimab PK sample;
- Collect ADA sample;
- Collect sample for INR assessment (only for patients currently receiving warfarin);
- Assess AEs; and
- Administer assigned study drug (after all other Visit 5 assessments).

6.3.6. Visit 6 (Week 6, Day 43 + 6 days)

The following procedures will be performed:

- Record prior/concomitant medications;
- Collect sample for chemistry and hematology assessments;
- Collect sample for IL-6 (total) assessment;
- Collect Ziltivekimab PK sample;
- Collect ADA sample;
- Collect sample for INR assessment (only for patients currently receiving warfarin); and
- Assess AEs.

6.3.7. Visit 7 (Week 8, Day 57 + 6 days)

The following procedures will be performed:

- Record prior/concomitant medications;
- Obtain vital signs prior to electrocardiogram (ECG) recording;
- Perform 12-lead ECG;
- Collect sample for chemistry and hematology assessments;
- Collect sample for IL-6 (total) assessment (predose);
- Collect Ziltivekimab PK sample;
- Collect ADA sample;
- Collect sample for INR assessment (only for patients currently receiving warfarin);
- Assess AEs; and
- Administer assigned study drug (after all other Visit 7 assessments).

6.3.8. Visit 8 (Week 10, Day 71 + 6 days)

The following procedures will be performed:

- Record prior/concomitant medications;
- Collect sample for chemistry and hematology assessments;
- Collect sample for IL-6 (total) assessment;
- Collect sample for hs-CRP assessment;
- Collect ADA sample;
- Collect sample for fibrinogen, SAA, NT-pro-BNP, hemoglobin and albumin assessments
- Collect sample for INR assessment (only for patients currently receiving warfarin); and
- Assess AEs.

6.3.9. Visit 9 (Week 12, Day 85 + 6 days)/Early Termination Visit for Treatment Period (ET1)

The following procedures will be performed:

- Record prior/concomitant medications;
- Obtain vital signs prior to electrocardiogram (ECG) recording;
- Perform 12-lead ECG;
- Collect sample for chemistry and hematology assessments;
- Collect sample for urinalysis (including albumin);
- Collect sample for lipids and subfractions assessment;
- Perform spot urine protein-creatine ratio assessment;
- Collect sample for IL-6 (total) assessment;
- Collect sample for hs-CRP assessment;
- Collect Ziltivekimab PK sample;
- Collect ADA sample;
- Collect sample for fibrinogen, SAA, NT-pro-BNP, hemoglobin and albumin assessments;
- Collect sample for INR assessment (only for patients currently receiving warfarin); and
- Assess AEs.

6.4. Safety Follow-Up Period (Visits 10 and 11)

All samples will be collected at approximately the same time (±1 hour) as when the predose sample is collected on Day 1

6.4.1. Visit 10 (Week 16, Day 113 +6 days)

The following procedures will be performed:

- Record prior/concomitant medications;
- Obtain vital signs;

- Collect sample for chemistry and hematology assessments;
- Collect sample for lipids and subfractions assessment;
- Collect sample for IL-6 (total) assessment;
- Collet sample for hs-CRP assessment;
- Collect Ziltivekimab PK sample;
- Collect ADA sample; and
- Assess AEs.

6.4.2. Visit 11 (Week 20, Day 141 +6 days)/Early Termination Visit for Safety Follow-up Period (ET2)

The following procedures will be performed:

- Record prior/concomitant medications;
- Perform limited physical examination;
- Obtain vital signs prior to ECG recording;
- Perform 12-lead ECG;
- Perform serum pregnancy test for women of childbearing potential only;
- Collect sample for chemistry and hematology assessments;
- Collect sample for IL-6 (total) assessment;
- Collect sample for hs-CRP assessment;
- Collect Ziltivekimab PK sample;
- Collect ADA sample; and
- Assess AEs.

7. EFFICACY ASSESSMENTS

7.1. Primary Efficacy (Pharmacodynamic) Endpoint

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 hs-CRP test performed during Screening may be repeated 1 time prior to Day 1. The hs-CRP results after randomization will be blinded.

7.2. 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.

7.3. Pharmacokinetics and Pharmacokinetic-Pharmacodynamic Modeling

The serum trough levels of Ziltivekimab will be measured at all site visits, beginning with

Visit -1. The area under the curve (AUC) 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.

8. SAFETY ASSESSMENTS

8.1. Adverse Events

An AE is any undesirable event or any untoward medical occurrence that occurs in a participant during the course of a study or the protocol-defined time after study termination, whether or not that event is considered study drug-related.

Examples include:

- Any treatment-emergent signs and symptoms (events that are marked by a change from the patient's Baseline/entry status [eg, an increase in severity or frequency of preexisting (already present at the time of informed consent) abnormality or disorder]);

  Note: Any medical condition already present at informed consent should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at Baseline change in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

- All reactions from study drug, abuse of drug, withdrawal phenomena, sensitivity, or toxicity to study drug;
- Apparently unrelated illnesses;
- Injuries or accidents (eg, for a fall secondary to dizziness, record "dizziness" as the event and include the information about the fall in the comment/narrative section and information about any injury secondary to the fall as part of the "outcome");
- Exacerbations (increase in frequency or severity) of symptomatology; subjective patient-reported events; new clinically significant abnormalities in clinical laboratory testing, physiological testing, or physical examinations; and
- Abnormal laboratory findings considered by the Investigator to be clinically significant. In general, an abnormal laboratory value should not be recorded as an AE unless:
  - It is associated with clinical signs or symptoms;
  - It requires an intervention;
  - It results in a SAE; or
  - It results in study termination or interruption/discontinuation of study treatment.

  However, if none of the above applies, but the laboratory abnormality is considered clinically significantly worsened, it should be reported as a laboratory AE (eg, "increased white blood cell count"). When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record "anemia" rather than "low hemoglobin").

8.2. Serious Adverse Events

An SAE is any AE, occurring at any dose and regardless of causality, that:

- Results in death;
- Is life-threatening. Life-threatening means that in the opinion of the Investigator or Study Sponsor, the patient was at immediate risk of death from the reaction as it occurred, (ie, it

does not include a reaction that hypothetically might have caused death had it occurred in a more severe form);

- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned before the signing of the ICF, are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned);
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions;
- Is a congenital anomaly/birth defect; or
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A distinction should be made between the terms "serious" and "severe" since they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe MI). The event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE if the event does not meet the serious criteria. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted serious criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.3. Adverse Events of Special Interest

The following AEs of special interest (AESIs) must be reported to the Sponsor within 24 hours of the Investigator's awareness, even if not meeting the definition of a SAE:

- Serious infections;
- CTCAE Grade ≥3 injection-related reactions;
- Gastrointestinal perforations;
- CTCAE Grade ≥3 anaphylaxis occurring at any time, even if considered unrelated to the study drug. An eCRF for the collection of the details of such reactions will be available in the EDC;
- 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; and

- Malignancies.

8.4. Assessment of Causal Relationship

The causal association of AEs to study drug administration should be determined using the categories 'related' and 'unrelated.' The following descriptions should be used to determine the causality assessment of suspected adverse reactions:

Related (Related/Definite, Probable, Possible):

Related/Definite – The AE follows a reasonable temporal sequence from the time of study drug administration; and/or follows a known response pattern to the study drug; and was known not to have been produced by other factors such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Probable – The AE follows a reasonable temporal sequence from the time of study drug administration; and/or follows a known response pattern to the study drug; and was unlikely to have been produced by other factors such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Possible – The AE follows a reasonable temporal sequence from the time of study drug administration; and/or follows a known response pattern to the study drug; but could have been produced by other factors such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Unrelated (Unlikely, Unrelated):

Unlikely – The AE does not follow a reasonable temporal sequence from the time of study drug administration; and was most likely produced by other factors such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Unrelated – This category is applicable to those AEs that are judged to be clearly and incontrovertibly due only to extraneous causes (the patient's clinical state, therapeutic intervention, or concomitant therapy) and do not meet the criteria for study drug relationship listed under Related/Definite, Probable, Possible, or Unlikely.

An AE with causal relationship not initially determined will require follow-up to assign causality.

8.5. Assessment of Severity

The Investigator must determine the severity of the event or laboratory value according to the criteria below. Severity describes the intensity of the AE or laboratory value.

Assessment of severity:

Mild – Awareness of sign or symptom, but easily tolerated; laboratory value mildly outside normal reference range but not clinically significant.

Moderate – Discomfort enough to cause interference with normal daily activities; laboratory value moderately outside normal reference range and clinically significant.

Severe – Inability to perform normal daily activities; laboratory value severely outside normal reference range and clinically significant.

8.6. Adverse Event Reporting

The AE reporting period starts at the time of informed consent and continues through Visit 11 Patients in this study who experience a drug-related AE or SAE will be followed until the AE or SAE is resolved or stabilizes per the Investigator's judgment, even if this occurs after the final study visit. All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded and reported on the appropriate eCRF. When a unifying diagnosis has been made that accounts for several possible signs and/or symptoms, the unifying diagnosis should be selected as the AE term. For example, the combination of general malaise, mild fever, headache, and rhinitis should be described as "upper respiratory syndrome" if this diagnosis has been made, rather than reporting the individual symptoms as separate events.

If any laboratory test is newly abnormal during the Treatment Period or Safety Follow-Up Period, it will be followed at the discretion of the Investigator. Abnormalities of laboratory tests which are, in the opinion of the Investigator, clinically significantly worse compared to Baseline, or for which a medical intervention is initiated, should be reported as AEs on the AE eCRF.

8.7. Reporting of Serious Adverse Events and Adverse Events of Special Interest

The SAE reporting period is the same as the AE reporting period. All SAEs that occur during the reporting period and regardless of causality must be reported by the Investigator to [redacted] within 24 hours of the knowledge of the occurrence by completing the SAE Form in the EDC system. Any pertinent source documents (eg, patient discharge summary or autopsy reports) should also be submitted as soon as they are available. Do not withhold submission of an SAE even if complete information about the event is not available at the time of the initial report. Follow-up information on the SAE should be sent promptly (within 24 hours of receipt) by the Investigator when any additional relevant information about the event becomes known to the Investigator, or as requested by [redacted] or Corvidia. After the reporting period, any SAE that the Investigator considers related to study drug must be reported to [redacted] or the Sponsor/designee.

Safety Contact Information: [redacted]
[redacted]
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

Hypersensitivity reactions (see Section 5.6.1) occurring during the study drug administration and anaphylaxis occurring after study drug administration should be reported as AEs or SAEs within the EDC AE and SAE eCRFs within 24 hours of the site's awareness of the event. Please submit as much information as is available with the initial report.

Corvidia will immediately notify the Investigator about important safety or toxicology information as it becomes available. It is the responsibility of the Investigator to promptly notify the IRB/IEC about new and relevant safety information regarding the study drug, including serious adverse drug reactions involving risk to human subjects, in accordance with the applicable policies. An unexpected event is one that is not listed by nature or severity in the IB.

8.8. Pregnancy Reporting

If a woman who is a study patient becomes pregnant or a woman suspects she is pregnant from a male study patient, the Investigator should be informed immediately. The Sponsor must, in turn, also be notified by the Investigator immediately by completing an Exposure In Utero form and faxing or emailing it to [redacted] (see Section 8.7). The pregnancy must be followed up through delivery or other fetal outcome. For any abnormal fetal outcome, including congenital anomaly or birth defect, spontaneous or therapeutic abortion, still birth, pre-mature birth, or other outcome other than live normal birth, the Investigator should promptly report to the Sponsor/[redacted] the abnormal fetal outcome on an SAE form within 24 hours of knowledge of the event.

8.9. Expedited Reporting

Any AE that is both unexpected (not consistent with the applicable product information) and also meets the definition of an SAE/serious adverse reaction would be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR). The Sponsor/designee will report all relevant information for SUSARs that are fatal or life-threatening as soon as possible to the applicable regulatory authorities and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case.

All other SUSARs (except fatal/life-threatening as noted above) will be reported to the applicable regulatory authorities as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee. Additionally, expected fatal or life-threatening serious adverse reactions must also be reported to the PMDA as soon as possible but within 15 days of first knowledge by the Sponsor/designee, and must also be reported to Investigators.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational study drug.

8.10. Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s), or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer,

respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of investigational product are not considered reportable as medication error.

- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A Special Situations Report form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to [redacted] (contact information listed in Section 8.7) within 24 hours of knowledge of the event. All AEs associated with these special situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

8.11. Safety Endpoints

The safety endpoints include the following:

- Description of safety assessments by treatment group and dose. Safety assessments include AEs, SAEs, vital signs, ECG results, and clinical laboratory evaluations;
- Proportion of patients with AEs leading to discontinuation;
- Description and frequency of AESIs by treatment group; and
- Description of ADAs (binding and neutralizing).

8.12. Clinical Laboratory Evaluations

Samples for chemistry, hematology, urinalysis, and lipid laboratory evaluations will be obtained as indicated in Appendix A and assessed at the central laboratory. See Appendix B for a complete list of analytes. Lipids and subfractions will be assessed after 8 hours of fasting.

Serum pregnancy tests will be performed for women of childbearing potential only at Visits -1 and 11 and assessed at the central laboratory.

INR will be performed by the local laboratory only for patients currently receiving warfarin.

8.13. Vital Signs

Vital signs will be measured as indicated in Appendix A. Vital signs include temperature, respiratory rate, heart rate, and blood pressure. Patients may be re-evaluated within 2 weeks, at the discretion of the Investigator, if antihypertensive therapy has been started or increased as a result of initial blood pressure measured at Screening. Whenever possible, vital signs will be obtained after at least 5 minutes resting in the supine position or a semirecumbent position. Vital signs will be obtained prior to ECG recordings.

8.14. Electrocardiograms

ECGs will be performed as indicated in Appendix A. Standard 12-lead ECGs will be recorded in the supine position (or with the patient as flat as possible) after vital sign assessments. The ECG will be locally read by the Investigator.

8.15. Physical Examinations

Limited physical examinations will be performed as indicated in Appendix A. A limited physical examination will include examination of the skin, oropharynx, lungs, heart, abdomen, extremities (including feet), and any areas suggested by symptoms, with particular attention to signs of infection. This may be performed by a physician-Investigator. Abnormal findings will be recorded in the source documents.

9. STATISTICS

Details of all planned analyses will be provided in the Statistical Analysis Plan.

9.1. Analysis Populations

The following analysis populations are defined for the different types of data analysis:

- Intent-to-Treat (ITT) Population: all randomized patients;
- Per-Protocol Population: all randomized patients who complete the study and do not incur a significant protocol violation;
- PK Population: all randomized patients who receive study drug and have at least 1 postdose PK blood sample; and
- Safety Population: all randomized patients who receive study drug.

9.2. Statistical Methods

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 (n), 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 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.

9.2.1. Analysis of Efficacy

For efficacy (PD) variables, the median difference between each active group and placebo will be analyzed. Efficacy analysis will be performed using the nonparametric Hodges-Lehmann method to estimate median differences between each active group and placebo, associated 95% confidence intervals, and p-values. Additionally, the nonparametric analysis will adjust for the randomization stratification variable CKD Stage (3 vs. 4 and 5)..

For the efficacy variables, the observed values and changes from Baseline will be summarized by treatment group using descriptive statistics and the ITT Population.

9.2.1.1. Primary efficacy (pharmacodynamic) analysis

The overall familywise error rate will be controlled at $\alpha = 0.05$ 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.

9.2.1.2. Sensitivity analysis

Sensitivity analysis will be performed for the primary efficacy endpoint using the following methods:

1. The nonparametric analysis method used to analyze the primary efficacy endpoint will be performed on the per-protocol population.
2. Analysis of hs-CRP on a log scale, using log of ratio to baseline as the outcome variable, will be performed using mixed models for repeated measures on the ITT population.
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 group 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 assumption. The rest of missing values in the placebo arm and active arms will be imputed using the observed data under the missing at random 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 After the multiple imputation step, each log-transformed imputed dataset will be analyzed using the analysis of covariance model (not repeated measures and with no random effects) to produce treatment difference estimates for ratio to baseline, treatment ratio estimates, 95% confidence intervals, and p-values.

Details of sensitivity analysis will be provided in the statistical analysis plan（SAP).

9.2.2. Analysis of Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Modeling

9.2.2.1. 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.

9.2.2.2. 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.

9.2.3. Analysis of Safety

9.2.3.1. Adverse events

The AE verbatim descriptions (Investigator terms from the eCRF) will be classified into medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to primary System Organ Class (SOC) and preferred term (PT) using the latest version of the MedDRA.

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.

The number (percentage) of patients reporting TEAEs and SAEs for each PT will be tabulated by SOC, by SOC and severity, and by SOC and relationship to study drug. If more than 1 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.

AESIs will be summarized by treatment group and dose.

9.2.3.2. Clinical laboratory evaluations

Clinical laboratory values (excluding efficacy laboratory parameters) will be summarized by treatment group, including changes from Baseline at each visit.

9.2.3.3. 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 (systolic blood pressure increase or decrease from Baseline >25% mmHg, >160 mmHg, or <90 mmHg; heart rate >100 beats per minute or <50 beats per minute; and respiration rate >24 breaths per minute) will be summarized.

9.2.3.4. 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.

9.2.3.5. Physical examination

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

9.2.3.6. Anti-drug antibodies

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.

9.2.3.7. Bleeding events

Bleeding events will be classified using the TIMI Bleeding Classification in Table 3.[14]

Table 3 Thrombolysis in Myocardial Infarction 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] + [number of transfused units × 3]. Hct = hematocrit; Hgb = hemoglobin; TIMI = Thrombolysis in Myocardial Infarction. Source: Rao SV, O'Grady K, Pieper KS, et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. *J Am Coll Cardiol*. 2006;47(4):809-816	

9.2.4. Interim Analysis

No interim analysis is planned for the study.

9.2.5. 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 COR- 001-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.

10. DATA MANAGEMENT AND RECORD KEEPING

10.1. Data Management

10.1.1. Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2. Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3. Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the US Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4. Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5. Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2. Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study drug, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement.

Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3. End of Study

The end of the study is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last patient in the study. Patients alive at the end of the study who require further follow-up may be entered into a separate long-term follow-up study.

11. INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1. Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2. Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and wellbeing of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Japanese Ministerial Ordinance on GCP for Drugs regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

11.3. Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, Japanese Ministerial Ordinance on GCP for Drugs regulations, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC, and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4. Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review witthe Investigator and site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5. Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the PMDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6. Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7. Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any

study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8. Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under US 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.9. Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out patient liability insurance for all patients who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.10. Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial notification (CTN).

The study will commence (ie, initiation of study centers) when the CTN and favorable Ethics opinion have been received.

12. STUDY ADMINISTRATIVE INFORMATION

12.1. Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days of implementation of the protocol amendment.

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APPENDIX A: SCHEDULE OF PROCEDURES

	Screening: Days -14 Through -1[a]	Treatment Period: Baseline Through Week 12									Safety Follow-Up: Weeks 12 Through 20	
Visit	**-1**	**1**	**2[p]**	**3**	**4[p]**	**5**	**6[p]**	**7**	**8**	**9/ET1**	**10**	**11/ET2**
Week	**-2**		**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12/ET1**	**16**	**20/ET2**
Day	**-14 to -4**	**1**	**8+3 days**	**15+3 days**	**22+3 days**	**29+3 days**	**43+6 days**	**57+6 days**	**71+6 days**	**85+6 days**	**113+6 days**	**141+6 days**
Informed consent[b]	X											
Inclusion/exclusion criteria	X	X[c]										
Demographic information	X											
Medical history/update	X	X										
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Limited physical examination[d]	X											X
Vital signs[e]	X	X		X	X	X		X		X	X	X
Infectious disease screen[f]	X[g]											
Serum pregnancy test[h]	X											X
FSH for postmenopausal women	X											
12-lead ECG[i]	X					X		X		X		X
Chemistry and hematology[n]	X[g]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (including albumin)[j]	X	X								X		
Lipids and subfractions (fasting 8 hours)[k,n]	X	X								X	X	
Spot urine protein-creatinine ratio[n]	X									X		
Screening IL-6 (central)	X											
IL-6 (Total)[n]		X[l]	X	X	X	X	X	X	X	X	X	X
hs-CRP[m,n]	X	X	X	X		X			X	X	X	X
BMI		X										
Ziltivekimab PK[n]	X	X	X	X	X	X	X	X		X	X	X

	Screening: Days -14 Through -1[a]	Treatment Period: Baseline Through Week 12									Safety Follow-Up: Weeks 12 Through 20	
Visit	**-1**	**1**	**2[p]**	**3**	**4[p]**	**5**	**6[p]**	**7**	**8**	**9/ET1**	**10**	**11/ET2**
Week	**-2**		**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12/ET1**	**16**	**20/ET2**
Day	**-14 to -4**	**1**	**8+3 days**	**15+3 days**	**22+3 days**	**29+3 days**	**43+6 days**	**57+6 days**	**71+6 days**	**85+6 days**	**113+6 days**	**141+6 days**
Randomization		X										
Study drug administration (post-assessments)		X				X		X				
ADA[n]	X	X	X	X	X	X	X	X	X	X	X	X
Fibrinogen, serum amyloid A, NT-pro-BNP, hemoglobin and albumin[n]		X							X	X		
INR[o]		X	X	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibody; BMI = body mass index; ECG = electrocardiogram; ET1 = Early Termination for Treatment Period, ET2 = Early Termination for Safety Follow-up Period; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; IL = interleukin; INR = international normalized ratio; lab = laboratory; PI = Principal Investigator; PK = pharmacokinetic(s).

[a] Screening may be extended up to 1 week to allow for retesting of a hs-CRP result that did not meet inclusion criteria.
[b] Signed informed consent must be obtained before any study-related procedures are performed.
[c] Inclusion/exclusion criteria will be reaffirmed, and any updates since Screening will be recorded.
[d] A limited physical examination will include examination of the skin, oropharynx, lungs, heart, abdomen, extremities (including feet), and any areas suggested by symptoms, with particular attention to signs of infection. This may be performed by a physician-Investigator. Abnormal findings will be recorded in the source documents.
[e] Vital signs include temperature, respiratory rate, heart rate, and blood pressure. Patients may be re-evaluated within 2 weeks, at the discretion of the PI, if antihypertensive therapy has been started or increased as a result of initial blood pressure measured at Screening. Whenever possible, vital signs will be obtained after at least 5 minutes resting in the supine position or a semirecumbent position. Vital signs will be obtained prior to ECG recordings.
[f] Infectious disease screen will include HIV-1 and HIV-2, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis C antibody, and mycobacterium tuberculosis test. For the mycobacterium tuberculosis test, QuantiFERON is preferred, but a purified protein derivative skin test read within 48 to 72 hours by a qualified healthcare professional may also be performed (https://www.cdc.gov/tb/publications/factsheets/teseting/skintesting/htm).
[g] If the test results are delayed, come back unable to perform analysis, come back indeterminate, or require confirmatory testing, the screening window may be extended until central lab results are available.
[h] For women of childbearing potential only, a serum pregnancy test for β-human chorionic gonadotropin will be performed.
[i] Standard 12-lead ECGs will be recorded in the supine position (or with the patient as flat as possible) after vital sign assessments. The ECG will be locally read by the Investigator.
[j] A portion of urine will be frozen and stored for future analysis.

[k] Lipids and subfractions will be assessed after 8 hours of fasting.
[l] Predose sampling on Day 1.
[m] Test may be repeated 1 time prior to Day 1. hs-CRP values of 1.5 to <2 mg/L should be retested. Results after randomization will be blinded.
[n] For Visit 1, Visit 5 and Visit 7, all sample will be collected within 1 hour ±30 minutes prior to study drug administration. For other visits, all samples should be collected at approximately the same time (±1 hour) as when the predose sample is collected on Day 1.
[o] INR will be performed by the local lab only for patients currently receiving warfarin.
[p] Visit 2, 4, and 6 can be converted to phone visits, with the following assessments performed: Prior/concomitant medications; assess adverse events.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate (or carbon dioxide)
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate [1]
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid
Direct bilirubin	

[1] Estimated glomerular filtration rate will be calculated by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation (https://www.kidney.org/content/ckd-epi-creatinine-equation-2009).

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count indices [1]
Reticulocyte count	White blood cell count and differential [2]

[1] Red blood cell count indices include mean corpuscular volume and red cell distribution width.
[2] Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Albumin	Bilirubin
Blood	Glucose
Ketones	Leukocyte esterase
Microscopy [1]	Nitrite
pH	Protein
Specific gravity	Spot urine protein-creatinine ratio Urobilinogen

[1] Microscopy is performed only as needed based on positive dipstick test results.

Endocrinology

β-human chorionic gonadotropin [1]	Follicle-stimulating hormone [2]

[1] Serum pregnancy test will be performed for women of childbearing potential only.
[2] Postmenopausal women must have had no menstrual bleeding for at least 1 year before initial dosing and either be over the age of 60 years or have an elevated plasma

follicle-stimulating hormone level (ie, >40 mIU/mL) at Screening.

Lipids and Subfractions

High density lipoprotein-cholesterol	Low density lipoprotein-cholesterol Total cholesterol
Triglycerides	

Infectious Disease Screen

Hepatitis B surface antibody	Hepatitis B surface antigen
Hepatitis C antibody	Human immunodeficiency virus (HIV)-1 and HIV-2
Mycobacterium tuberculosis test	

Inflammation and cardiac risk marker

Fibrinogen	Serum amyloid A,
NT-pro-BNP	

APPENDIX C: GUIDANCE ON CONTRACEPTION

Patients must agree to comply with the following contraception and reproduction restrictions of the study:

a. Women of childbearing potential must be using a method of contraception that is "highly effective" (ie, <1% failure rate) for at least 3 months following the last dose of study drug.

   OR

b. Postmenopausal women must have had no menstrual bleeding for at least 1 year before initial dosing and either be over the age of 60 years or have an elevated plasma follicle-stimulating hormone level (ie, >40 mIU/mL) at Screening.

   AND

c. Women of childbearing potential must have a documented negative serum pregnancy test result at Screening.

d. For the purposes of the proposed study, "highly effective" contraceptive methods are defined as those, alone or in combination, that result in a low failure rate (ie, <1% per year) when used consistently and correctly, and include the following:
   - Surgical sterilization at least 6 months before study drug administration;
   - Implants;
   - Levonorgestrel and Copper T intrauterine devices; and
   - Sexual abstinence.

Patients who prefer methods that evidence a higher (6% to 9%) failure rate with typical use will be required to employ at least 2 methods of contraception concurrently. These methods include the following:

- Injectable hormone depots;
- Oral contraceptive pill;
- Hormone patch; and
- Vaginal ring.

Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception.

All male patients, from the day of dosing until the final study visit, unless surgically sterile, must be willing to use a condom with a partner (male patients with partners of childbearing potential must be willing to use 2 effective methods of birth control, 1 should be condom with spermicide) to prevent pregnancy and drug exposure of a partner, and refrain from donating sperm or fathering a child.

https://www.cdc.gov/reproductivehealth/contraception/index.htm

Investigators may contact the Medical Monitor to discuss questions regarding appropriate contraception. The guidance will follow that described in the document [redacted] and will comply with Food and Drug Administration M3(R2).