Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03926117
Sponsor trial ID:	NN6018-4779
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 IL-6 inhibition (RESCUE)
Document date	23 December 2019

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate REduction in Inflammation in PatientS with advanced Chronic Renal Disease Utilizing Antibody MEdiated IL-6 inhibition (RESCUE)

DRUG NAME:	Ziltivekimab (human monoclonal antibody to IL-6)
PROTOCOL NUMBER:	COR-001-02
PHASE:	2
IND:	140,097
TRIAL SPONSOR:	Corvidia Therapeutics Inc. 35 Gatehouse Drive Waltham MA 02451
MEDICAL MONITOR:	[redacted] Corvidia Therapeutics Inc. Phone: [redacted] Email: [redacted]
DOCUMENT DATES:	Original: 05 November 2018 Protocol Amendment 1: 05 December 2018 Protocol Amendment 2: 24 January 2019 Protocol Amendment 3: 16 April 2019 Protocol Amendment 4: 25 June 2019 Protocol Amendment 5: 23 December 2019

Redacted protocol

Includes redaction of personal identifiable information only.

Confidentiality Statement

[redacted]

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "**A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate REduction in Inflammation in PatientS with advanced Chronic Renal Disease Utilizing Antibody MEdiated IL-6 inhibition (RESCUE)**" and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312 and all locally applicable laws.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Corvidia Therapeutics Inc.

_____

Signature of Principal Investigator

_____ _____

Name of Principal Investigator (Print) Date (DD Month YYYY)

SPONSOR APPROVAL PAGE

Product name: Ziltivekimab

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate REduction in Inflammation in PatientS with advanced Chronic Renal Disease Utilizing Antibody MEdiated IL-6 inhibition (RESCUE)

Protocol number: COR-001-02

Release date: 23 December 2019

We, the undersigned, confirm that this Clinical Study Protocol is accurate.

Signed: [redacted] Date: [redacted]

Corvidia Therapeutics Inc.

Signed: [redacted] Date: [redacted]

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PROTOCOL 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 IL6 Inhibition (RESCUE)
Study Number	COR-001-02
Study Phase	2
Objectives	Patients with non-dialysis-dependent chronic kidney disease (NDD-CKD), who have evidence of systemic inflammation with increased cardiovascular risk, will be enrolled into this trial. The purpose of this trial is to determine a dose to select for a potential cardiovascular outcome trial with Ziltivekimab. Primary objective: • To evaluate the effects of Ziltivekimab compared to placebo on markers of inflammation (i.e. high-sensitivity C-reactive protein [hs-CRP]). Secondary objectives: • To evaluate the effects of Ziltivekimab compared to placebo on markers of inflammation and cardiovascular risk: serum amyloid A (SAA) and fibrinogen. Pharmacokinetic objectives: • To evaluate the pharmacokinetics (PK) and PK-Pharmacodynamic (PK-PD) modeling of Ziltivekimab following multiple doses at three different levels. Safety objectives: • To evaluate the safety of three dose levels of Ziltivekimab compared to placebo. Exploratory objectives: • To evaluate the effects of Ziltivekimab compared to placebo on markers of anemia (hemoglobin). • To evaluate the effects of Ziltivekimab compared to placebo on markers of inflammation-malnutrition (i.e. albumin). • To evaluate the effects of Ziltivekimab compared to placebo on markers of cardiovascular risk (i.e. N-terminal prohormone-B-type natriuretic peptide [NT-pro-BNP]). • To evaluate the effects of Ziltivekimab compared to placebo on additional markers of cardiovascular risk (suppression of tumorigenicity 2 [ST2]). • To evaluate the effects of Ziltivekimab compared to placebo on

	markers of atherosclerosis risk: LDL-C, triglycerides, ApoB, ApoA1, ApoB/ApoA1, lipid profile by nuclear magnetic resonance (NMR) spectroscopy, and Lp(a). • To evaluate the effects of Ziltivekimab compared to placebo on markers of kidney function, (i.e. cystatin C, estimated GFR) and kidney damage, (i.e. urine albumin-to-creatinine ratio [UACR]). • To evaluate the effects of three dose levels of Ziltivekimab compared to placebo on patient reported outcomes (PRO): Patient-Reported Outcomes Measurement Information System (PROMIS®) Fatigue 13a short form, selected items from the PROMIS fatigue item bank, the Optum SF-36 v2® Health Survey, a Corvidia PRO, the PROMIS interest in sexual activity item, the patient global impression of change (PGIC), patient global impression of severity (PGIS), and the EQ-5D-5L. • To evaluate the psychometric properties of the PROMIS Fatigue 13a short form and selected items from the PROMIS fatigue item bank, and the Corvidia electronic PRO (ePRO) items in CKD patients. • To evaluate the effects of Ziltivekimab on systemic iron availability: transferrin saturation (TSAT), reticulocyte hemoglobin content (CHr) and total iron binding capacity (TIBC), systemic iron stores (serum ferritin), serum iron and systemic iron regulation (serum hepcidin). • To evaluate the effects of Ziltivekimab compared to placebo on markers of cardiovascular risk (i.e. NT-pro-BNP) in patients with baseline NT-pro-BNP > 250 pg/mL. • To evaluate the effects of Ziltivekimab compared to placebo on markers of anemia in patients with baseline hemoglobin < 11 g/dL. • To evaluate the effects of Ziltivekimab compared to placebo on markers of inflammation-malnutrition (i.e. albumin) in patients with baseline albumin < 4.0 g/dL.
Study Design	This is a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy, safety, and pharmacokinetics of Ziltivekimab at three dose levels (7.5 mg, 15 mg or 30 mg) compared to placebo in patients with stage 3-5 CKD, not on dialysis, who have evidence of inflammation with high cardiovascular risk. Patients will undergo a Screening Period of up to 14-days during which inclusion and exclusion criteria will be evaluated. Patients who meet all inclusion criteria and no exclusion criteria will be randomized to one of three Ziltivekimab dose levels (7.5 mg, 15 mg or 30 mg) or placebo for a 24-week Treatment Period. Patient randomization will be stratified by baseline hemoglobin (≥11 or <11 g/dL) and CKD stage (3, 4 or 5).

	Approximately 240 patients will be randomized 1:1:1:1 (60 per group) into the trial. All patients must meet the inclusion/exclusion criteria. After the Screening Period, randomized patients will be dosed every 28 days out to Week 21. The primary, secondary and exploratory endpoints will be analyzed after 13 weeks of treatment and then followed for additional exploratory efficacy analyses through Week 24. Selected efficacy endpoints and safety assessments will evaluated in the Follow-up Period Week 25 though Week 32 (Figure 5). The patient will be randomized on Day 1 and the first dose of study drug should be administered after all assessments are conducted. Doses of study drug will be administered every 28-days for a total of 6 treatments (Weeks 1, 5, 9, 13, 17, and 21). Study visits will follow the schedule of events (Table 2).
Study Periods:	The study will consist of three periods: Screening, Treatment Period, and Safety Follow-Up Period. The total study duration for an individual patient will be approximately 8-9 months. Screening Period: up to 2 weeks [Days -14 to -1] • Starts with the first date that Initial Screening procedures were performed. The first procedure also defines the initial screening visit date Treatment Period: 24 weeks [Week 1, Day 1 through Week 24 • Starts with the first administration of study drug/randomization (Day 1) Safety Follow-Up Period: 8 weeks [Weeks 25 through 32] • Safety period starts 4-weeks after last treatment dose 6.
Inclusion Criteria:	After signing an informed consent form approved by the Investigator's Institutional Review Board (IRB) or Independent Ethics Committee (IC) to be eligible, potential study patients must meet all of the following criteria: 1) Age ≥18 years at the time of signing of the Informed Consent Form (ICF). 2) Stage 3-5 NDD-CKD, i.e. estimated glomerular filtration rate (eGFR) >10 and <60 mL/min/1.73 m^2 using the CKD-EPI Creatinine Equation (www.kidney.org/content/ckd-epi-creatinine-equation-2009). 3) Serum hs-CRP level ≥2.0 mg/L measured during the Screening Period. (Note: Targeting patients with a history of advanced stage CKD, atherosclerotic cardiovascular disease, anemia, metabolic syndrome, diabetic retinopathy and diabetes for screening will help increase the chances of identifying patients with CRP ≥2.0) 4) The patient agrees to comply with the contraception and reproduction restrictions of the study (Appendix G):

	a) Women of childbearing potential must be using a method of contraception, that is "highly effective" (i.e., <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 (i.e., >40 mIU/mL) at Screening; c) Women of childbearing potential must have a documented negative pregnancy test result at Screening. Patients with elevated β-HCG levels believed to be due to end-stage renal disease may be enrolled if documented to not be pregnant; 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.
Exclusion Criteria:	Participants are excluded from the study if any of the following criteria apply: **Laboratory Values** 1. Absolute neutrophil count <2.0 x 10^9/L during screening. 2. Platelet count <120 x 10^9/L during screening. 3. Spot urine protein to creatinine ratio >4000 mg/g, or 4.0 g/g. 4. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5x ULN during screening. 5. Positive testing for tuberculosis (TB) during screening. Blood testing (e.g., QuantiFERON) is preferred but a purified protein derivative (PPD) skin test read within 48-72 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-1 (HIV-1) or HIV-2 infection by serology measured during screening. 7. Hepatitis B or C by serology (e.g. 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 SBP >160 mmHg or an average diastolic blood pressure (DBP) >100 mmHg during screening. Patients may be re-evaluated within 2 weeks, at the discretion of the investigator for this criterion if anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure being above these limits. 15. Planned coronary revascularization (PCI or CABG) or any other major surgical procedure. 16. Major cardiac surgical, non-cardiac surgical or major endoscopic procedure within the past 6 months prior to Randomization. 17. History of New York Heart Association Class IV congestive heart failure within 12-weeks prior to randomization. 18. Actively treated or active malignancy during the 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. 19. History of bone marrow or solid organ transplant or anticipated to receive an organ transplant during the time frame of the study. 20. Known allergy to the study drug or any of its ingredients. **Prior or Current Medications** 21. Received an investigational drug within 30-days prior to screening visit. 22. Received a live vaccine product within 14 days of study drug administration (Day 1) or expect to receive live

	vaccine during the Treatment Period (receiving a live vaccine within 14 days prior to enrollment is allowed). 23. Treatment with a hypoxia-inducible factor (HIF) stabilizer (e.g., molidustat, roxadustat) or an erythropoietin-mimetic, e.g., erythropoietin alpha or beta, darbopoietin alpha, or continuous erythropoiesis receptor activator (CERA), within 6-weeks prior to randomization or during treatment period. 24. Expected to receive any investigational drug or any of the exclusionary drugs listed in Section 15.1 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 is (or equivalent) is permitted if dose has been stable for at least 4 weeks prior to screening, and no dose changes are planned during study participation. 26. Use of systemic antibiotics, systemic antivirals, or systemic antifungals during the screening period ("Systemic" is defined as oral or intravenous drugs that are absorbed into the circulation). 27. Requiring an indwelling catheter of any type. **General Exclusions** 28. Currently breastfeeding. 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.
Test Product, Dose and Mode of Administration	The test product dose regimens to be examined in this study are: • Dose #1: Ziltivekimab, 7.5 mg per injection, administered 6 times (every 28-days) on Weeks 1, 5, 9, 13, 17, and 21, as a subcutaneous injection. • Dose #2: Ziltivekimab, 15 mg per injection, administered 6 times (every 28-days) on Weeks 1, 5, 9, 13, 17, and 21, as a subcutaneous injection. • Dose #3: Ziltivekimab, 30 mg per injection, administered 6 times (every 28-days) on Weeks 1, 5, 9, 13, 17, and 21, as a subcutaneous injection. Patients should receive 6 injections of their assigned dose during the

	trial. The total cumulative dosage will be 45 mg for those patients randomized to 7.5 mg per injection, 90 mg for those patients randomized to 15 mg per injection, and 180 mg for those patients randomized to 30 mg per injection.
Reference Therapy, Dose, and Mode of Administration	The reference dose regimens to be examined in this study are: • Matched placebo injections administered subcutaneously 6 times (every 28 days) at the same frequency as the active treatment in a given dose cohort, on Weeks 1, 5, 9, 13, 17 and 21.
Pharmacokinetics and PK-PD Modeling:	• Serum trough levels (C_{min}) of Ziltivekimab will be measured at all visits. On dosing Weeks 1, 5, 9, 13, 17, and 21, trough PK samples to be collected within approximately -0.5 h pre-dose. Single PK blood samples will also be collected on Weeks 2, 4, 7, 23, 24/ET, 28, and 32/ET around the same time as the pre-dose samples were collected on previous dosing visits. • The total IL-6 AUC will be described. • The relationship between trough Ziltivekimab levels and primary pharmacodynamic endpoints, specifically total plasma IL-6 and hs-CRP, will be described.
Safety Endpoints:	• Proportion of patients with AEs, SAEs, severe hematologic AEs, severe non-hematologic AEs, and AEs leading to discontinuation. • Proportion of subjects with thrombolysis in myocardial infarction (TIMI) major bleeding event. • Description and frequency of events of special interest by treatment group: o Serious infections. o Severe injection-related reactions. o Gastrointestinal perforations. o Hypersensitivity reaction during study drug administration. o Anaphylaxis occurring at any time, even if considered unrelated to the study drug. A CRF for the collection of the details of such reactions will be available in the electronic data capture (EDC) system. o Neutrophil <500/mm^3 (severe), or neutrophil <1000/mm^3 (severe) with evidence of concurrent infection. These events will be separately summarized by treatment group and dose. o Thrombocytopenia (platelet count <50,000/mm^3 [severe]) or platelet count <75,000/mm^3 (moderate) with evidence of concurrent TIMI major bleeding. These events will be separately summarized by treatment group and dose. o Malignancies. • Description of additional safety assessments by treatment group

	and dose: vital signs, electrocardiogram (ECG), clinical laboratory, and anti-drug antibodies (binding and neutralizing).
Primary Endpoint:	• Difference in percent change in hs-CRP levels from Baseline (average of the hs-CRP value prior to randomization and Day 1) to Week 13 between each active group and placebo.
Secondary Endpoints:	• Difference in change in SAA from Baseline to Week 13 between each active group and placebo. • Difference in percent change in fibrinogen from Baseline to Week 13 between each active group and placebo.
Exploratory Endpoints:	• Difference in change in SAA from Baseline to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in percent change in fibrinogen from Baseline to End of Treatment (Week 24) between each active group and placebo. • Difference in percent change in hs-CRP levels from Baseline to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in percent change in serum NT-pro-BNP from Baseline (average of the NT-pro-BNP value prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change in hemoglobin from Baseline (average of the two most recent hemoglobin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change in serum albumin from Baseline (average of the two most recent serum albumin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Proportion of patients achieving hs-CRP response at Week 13 and to End of Treatment (Weeks 23 through 24), defined as hs-CRP <2.0 mg/L in each active group and placebo. • Difference in change in ST2 from Baseline to Week 13 and to End of Treatment (Week 24) between each active group and placebo. • Difference in percent change in Lp(a) from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in percent change in LDL-C, triglycerides, ApoB, ApoA1, ApoB/ApoA1, and lipid profile by NMR spectroscopy from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change of creatinine based eGFR and cystatin C-

	based eGFR from Baseline to Week 13 and to the End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change of UACR from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change of the total fatigue score (PROMIS Fatigue 13a short form and selected items from the PROMIS Fatigue item bank) from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change of the PROMIS interest in sexual activity item from Baseline to Week 13 and to End of Treatment (Week 24) between each active group and placebo. • Difference in change of the Corvidia ePRO items from Baseline to Week 12 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change of the PGIS index from Baseline to Week 12 and to End of Treatment (Week 24) between each active group and placebo. • Descriptive analyses of the PGIC index at Weeks 5, 13 and End of Treatment (Week 24) in each active group and placebo. • Difference in change of the Optum SF-36 v2® Health Survey physical component summary (PCS), mental component summary (MCS) and domain scores from baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change of the EQ-5D-5L index from Baseline to Week 12 and to End of Treatment (Week 24) between each active group and placebo. • Evaluation of the psychometric properties of the PROMIS Fatigue 13a short form and selected items from the PROMIS Fatigue item bank and the Corvidia ePRO items in CKD patients – to be described in a PRO psychometric analysis plan. • Descriptive analyses by dose and treatment may be conducted on samples stored for analysis of exploratory biomarkers, genomic and transcriptomic analysis. • Difference in change in TSAT from Baseline to peak level, Week 13 and End of Treatment (Weeks 23 through 24), between each active group and placebo. • Difference in change in CHr from Baseline to peak level, Week 13 and to End of Treatment (Week 24) between each active group and placebo. • Difference in change in TIBC from Baseline to Week 13 and to

	End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change in serum ferritin from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change in serum iron from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo. • Difference in change in serum hepcidin from Baseline to Week 13 and to End of Treatment (Week 24) between each active group and placebo. • Difference in percent change in serum NT-pro-BNP from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo in patients with baseline NT-pro-BNP > 250 pg/mL. • Difference in change in hemoglobin from Baseline (average of the two most recent hemoglobin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo in patients with baseline hemoglobin < 11 g/dL. • Difference in change in serum albumin from Baseline (average of the two most recent serum albumin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo in patients with baseline albumin < 4.0 g/dL.
Sample Size	Approximately 240 (60 per group).
Statistical Methods Analysis	The following analysis Populations are defined for the different types of data analysis: • Intent-to-treat (ITT) analysis population: all patients randomized. • Per-protocol (PP) analysis population: all patients randomized who completed the study and did not incur a significant protocol violation. • Pharmacokinetics (PK) analysis population: all patients randomized and who received at least one dose of Test or Reference product and who had at least one post-dose PK blood sample. • Safety analysis population: all patients randomized and who received at least one dose of Test or Reference product. 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, quartiles (Q1 and Q3), minimum (min) and

	maximum (max) values for the observed value and change from baseline will be reported. Analysis of categorical variables will include frequency and percentage. For efficacy variables, the difference between each active group and placebo will be presented. A mixed model for repeated measures (MMRM) will be used for this purpose, with baseline hemoglobin (≥11 or <11 g/dL), CKD stage (3, 4 or 5), treatment groups, visit and treatment group-by-visit interaction as categorical fixed effects, baseline value and baseline-by-visit interaction will be included as covariates. The least square means for each dose, the least square mean differences from placebo along with the associated 95% confidence intervals (CIs) and p-values will be presented. If the normality assumption is not met, a nonparametric test will be selected for efficacy analysis.
Study Centers	Approximately 50-60 study sites
Sponsor	Corvidia Therapeutics Inc.

LIST OF ABBREVIATIONS, DEFINITIONS AND TERMS

Term	Definition
ACR	Albumin to creatine ratio
AE	Adverse event
ALT	Alanine aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
AUC	Area under the curve
β-hCG	β -Human chorionic gonadotropin hormone
BMP	Bone morphogenic protein
BMPR	Bone morphogenic protein receptor
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CEC	Clinical Events Committee (CEC)
CERA	Continuous erythropoiesis receptor activator
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CHr	Reticulocyte hemoglobin content
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula
Cmax/min	Maximum/minimum observed concentration
Ziltivekimab	Monoclonal antibody to IL-6
CRF	Case report forms
CRO	Contract research organization
CV	Cardiovascular
CV	Coefficient of variation
CVD	Cardiovascular disease
ECG	Electrocardiogram
EDC	Electronic data capture
ESA	Erythropoiesis-stimulating agent
eGFR	estimated glomerular filtration rate
ePRO	Electronic Patient-Reported Outcomes
EQ-5D-5L	(EuroQol-5D-5L
ERI	ESA resistance index (ESA weekly dose/targeted dry weight in kg*hemoglobin in g/dL)
ESRD	End stage renal disease

Term	Definition
FDA	Food and Drug Administration
FPN	Ferroportin
FSH	Follicle stimulating hormone
FWER	Familywise error rate
GCP	Good Clinical Practice
GCV	Geometric CV
GLP	Good Laboratory Practices
HAMP	Hepcidin gene
Hct	Hematocrit
HDL	High density lipoprotein
HFpEF	Heart Failure with Preserved Ejection Fraction
Hgb	Hemoglobin
HIF	Hypoxia-inducible factor
HIV	Human Immunodeficiency Virus
HR	Heart rate
HRadj	Adjusted hazard ratio
HRQoL	Health-related quality of life
hs-CRP	High sensitivity C-Reactive Protein
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL1RL-1	interleukin 1 receptor-like 1
IL-6	Interleukin-6
IL-6R	IL-6 receptor
IND	Investigational new drug
INR	International normalized ratio
iPTH	Intact parathyroid hormone
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IWRS	Interactive Web-Response System
kg	Kilogram
KDIGO	Kidney Disease: Improving Global Outcomes
LAV	Left atrial volume
LDL	Low density Lipoprotein
LHD	Low Hemoglobin density

Term	Definition
LLN	Lower Limit of Normal
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVMI	Left Ventricular Mass Index
MCS	Mental component summary
MCV	Mean corpuscular hemoglobin
mg	Milligram
MI	Myocardial infarction
MICS	Malnutrition-inflammation-cachexia syndrome
min	Minute
mL	Milliliter
MMRM	Mixed Model Repeated Measures
NDD-CKD	Non-dialysis-dependent chronic kidney disease
NMR	Nuclear magnetic resonance
NOAEL	No observed adverse effect level
NT-pro-BNP	N-terminal prohormone-B-type natriuretic peptide
PAP	Psychometric analysis plan
PBO	Placebo
PCS	Physical component summary
PD	Pharmacodynamic
PEW	protein-energy wasting
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	Principal Investigator
PK	Pharmacokinetic
PPD	Purified Protein Derivative
PRO	Patient-Reported Outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PROSAP	PRO statistical analysis plan
PT	Prothrombin Time
PTH	Parathyroid Hormone
RBC	Red Blood Cell
RDW	Red cell distribution width
RR	Respiratory Rate
RSf	Red cell size factor
SAA	Serum amyloid A
SAE	Serious adverse event

Term	Definition
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOP	Standard Operating Procedure
ST2	Suppression of tumorigenicity 2
SUSAR	Suspected Unexpected Serious Adverse Reaction
t½	Half-life
TB	tuberculosis
TBD	To be determined
TIBC	Total iron binding capacity
TIMI	Thrombolysis in Myocardial Infarction
TMP	Transmembrane Pressure
TSAT	Transferrin saturation
UACR	Urine albumin-to-creatinine ratio
UFR	Ultrafiltration Rate
ULN	Upper limit of normal
WBC	White blood cells

1 INTRODUCTION

1.1 Background

Ziltivekimab (COR-001), formerly MEDI5117, is an extended half-life human IgG1κ anti-human interleukin 6 (IL-6) monoclonal antibody designed with three 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 treatment of patients with the inflammatory sequalae of advanced chronic kidney disease (CKD). Inflammatory sequelae specifically include the following:

- Atherosclerotic Cardiovascular Disease (ASCVD)
- Congestive Heart Failure, Primarily Heart Failure with Preserved Ejection Fraction (HFpEF)
- Functional Iron Deficiency Anemia
- Malnutrition-Inflammation-Cachexia Syndrome

1.1.1 Atherosclerotic Cardiovascular Disease (ASCVD) in Patients with CKD

Patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) are 10 times more likely to die of atherosclerotic cardiovascular disease (ASCVD) than the general population (Gregg 2018). However, cardiovascular disease is frequently underdiagnosed and undertreated in patients with CKD. Inflammation is highly prevalent in patients with chronic kidney disease (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 trial data have demonstrated that inflammation is a key driver of atherosclerosis (Aday 2019). Circulating biomarkers of inflammation, including high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6), are associated with increased risk of cardiovascular events independent of cholesterol and other traditional risk factors. Randomized trials have shown that statins reduce hs-CRP, and the magnitude of hs-CRP reduction is proportional to the reduction in cardiovascular risk (Aday 2019; Ridker 2018a; Arici 2001).

1.1.1.1 Study of Heart and Renal Protection (SHARP)

The Study of Heart and Renal Protection (SHARP) assessed the associations between circulating CRP and LDL cholesterol levels and the risk of vascular and non-vascular outcomes (Storey 2018). Higher baseline CRP was associated with an increased risk of major vascular events (hazard ratio per 3x increase 1.28; 95% confidence interval 1.19-1.38). Higher baseline LDL cholesterol was also associated with an increased risk of major vascular

events (hazard ratio per 0.6 mmol/L higher LDL cholesterol; 1.14, 1.06-1.22). Higher baseline CRP was associated with an increased risk of a range of non-vascular events (1.16, 1.12-1.21), but there was a weak inverse association between baseline LDL cholesterol and non-vascular events (0.96, 0.92-0.99). The efficacy of lowering LDL cholesterol with simvastatin/ezetimibe on major vascular events, in the randomized comparison, was similar irrespective of CRP concentration at baseline however risk of increased CV events were significantly greater in patients who had elevated CRP on treatment. This "residual inflammatory risk" has increasingly become a viable pharmacologic target.

1.1.1.2 CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study)

To further assess the potential benefits of reducing residual inflammation as determined by hs-CRP reduction, CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) was a randomized, double-blind trial of 3 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 (Ridker 2017). The primary efficacy endpoint 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 years for placebo, 4.11 events per 100 years for 50 mg, 3.86 events per 100 years for 150 mg, and 3.90 events per 100 years for 300 mg. Compared to placebo, the 150 mg dose displayed a significant effect on the primary endpoint outcomes (hazard ratio [HR] vs placebo 0.85; $p=0.02075$; threshold $p=0.02115$). The 300 mg dose displayed a similar hazard ratio vs placebo (HR vs placebo 0.86), but did not reach significance versus 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 (Aday 2019).

1.1.1.3 CANTOS hs-CRP Threshold Analysis

In the CANTOS trial, 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 (Ridker 2018a). During the CANTOS trial, 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 0.75, 95% confidence intervals [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 (adjusted HR 0.90; 95% CI

0.79 - 1.02; p=0.11). Similar significant reductions (31%) in cardiovascular mortality (adjusted HR 0.69; 95% CI 0.56 - 0.85; p=0.0004) and all-cause mortality (adjusted HR 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.

1.1.1.4 CANTOS Patients with Moderate CKD

Patients in the CANTOS trial had serial monitoring of eGFR, creatinine, the urine to albumin ratio (UACR), and renal and urinary AE monitoring (Ridker 2018b). 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 m2 (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 non-fatal myocardial infarction, non-fatal 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 below 2 mg/L was 5.35 on , representing a 32% relative risk reduction between placebo and active which correlated to a number needed to treat (NNT) of eight.

1.1.1.5 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 trial 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 (Ridker 2016).

In the CANTOS trial, 4833 patients had IL-6 levels measured before randomization and after treatment (Ridker 2018c). 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 adjusted hazard ratio (HRadj) 0.68, 95% confidence interval (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 equal to or above 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, associates with reduced cardiovascular event rates, independent of lipid lowering.

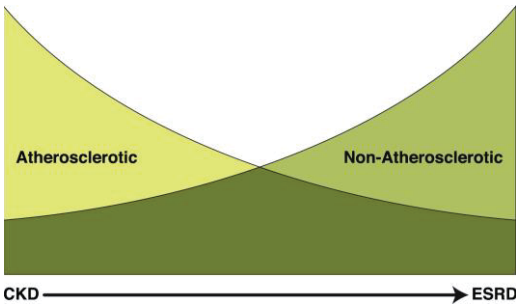
1.1.2 Congestive Heart Failure, Primarily Heart Failure with Preserved Ejection Fraction (HFpEF)

Cardiovascular disease (CVD) is the primary driver of morbidity and mortality in chronic kidney disease (CKD) at all stages, (US Renal Data System. 2002, Locatelli 2000). In end stage renal disease (ESRD), CVD mortality rate is up to 20 times higher than that of the general population (Foley 1998). While the severity of renal impairment is linked to CVD risk, accumulating evidence indicates that inflammation plays a key role in the progression of many forms of CKD and independently accounts for at least part of the increased risk of cardiac events in CKD patients (Go 2004).

In cardiovascular disease, C-reactive protein (CRP) has been established as a pathognomonic measure of systemic inflammation, whose elevation connotes risk, and whose lowering confers benefit. This relationship holds in the CKD population. As recently reported in the SHARP trial (*Study of Heart and Renal Protection*), which randomized 9270 patients with CKD to low-density lipoprotein cholesterol (LDL-C) lowering therapy or placebo, CRP was independently associated with both vascular (atherosclerotic) and non-vascular CVD (Storey 2018). In the AURORA trial (*A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events*), 2773 patients on hemodialysis, CRP and albumin were significant predictors of CV events independent of traditional risk factors (Solbu 2018). The CANTOS trial (*Canakinumab Anti-Inflammatory Thrombosis Outcomes Study*) evaluated the effects of an IL-1beta inhibitor, canakinumab, on CV events in patients with existing cardiovascular disease. The majority of overall mortality benefit was driven by the subset of patients with CKD, and the largest benefits accrued among those who had the most robust anti-inflammatory response, specifically these who achieved on-treatment CRP levels <2 mg/L (Ridker 2018a).The CRP lowering effect of canakinumab is mediated by inhibiting the IL-1β stimulation of IL-6 (Ridker 2016). Interleukin-6 is the major inflammatory cytokine responsible for stimulating the hepatic synthesis of C-reactive protein (Castell 1990). These data support the thesis that inflammation, systemically measured as increased CRP, is a surrogate for the effector molecule IL-6 which drives cardiovascular risk in CKD.

As CKD progresses to end-stage, cardiovascular risk shifts from atherosclerotic (as studied in the trials noted above) to non-atherosclerotic, specifically that of ventricular disease manifesting as arrhythmia, sudden cardiac death and heart failure, which has been termed "uremic cardiomyopathy" or "Cardio-Renal Syndrome Type 4" (Figure 1, Herzog 2014 and Ronco 2008).

Figure 1 **A conceptual framework of contributors to the cardiovascular disease burden in patients with advancing CKD**



Numerous studies have revealed a relationship between IL-6 driven inflammation, left ventricular hypertrophy and fibrosis, and an increase incidence in cardiovascular events in CKD (Barreto 2010, Rao 2005, Pecoits-Filho 2002a), with the level of inflammation as measured by CRP and IL-6 correlated with left ventricular hypertrophy as well as clinical outcomes (Park 2002, Spoto 2015).

The mechanisms by which IL-6 driven inflammation may be causal to the marked cardiac ventricular morbidity evident in advanced CKD populations can be described by two general themes:

1. *Hepcidin-independent direct IL-6 mediated cardiac myocyte hypertrophy and tissue fibrosis*
2. *Hepcidin-dependent IL-6 mediated myocyte iron dysregulation.*

In vitro studies show that IL-6 exerts a direct effect on the cardiac ventricle, inducing myocyte hypertrophy and tissue fibrosis, possibly through a macrophage-induced, aldosterone-dependent mechanism via activation of cardiac fibroblasts (Meléndez 2010, Ma 2012, Chou 2018). In a more recent line of investigation, the Sponsor's unpublished data further suggests that cardiac myocytes are susceptible to IL-6 mediated iron dysregulation which is exacerbated by ischemia-reperfusion (see Section 4.2.1.2). Specifically, a synergistic increase in hepcidin expression by IL-6 and bone morphogenic protein (BMP) is potentiated by hypoxia, and in aggregate notably increases cellular susceptibility to ischemia-reperfusion.

B-type natriuretic peptide (BNP) is a hormone produced by the myocardium. N-terminal (NT)-pro hormone BNP (NT-pro-BNP) is a non-active prohormone that is released from the same molecule that produces BNP. Both BNP and NT-pro-BNP are released in response to changes in pressure inside the heart. N-Terminal pro-B-type natriuretic peptide (NT-pro-BNP) level predicts underlying heart disease in the general population. The association between NT-pro-BNP level and coronary artery disease (CAD) and left ventricular hypertrophy (LVH) was determined in 207 ambulatory patients with CKD not on dialysis therapy. NT-pro-BNP levels were elevated in 116 patients (56%), and 67 patients (33%) had experienced prior CAD events (myocardial infarction or revascularization). After adjustment for glomerular filtration rate, cTnT level, age, and diabetes, NT-pro-BNP remained an independent indicator of prior CAD events for patients with echocardiograms, NT-pro-BNP level predicted prior CAD events independent of LVH. NT-pro-BNP level elevation in asymptomatic patients with CKD reflects underlying ischemic heart disease and hypertrophy independent of renal function in a population with anticipated high cardiac morbidity (DeFilippi 2005). The longitudinal Cardiovascular and Renal Outcome in CKD 2-4 Patients-The Fourth Homburg Evaluation Study, prospectively studied 496 patients with CKD stages G2-G4. Left ventricular mass index, left atrial volume index, diastolic left ventricular function, and systolic left ventricular function were assessed echocardiographically as well as levels of NT-pro-BNP. During a mean follow-up of 4.5 years, 104 patients suffered decompensated heart failure or all-cause mortality, and 127 patents had atherosclerotic events or all-cause mortality. NT-pro-BNP remained an independent predictor for both end points in multivariate analysis, whereas left ventricular mass index, left atrial volume index, and diastolic left ventricular function did not. This data confirmed that NT-pro-BNP is an independent predictor of adverse outcomes in patients with CKD (Understellar 2016).

1.1.3 Functional Iron Deficiency (the Anemia of Chronic Disease)

Anemia is nearly universal among patients with advancing renal disease unless treated with erythropoiesis stimulating agents (ESAs) and supplemental iron (Biggar 2017). The etiology of this anemia is that of EPO deficiency alongside IL-6 driven inflammation, which stimulates the production of the protein hepcidin (Wrighting 2006, Babitt 2012). Hepcidin, a peptide hormone which is mainly synthesized in the liver, reduces extracellular iron in the body by several mechanisms: 1) it lowers dietary iron absorption by reducing iron transport across gut mucosal cells (enterocytes); 2) it reduces iron exit from macrophages, the main site of iron storage; and 3) it reduces iron exit from the liver (Reichert 2017, Sun 2012). This pathophysiologic state represents an inefficiency of erythropoiesis, as evident by the need for initiation of ESAs and iron supplementation prior to the loss of EPO-synthetic capacity by the kidney, in order to maintain serum hemoglobin at an acceptable value (Mercadal 2012). These high doses of ESAs and the maintenance of a high ferritin level are associated with

increased risk of cardiovascular complications, the former of which is highlighted by the Agency's boxed warning on ESA product labeling advising conservative serum hemoglobin targets. Furthermore, the Sponsor's unpublished data describes a novel, intermediate hormonal mechanism which may be causal in driving this observed erythropoietin-mediated cardiac injury.

Randomized controlled trials of ESA therapy studying normalization of Hb have failed to demonstrate any beneficial effect on cardiovascular outcomes or death. Instead, these trials have indicated some potential harmful effects (Singh 2006, Besarab 1998). On the basis of this evidence, the recommended Hb initiation level for ESA use in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines has been modified from 11 to <10 g/dL with the statement that it is no longer recommended to maintain Hb values above 11.5 g/dL (KDIGO 2012). The suggested target level by the European Renal Best Practice group is 10-12 g/dL and recommend not letting Hb fall below 10 g/dL (Locatelli 2013). In addition, the FDA and EMA recommend that ESA should be used at the lowest possible dose to control anemia and avoid blood transfusions; see Information for Healthcare Professional: Erythropoiesis Stimulating Agents (ESA) US FDA 2011.

Pre-clinically, IL-6 has been shown to affect the described derangements in iron handling (MacDougall 2005, Sun 2012), and clinically anti-IL-6 therapies improve anemia in non-renal inflammatory conditions. Specifically, anti-IL-6 therapies have been shown to reduce serum hepcidin and increase serum hemoglobin in Multicentric Castleman's Disease, Rheumatoid Arthritis, as well as advanced pulmonary malignancy (Song 2010, Song 2013, Bayliss 2011). In hemodialysis, the Sponsor's investigation (NCT02868229) has shown that neutralizing IL-6 increases iron availability and ESA sensitivity. Therefore, the Sponsor proposes that in the inflammatory milieu of CKD, anti-IL-6 therapy would release iron from tissue stores, enabling its availability to erythroid precursors, enhancing red blood cell production, and improving anemia independent of the need for exogenous ESA or iron administration. Given the strong, direct relationship between ESA dose and cardiovascular complications, as well as the risk of iron overload with chronic administration of IV iron, the Sponsor believes that Ziltivekimab would fulfill a clear, present and pervasive need in the treatment of anemia in the CKD setting.

1.1.4 Malnutrition-Inflammation-Cachexia Syndrome including hypoalbuminemia

Persistent inflammation in CKD is also one of the key players in the development of malnutrition/protein-energy wasting (PEW), which led to the description of the malnutrition-inflammation-cachexia syndrome (MICS) in CKD (Kalantar-Zadeh 2003, Kalantar-Zadeh 2005). Hypoalbuminemia is strongly associated with mortality in dialysis patients (Kalantar-

Zadeh 2005b) as well as non-dialysis dependent CKD, which when included as part of a "malnutrition inflammation score" with IL-6 and CRP strongly predicts 36-month mortality (Jagadeswaran 2018). Although historically hypoalbuminemia has been attributed to malnutrition, the recent lack of effect of oral nutritional supplementation on serum albumin strongly suggest that inflammation is the causal factor in hypoalbuminemia, especially when placed in the context of a direct link between IL-6 and hepatic albumin synthesis, and clinically, anti-IL-6 therapy can raise serum albumin in non-renal patients (Benner 2018, de Mutsert 2009, Ohsugi 2007). At this time, no therapy is indicated to improve hypoalbuminemia in patients with CKD.

1.2 Description of Ziltivekimab

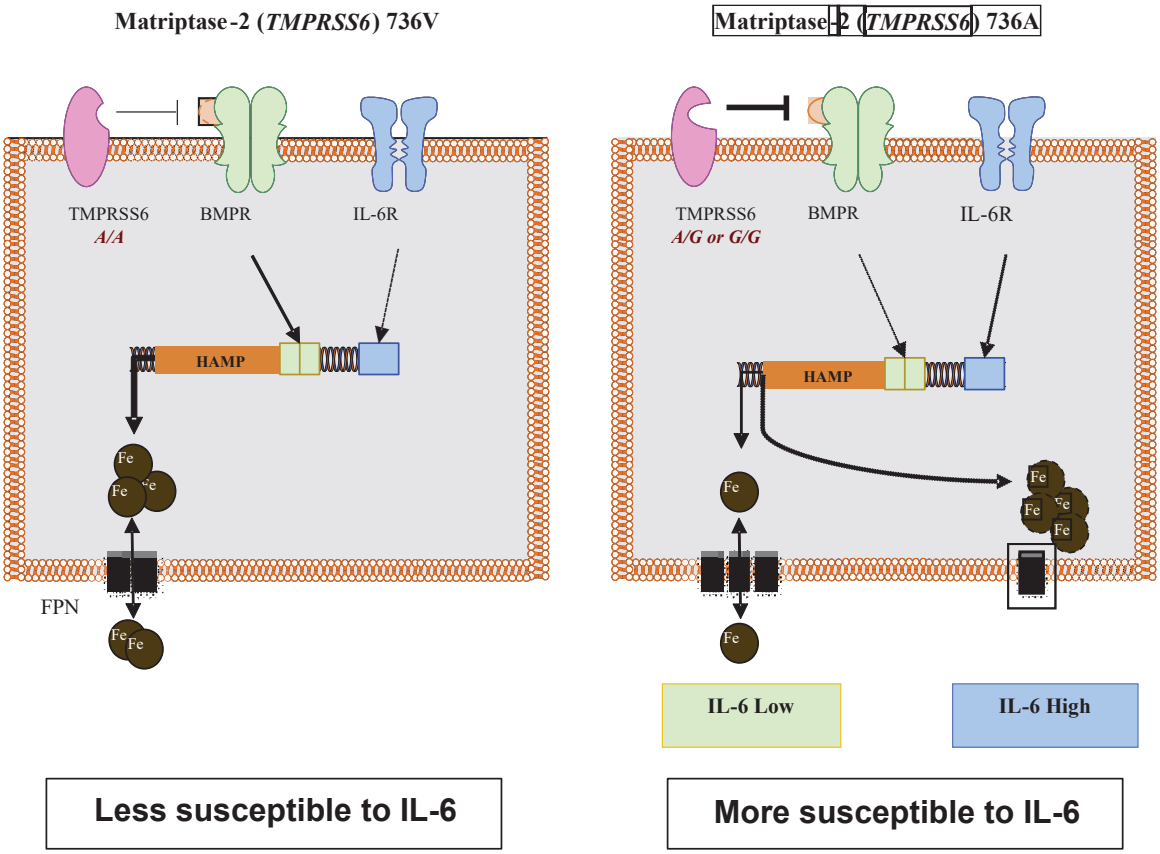
Ziltivekimab is an extended half-life anti-IL-6 antibody (human IgG1κ anti-human IL-6 monoclonal antibody) with three amino acid substitutions ("YTE") in the CH2 region of the Fc domain designed to decrease clearance, and thereby dosing frequency. Additional information about the mechanism and structure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

Alleviation of inflammatory anemia with anti-IL-6 therapy comes from published work regarding the use of said therapy in humans in non-renal inflammatory conditions. Tocilizumab (Roche) and clazakizumab (Alder Biopharmaceuticals) have both shown ability to raise hemoglobin in rheumatoid arthritis, Castleman's disease and advanced malignancy (Song 2010, Song et al 2013, Bayliss 2011). By example, the administration of tocilizumab (anti-IL-6 receptor antibody) reverses signs of inflammation, improves iron availability, and increases hemoglobin in Castleman's patients.

Although anti-IL-6 therapies have not been tested in dialysis patients to date, published and Sponsor's unpublished data in a large prevalent dialysis population documents a correlation between serum IL-6 levels and the degree of ESA hypo-responsiveness (i.e., erythropoietin dose requirement divided by achieved serum hemoglobin) (Won 2012 and see Section 2 of the Ziltivekimab IB).

However, the influence of IL-6 is not universal, and appears over-represented in a specific, genotypically defined subpopulation. Based on non-clinical study and retrospective review of dialysis populations (data on file), it appears a genotypic variation in the iron-control system of mammalian cells can render tissues more or less susceptible to IL-6 based inflammation and dictate the influence of this inflammation on clinical outcomes (Figure 2).

Figure 2 A model for the influence of genetic variation on IL-6 –mediated cellular iron handling



Matriptase-2 (TMPRSS6) = serine protease suppressor of HAMP (hepcidin gene) mRNA expression; 736V = normal allele; 736A = risk allele; BMPR = BMP receptor; IL-6R = IL-6 receptor; FPN = ferroportin; Fe = iron

1.3 Summary of Relevant Nonclinical Experience with Ziltivekimab

For information regarding nonclinical pharmacology, pharmacokinetics 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 Rheumatoid Arthritis Patients (D4430C00001)

This study was a Phase 1, double-blind, placebo-controlled single ascending dose study in rheumatoid arthritis patients (Study D4430C00001) which 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.

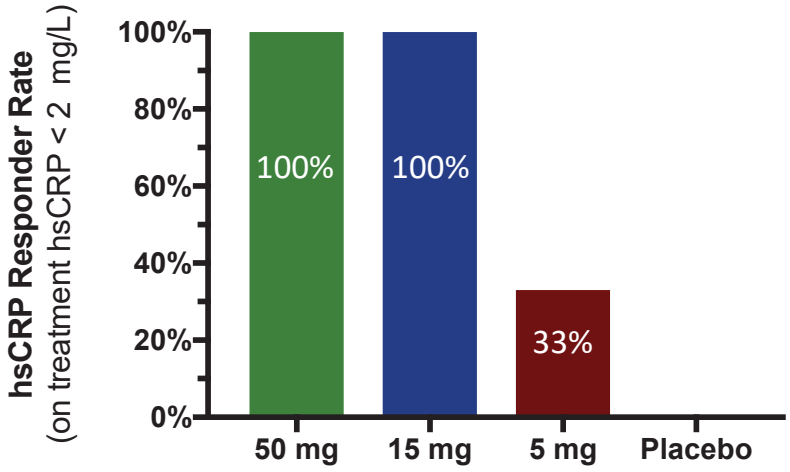
1.4.2 Phase 1 Study in Patients with CKD (COR-001-SC1)

This study was a Phase 1 Randomized, Double-Blind, Placebo-Controlled, Cohort Dose-Escalation Study in Patients with CKD to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of a Single Dose of Ziltivekimab. The study population had moderate-to-severe CKD (i.e., eGFR 20-60 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 (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 post dose in all patients. Ziltivekimab concentrations increased in a dose dependent manner. Terminal slopes (half-life) appeared similar for 5 and 15 mg doses, suggesting linear PK. High intersubject variability among the three 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 two 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 3 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 hsCRP levels was observed in the Ziltivekimab dose groups throughout the first eight weeks post randomization, while levels in the placebo group increased over time.

Figure 3 Percentage of CKD patients treated with Ziltivekimab or Placebo who achieved an hs-CRP level of < 2.0 mg/L from Baseline to Week 32



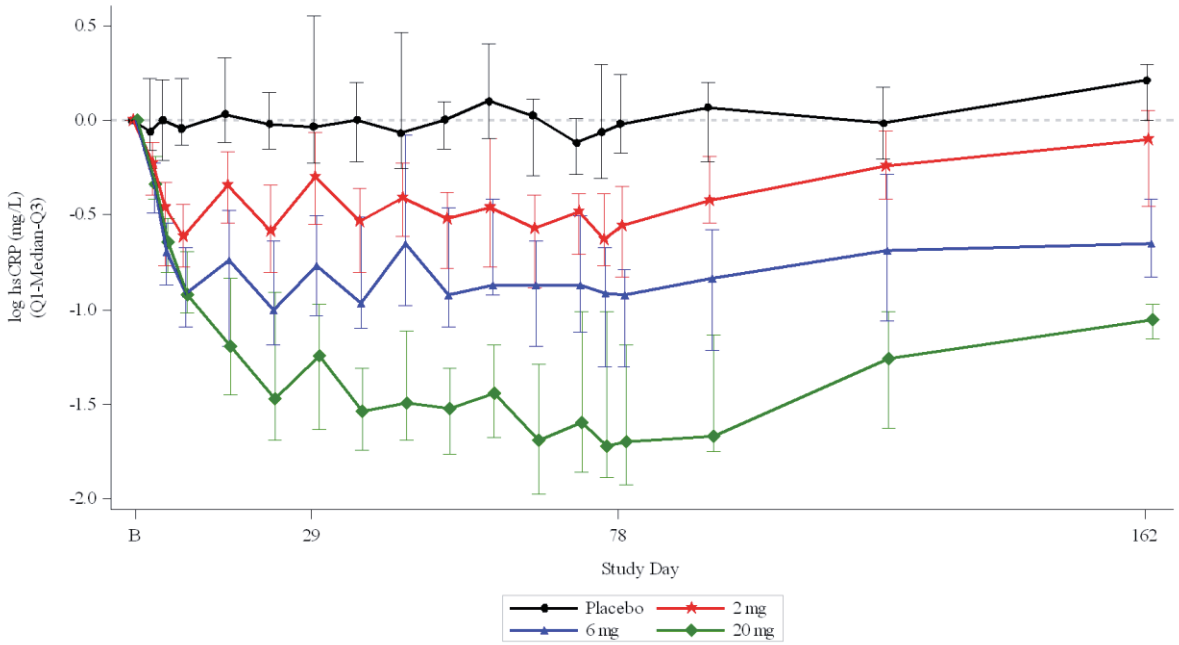
During the study, 33 AEs were reported by 12 subjects. The only adverse event reported by more than one subject (n=3) was upper respiratory tract infection. Other than one report of diarrhea, none of the other AEs were considered related to the study product. During the study, one subject on placebo reported an SAE (acute cardiac failure), there were no deaths and no subject discontinued the study as of February 01, 2018.

1.4.3 Phase 1/2 Study in CKD Patients 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, Pharmacokinetics, and Pharmacodynamics of Multiple IV Doses of Ziltivekimab. 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 may be found in the IB.

Figure 4 Ziltivekimab causes Dose-Dependent Decreases in hs-CRP from Baseline in ESRD Patients



Abbreviations: hs-CRP = high-sensitivity C-reactive protein; N = number of subjects
Note: Ziltivekimab (2 mg, 6 mg or 20 mg IV) Q2 weeks; Data from Pharmacodynamic Analysis Population.
Note: After checking the data normality, the parameter was shown as Median (Q1/Q3).
Source: Protocol No: COR-001-01 Final Analysis

There was a greater incidence of Treatment Emergent Adverse Events (TEAE) 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 one TEAE, and the two TEAEs that occurred at the highest incidence in the trial were reported in this treatment group (congestive cardiac failure and dyspnea which each occurred in 4 patients).

Serious adverse events (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 reporting a total 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 ([redacted]) and cardiac arrest ([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 Investigator Brochure.

1.4.4 Conclusions on Ziltivekimab Treatment of Anemia in CKD

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 anemia-associated CVD in the proposed patient population.

2 STUDY GOAL AND OBJECTIVES

Patients with NDD-CKD, who have evidence of systemic inflammation with increased cardiovascular risk, will be enrolled into this trial. The purpose of this trial is to determine a dose to select for a potential cardiovascular outcome trial with Ziltivekimab. The current trial will determine which dose of Ziltivekimab will have a significant reduction in hs-CRP with acceptable increases in LDL-C or triglycerides and without clinically meaningful reductions in neutrophils and platelet counts. Doses to be tested will be 7.5 mg, 15 mg and 30 mg subcutaneous monthly compared to placebo for six months.

2.1 Primary objective:

To evaluate the effects of Ziltivekimab compared to placebo on markers of inflammation (i.e. hs-CRP).

2.2 Secondary objectives:

To evaluate the effects of Ziltivekimab compared to placebo on markers of inflammation and cardiovascular risk: serum amyloid A (SAA) and fibrinogen.

2.3 Pharmacokinetic objectives:

To evaluate the pharmacokinetics (PK) and PK-Pharmacodynamic (PK-PD) modeling of Ziltivekimab following multiple doses at three different levels.

2.4 Safety objectives:

To evaluate the safety of three dose levels of Ziltivekimab compared to placebo.

2.5 Exploratory objectives:

To evaluate the effects of Ziltivekimab compared to placebo on markers of anemia (hemoglobin).

To evaluate the effects of Ziltivekimab compared to placebo on markers of inflammation-malnutrition (i.e. albumin).

To evaluate the effects of Ziltivekimab compared to placebo on markers of cardiovascular risk (i.e. N-terminal prohormone-B-type natriuretic peptide [NT-pro-BNP]).

To evaluate the effects of Ziltivekimab compared to placebo on additional markers of cardiovascular risk (suppression of tumorigenicity 2 [ST2]).

To evaluate the effects of Ziltivekimab compared to placebo on markers of atherosclerosis risk: LDL-C, triglycerides, ApoB, ApoA1, ApoB/ApoA1, lipid profile by nuclear magnetic resonance (NMR) spectroscopy, and Lp(a).

To evaluate the effects of Ziltivekimab compared to placebo on markers of kidney function, (i.e. cystatin C, estimated GFR) and kidney damage, (i.e. urine albumin-to-creatinine ratio [UACR]).

To determine Ziltivekimab trough drug levels following multiple Ziltivekimab doses at three different dose levels.

To evaluate the effects of three dose levels of Ziltivekimab compared to placebo on patient reported outcomes (PRO): Patient-Reported Outcomes Measurement Information System (PROMIS®) Fatigue 13a short form, selected items from the PROMIS fatigue item bank, the Optum SF-36 v2® Health Survey, a Corvidia PRO, the PROMIS interest in sexual activity item, the patient global impression of change (PGIC), patient global impression of severity (PGIS), and the EQ-5D-5L.

To evaluate the psychometric properties of the PROMIS Fatigue 13a short form and selected items from the PROMIS fatigue item bank, and the Corvidia electronic PRO (ePRO) items in CKD patients.

To evaluate the effects of Ziltivekimab on systemic iron availability: transferrin saturation (TSAT), reticulocyte hemoglobin content (CHr) and total iron binding capacity (TIBC), systemic iron stores (serum ferritin), serum iron and systemic iron regulation (serum hepcidin).

To evaluate the effects of Ziltivekimab compared to placebo on markers of cardiovascular risk (i.e. NT-pro-BNP) in patients with baseline NT-pro-BNP > 250 pg/mL.

To evaluate the effects of Ziltivekimab compared to placebo on markers of anemia in patients with baseline hemoglobin < 11 g/dL.

To evaluate the effects of Ziltivekimab compared to placebo on markers of inflammation-malnutrition (i.e. albumin) in patients with baseline albumin < 4.0 g/dL.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan: Description

This is a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy, safety, and pharmacokinetics of Ziltivekimab at three dose levels (7.5 mg, 15 mg or 30 mg) compared to placebo in patients with stage 3-5 CKD, not on dialysis, who have evidence of inflammation with high cardiovascular risk.

Patients will undergo a Screening Period of up to 14-days during which inclusion and exclusion criteria will be evaluated. Patients who meet all inclusion criteria and no exclusion criteria will be randomized to one of three Ziltivekimab dose levels (7.5 mg, 15 mg or 30 mg) or placebo for a 24-week Treatment Period. Patient randomization will be stratified by baseline hemoglobin (≥11 or <11 g/dL) and CKD stage (3, 4 or 5).

Approximately 240 patients will be randomized 1:1:1:1 (60 per group) into the trial. All patients must meet the inclusion/exclusion criteria. After the Screening Period, randomized patients will be dosed every 28 days out to Week 21. The primary, secondary and exploratory endpoints will be analyzed at 13 weeks of dosing and then followed for additional exploratory efficacy analyses through Week 24, and then selected efficacy endpoints and safety assessments will evaluated in the Follow-up Period Week 25 though Week 32 (Figure 5). The primary, secondary, and exploratory endpoint evaluation will take place at the end of Week 13, and the additional exploratory evaluations will take place at the End of Treatment (Weeks 23 and 24).

The patient will be randomized on Day 1 and the first dose of study drug should be administered after all assessments are conducted. Doses of study drug will be administered every 28-days for a total of 6 treatments (Weeks 1, 5, 9, 13, 17 and 21). Study visits will follow the schedule of events (Table 2).

3.1.1 Pharmacokinetic and PK-PD Modeling

- Serum trough levels (C_{min}) of Ziltivekimab will be measured at all visits. On dosing Week 1, 5, 9, 13, 17, and 21, trough PK samples to be collected within approximately -0.5 h pre-dose. Single PK blood samples will also be collected on Weeks 2, 4, 7, 23, 24/ET, 28, and 32/ET around the same time as the pre-dose samples were collected on previous dosing visits.
- The total IL-6 AUC will be described.
- The relationship between trough Ziltivekimab levels and primary pharmacodynamic endpoints, specifically total plasma IL-6 and hs-CRP, will be described.

3.1.2 Safety Endpoints

- Proportion of patients with AEs, SAEs, severe hematologic AEs, severe non-hematologic AEs, and AEs leading to discontinuation.
- Proportion of subjects with thrombolysis in myocardial infarction (TIMI) major bleeding event.
- Description and frequency of events of special interest by treatment group:
  - Serious infections.
  - Severe injection-related reactions.
  - Gastrointestinal perforations.
  - Hypersensitivity reaction during study drug administration.
  - Anaphylaxis occurring at any time, even if considered unrelated to the study drug. A CRF for the collection of the details of such reactions will be available in the electronic data capture (EDC) system.
  - Neutrophil <500/mm^3 (severe) or neutrophil <1000/mm^3 (severe) with evidence of concurrent infection. These events will be separately summarized by treatment group and dose.
  - Thrombocytopenia (platelet count <50,000/mm^3 [severe]) or platelet count <75,000/mm^3 (moderate) with evidence of concurrent TIMI major bleeding. These events will be separately summarized by treatment group and dose.
  - Malignancies
- Description of additional safety assessments by treatment group and dose: vital signs, electrocardiogram (ECG), clinical laboratory, and anti-drug antibodies (binding and neutralizing).

3.1.3 Pharmacodynamic Endpoints

3.1.3.1 Primary

- Difference in percent change in hs-CRP levels from Baseline (average of the hs-CRP value prior to randomization and Day 1) to Week 13 between each active group and placebo.

3.1.3.2 Secondary

All secondary and exploratory analyses will be performed with the Intent-to-Treat (ITT) population.

- Difference in change in SAA from Baseline to Week 13 between each active group and placebo.
- Difference in percent change in fibrinogen from Baseline to Week 13 between each active group and placebo.

3.1.3.3 Exploratory

- Difference in percent change in hs-CRP levels from Baseline to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in percent change in serum NT-pro-BNP from Baseline (average of the NT-pro-BNP value prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change in SAA from Baseline to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in percent change in fibrinogen from Baseline to End of Treatment (Week 24) between each active group and placebo.
- Difference in change in hemoglobin from Baseline (average of the two most recent hemoglobin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change in serum albumin from Baseline (average of the two most recent serum albumin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Proportion of patients achieving hs-CRP response at Week 13 and to End of Treatment (Weeks 23 through 24), defined as hs-CRP <2.0 mg/L in each active group and placebo.
- Difference in change in ST2 from Baseline to Week 13 and to End of Treatment (Week 24) between each active group and placebo.
- Difference in percent change in Lp(a) from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in percent change in LDL-C, triglycerides, ApoB, ApoA1, ApoB/ApoA1, and lipid profile by NMR spectroscopy from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of creatinine based eGFR and cystatin C-based eGFR from Baseline to Week 13 and to the End of Treatment (Weeks 23 through 24) between each active group and placebo.

- Difference in change of UACR from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of the total fatigue score (PROMIS Fatigue 13a short form and selected items from the PROMIS Fatigue item bank) from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of the PROMIS interest in sexual activity item from Baseline to Week 13 and to End of Treatment (Week 24) between each active group and placebo.
- Difference in change of the Corvidia ePRO items from Baseline to Week 12 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of the PGIS index from Baseline to Week 12 and to End of Treatment (Week 24) between each active group and placebo.
- Descriptive analyses of the PGIC index at Weeks 5, 13 and End of Treatment (Week 24) in each active group and placebo.
- Difference in change of the Optum SF-36 v2® Health Survey physical component summary (PCS), mental component summary (MCS) and domain scores from baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of the EQ-5D-5L index from Baseline to Week 12 and to End of Treatment (Week 24) between each active group and placebo.
- Evaluation of the psychometric properties of the PROMIS Fatigue 13a short form and selected items from the PROMIS Fatigue item bank and the Corvidia ePRO items in CKD patients – to be described in a PRO psychometric analysis plan.
- Descriptive analyses by dose and treatment may be conducted on samples stored for analysis of exploratory biomarkers, genomic and transcriptomic analysis.
- Difference in change in TSAT from Baseline to peak level, Week 13 and End of Treatment (Weeks 23 through 24), between each active group and placebo.
- Difference in change in CHr from Baseline to peak level, Week 13 and to End of Treatment (Week 24) between each active group and placebo.
- Difference in change in TIBC from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change in serum ferritin from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.

- Difference in change in serum iron from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change in serum hepcidin from Baseline to Week 13 and to End of Treatment (Week 24) between each active group and placebo.
- Difference in percent change in serum NT-pro-BNP from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo in patients with baseline NT-pro-BNP > 250 pg/mL.
- Difference in change in hemoglobin from Baseline (average of the two most recent hemoglobin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo in patients with baseline hemoglobin < 11 g/dL.
- Difference in change in serum albumin from Baseline (average of the two most recent serum albumin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo in patients with baseline albumin < 4.0 g/dL.

3.2 Study Schematic

Figure 5 Study Flow

Ziltivekimab Dose Level 1, 2 or 3 (N=180); N=60 in each level

Placebo (N=60)

	Screening		Treatment Period											Safety F/Up	
Visit Number	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11/ET**	**12**	**13/ET**
Visit Day Window	**-14**	**-7**	**1**	**8**	**22**	**29-35**	**43-49**	**57-63**	**85-91**	**113-119**	**141-147**	**155-161**	**162-168**	**190-196**	**218-224**
Visit Window		**±2**	**1**	**±2**	**±2**										
Visit Week	**-2**	**-1**	**1**	**2**	**4**	**5**	**7**	**9**	**13**	**17**	**21**	**23**	**24/ET**	**28**	**32/ET**

3.3 Blinding and Randomization

3.3.1 Randomization

Treatments will be assigned to randomized patients via an interactive web-response system (IWRS). Patients (N=240) will be randomized in 1:1:1:1 ratio to Ziltivekimab Dose #1 (7.5 mg), Ziltivekimab Dose #2 (15 mg), Ziltivekimab Dose #3 (30 mg) or matching Placebo, as they meet all entry criteria. Patients will be stratified by baseline hemoglobin (≥11 or <11 g/dL) and CKD stage (3, 4 or 5). Note that CKD stage is stratified into two categories: (1) stage 3 and (2) stages 4 or 5.

3.3.2 Blinding

This study is double-blind. The patients, investigators, site personnel, site monitors and Sponsor and the Contract Research Organization (CRO) clinical operational personnel will be blinded to the treatment assignment (see Section 12.2 for details). Ziltivekimab and matching placebo will be provided as a liquid for subcutaneous injection.

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

3.3.3 Unblinding

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.

3.4 Duration of the Study

The study will consist of three periods: Screening, Treatment Period, and Safety Follow-Up Period. The total study duration for an individual patient will be approximately 8-9 months. The study period durations are as follows:

Screening Period: up to 2 weeks [Days -14 to -1]

- Starts with the first date that Initial Screening procedures were performed. The first procedure also defines the initial screening visit date

Treatment Assessment Period: 24 weeks [Week 1, Day 1 through Week 24,]

- Starts with the first administration of study drug/randomization (Day 1)

Safety Follow-Up Period: 8 weeks [Weeks 25 through 32]

- Safety period starts 4-weeks after last treatment dose 6.

3.5 Discussion of Study Design, Including Choice of Control Arm

The study is a randomized, double-blind, placebo-controlled trial. Randomization and double-blinding are being used to minimize bias. The treatment duration (Weeks 1 through 24) was chosen as the shortest duration needed to evaluate the pharmacodynamic effect of said doses on the proposed inflammatory, hematologic and cardiovascular endpoints. Sample size calculations were performed for several pharmacodynamics endpoints and these are presented in Section 11.1.

3.5.1 Study Population and Control Arm

As there are currently no drugs approved for the treatment of functional iron deficiency and reduction of hs-CRP, there are no options for an active comparator.

The study is being conducted in the target population because the pharmacodynamic endpoints (inflammation, functional iron deficiency, and increased cardiovascular risk) cannot be evaluated in healthy volunteers.

3.5.2 Rationale for Dosing and Length of Safety Evaluation

Inhibition of free IL-6 greater than 90% is needed to achieve biologic effect, because growth factors and soluble cytokines in general are able to elicit signaling with receptor occupancies of less than 10%. A basic logarithmic dose escalation scheme was used after modeling of

IL-6 binding and the PK-PD (hs-CRP) relationship from the concluded Phase 1 trial in RA patients (Study D4430C00001). Based on the clearance of Ziltivekimab (dictated by the "YTE" Fc mutation), the duration of safety monitoring and follow-up for PK, IL-6, and antibody testing to 32 weeks is planned.

3.5.3 Rationale for the Efficacy Endpoints

The inflammatory pharmacodynamic endpoint of hs-CRP was chosen as the primary endpoint because it is a direct measure of IL-6 function (specifically hs-CRP genes are induced by IL-6). The inflammatory biomarker hs-CRP has been shown to be a strong component in the prediction of cardiovascular risk to an extent approximately equivalent to total and high-density cholesterol (HDL) levels. Further data support that hs-CRP levels while on statin therapy are a large predictor of cardiovascular risk to a similar extent to those seen with LDL (Ridker 2016). However, CRP has a short circulating half-life of approximately 19 hours in which the plasma concentration is largely impacted by the rate of production through the biochemical pathway. Thus, CRP has not previously been considered an adequate target for intervention.

The biochemical pathway of CRP production is downstream regulated by IL-6 expression which is itself regulated by the downstream expression of IL-1, specifically the inhibition of the IL-1β-producing NOD-like receptor family pyrin domain containing 3 inflammasome. Thus, hs-CRP levels can be considered downstream surrogate biomarkers of both IL-6 and IL-1 expression when evaluating compounds which regulate their specific respective actions. Inhibition of IL-6 or IL-1 expression for the ultimate outcome of a reduction in circulating hs-CRP levels has been undertaken in several recent clinical studies (Ridker 2016).

The secondary endpoints include evaluations of fibrinogen and serum amyloid A (SAA). Fibrinogen is an acute phase reactant and a mediator of coagulation and therefore a marker of cardiovascular risk and a predictor of future cardiovascular risk (Ridker 2012). The difference in percent change in fibrinogen will be evaluated from Baseline to Week 13 between each active group and placebo. SAA is another acute phase reactant that was selected as an additional secondary endpoint because it is persistently elevated in chronic inflammatory conditions and elevated levels predict cardiovascular risk in humans (Shridas 2019). The difference in change in SAA will be evaluated from Baseline to Week 13 between each active group and placebo.

The exploratory endpoints include evaluations of NT-pro-BNP, ST2, albumin and hemoglobin. Serum NT-pro-BNP is a marker of cardiovascular risk and a predictor of future cardiovascular risk. Percent change in serum NT-pro-BNP will be evaluated from Baseline to Week 13 and to End of Treatment between each active group and placebo. Suppression of

tumorigenecity 2 (ST2) is a prognostic marker for heart failure with preserved and reduced ejection fraction. ST2 is a member of the interleukin 1 receptor family, also known as interleukin 1 receptor-like 1 (IL1RL-1). High circulating level of ST2 is associated to increased cardiovascular disease mortality and markers of metabolic dysfunction in subjects with atherosclerotic disease.

Serum albumin was selected as an additional exploratory endpoint because it is also closely negatively correlated with inflammation in the CKD population and is therefore also being analyzed as a marker of inflammation. Changes in serum albumin will be evaluated from Baseline to Week 13 and to End of Treatment between each active group and placebo. Hemoglobin was selected as an exploratory endpoint because of its sensitivity to IL-6. Changes in hemoglobin will be evaluated from Baseline to Week 13 and to End of Treatment between each active group and placebo.

In the inflammatory state, through the direct action of IL-6 there is overproduction of "the master iron regulator" hepcidin, a protein which prohibits cellular iron transport via degradation of ferroportin, the only known iron export channel in humans. This elicits a functional iron blockade that leads to anemia. Changes in serum hepcidin will be evaluated from Baseline to Week 13 and to End of Treatment between each active group and placebo.

Additional hematologic pharmacodynamic endpoints chosen include TSAT, CHr, TIBC, iron, and ferritin. These endpoints are intended to evaluate the effects of reducing inflammation on functional iron deficiency anemia. It is hypothesized that CHr will increase as iron is released from tissue stores. TSAT is also expected to increase over time as more iron is mobilized, until iron is utilized for erythropoiesis (reflected in rising hemoglobin).

Supportive pharmacodynamic endpoints include LDL-C, triglycerides, ApoB, ApoB/A1, and Lp(a). Biomarkers for CKD will be evaluated including cystatin C, creatinine, and UACR.

Finally, inflammation is known to affect systemic symptoms, notably fatigue and skeletal muscle strength; assessments will be made for selected items from the PROMIS Fatigue and 13a short form, Optum SF-36 v2® Health Survey, Corvidia ePRO, PGIS, PGIC, and EQ-5D-5L.

3.5.4 Rationale for the Dose Regimens

The main goal of Ziltivekimab dosing in the planned Phase 1/2 CKD patient study is to attain and maintain serum Ziltivekimab concentrations sufficient for ≥90% IL-6 binding over the treatment period, with a secondary goal of reducing hs-CRP to below 2 mg/L while keeping the highest planned dose more than 20-fold below the no adverse effect level (NOAEL) observed in primates.

3.5.4.1 Pharmacokinetic modeling

To date, the Ziltivekimab clinical program is comprised of 2 studies, both of which are placebo-controlled ascending dose studies. In the first of these studies (Study COR-001-01), patients with ESRD were administered intravenous (IV) infusions of study drug every 2 weeks for a total of 6 doses. Ten patients per cohort were randomized in a 1:4 ratio to placebo or Ziltivekimab (2, 6, and 20 mg).

In the second study (Study COR-001-SC1), patients with CKD were administered single subcutaneous (SC) doses of study drug. Four patients per cohort were randomized in a 1:3 ratio to placebo or Ziltivekimab (5, 15, and 50 mg).

The PK parameters are generally consistent with those expected for a monoclonal antibody. Absolute bioavailability (F) of SC administered Ziltivekimab is 69%, and the mean time of occurrence for peak serum Ziltivekimab concentrations (t_{max}) after SC dosing ranged from 8 to 15 days, with an absorption half-life of 3 days. Terminal elimination half-lives ($t_{1/2,z}$) differed between the ESRD patients (mean $t_{1/2,z}$ ranging from 38 to 44 days) and CKD patients (mean $t_{1/2,z}$ ranging from 48 to 56 days). While these results suggest that the rate of Ziltivekimab elimination may increase with decreasing renal function, a prior observation in rheumatoid arthritis patients that Ziltivekimab clearance is much slower than the glomerular filtration rate implies that the apparent elimination rate difference is not due to renal function per se, but more likely other physiological changes that accompany decreased renal function.

3.5.4.2 Correspondence of proposed doses to those used in prior clinical studies

Based on the clinical PK for Ziltivekimab described above, especially the F of 69.3% for SC dosing, the correspondence of proposed SC doses can be derived. Table 1 provides a summary of the SC doses that would correspond to the Ziltivekimab doses used in prior studies. From this perspective, the proposed 7.5 and 15 mg q4w x 6 regimens are well within the range of exposures considered safe in the prior clinical study, and the proposed 30 mg q4w x 6 regimen is less than the exposure associated with adverse changes in laboratory parameters in the prior clinical study.

Table 1 Summary of IV doses used in Study COR-001-01 with SC doses that represent corresponding exposure

COR-001-01 Dose	IV Dosing q2w (mg)	IV Dosing q4w[a] (mg)	IV Dosing Cumulative Dose[b] (mg)	SC Dosing q4w[c] (mg)	SC Dosing Cumulative Dose[c] (mg)	SC Dosing Monthly Dose[d] (mg)
2 mg q2w x12	2	4	24	5.8	34.6	5.8
6 mg q2w x12	6	12	72	17.3	103.9	17.3
20 mg q2w x12	20	40	240	57.7	346.3	57.7

Abbreviations: IV, intravenous; SC, subcutaneous; q2w, every 2 weeks; q4w, every 4 weeks.

[a] Cumulative dose administered every 4 weeks, i.e., the total of 2 q2w doses given within a 4 week period.

[b] Cumulative dose over the duration of the study, i.e., the total of 12 q2w doses given during the study.

[c] Corresponding SC dose, assuming bioavailability (F) of 69.3%.

[d] Monthly SC dose for 6 monthly doses that corresponds to the SC cumulative dose, i.e., SC cumulative dose divided by 6.

3.5.4.3 Exposure for proposed doses relative to IL-6 binding

In the planned study, median trough serum Ziltivekimab concentrations for the 6th dose of 723, 1446, and 2892 ng/mL are expected to be attained with the proposed 7.5, 15, and 30 mg q4w doses, respectively. Those concentrations are sufficient to ensure >99% of plasma IL-6 would be bound (i.e., <1% free IL-6). It is reasonable to expect that this magnitude of IL-6 binding would be associated with perturbation of inflammatory processes.

3.5.4.4 Exposures for proposed doses relative to the exposures at NOAEL dose in the toxicology study

COR-001-02 will utilize SC doses of 7.5, 15, and 30 mg administered q4w for a total of 6 months. Based on the clinical PK for Ziltivekimab described above, exposures for the planned doses were estimated. Those exposures were then compared to those attained in a 26-week Good Laboratory Practice (GLP)-compliant toxicology study in cynomolgus monkeys (Study 20134998) to determine the safety factors for the planned clinical study doses.

For these planned doses, safety factors relative to the exposures at the NOAEL SC dose in the 26-week monkey study are at least 76-fold for the C_{max} after the 6th dose, and at least 118-fold for the cumulative $AUC_{0-\infty}$ for the 6 doses.

3.5.4.5 Exposures for proposed doses relative to the exposures associated with clinically meaningful PD changes in prior clinical studies

In the prior clinical studies, hs-CRP has been found to be a sensitive response to Ziltivekimab exposure, with clinically meaningful decreases even at the lowest doses tested. Decreases were attained soon after the first dose, and the decreases were more prolonged as the Ziltivekimab dose is increased. Therefore, it is reasonable to expect that clinically

meaningful hs-CRP reduction can be attained with the proposed SC 7.5, 15, and 30 mg q4w x 6 regimens.

3.6 Safety Plan and Monitoring

Please see the Guidance to Investigators section of the IB for a description of safety findings from other IL-6 monoclonal antibodies and guidance for clinical monitoring.

3.7 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 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 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 study allows an over 20-fold margin to NOAEL in the non-clinical toxicology program.

Available data for anti-IL6R (tocilizumab) and anti-IL6 (siltuximab) therapies suggest neutralization of IL-6 have acceptable safety and tolerability profiles 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 (Sakai 2015, Sanofi 2016). Gastrointestinal perforation has been associated with anti-IL-6 therapy, however data suggests proper exclusion criteria may mitigate these risks (Tanaka 2014).

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 ICF documenting their understanding of these risks and willingness to participate in the study.

4 SELECTION OF STUDY POPULATION AND CRITERIA FOR WITHDRAWAL

4.1 Inclusion Criteria

After signing an informed consent form approved by the Investigator's Institutional Review Board (IRB) or Independent Ethics Committee (IEC) to be eligible, potential study patients must meet all of the following criteria:

1) Age ≥18 years at the time of signing of the Informed Consent Form (ICF).
2) Stage 3-5 NDD-CKD, i.e. estimated glomerular filtration rate (eGFR) >10 and <60 mL/min/1.73 m^2 using the CKD-EPI Creatinine Equation (www.kidney.org/content/ckd-epi-creatinine-equation-2009).
3) Serum hs-CRP level ≥2.0 mg/L measured during the Screening Period. (Note: C-reactive protein may not be commonly measured in patients with CKD. Targeting patients with a history of advanced stage CKD, ASCVD, anemia, metabolic syndrome, diabetic retinopathy and diabetes for screening will help increase the chances of identifying patients with CRP ≥2.0)
4) The patient agrees to comply with the contraception and reproduction restrictions of the study (Appendix G):
   a) Women of childbearing potential must be using a method of contraception, that is "highly effective" (i.e., <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 (i.e., >40 mIU/mL) at Screening;
   c) Women of childbearing potential must have a documented negative pregnancy test result at Screening. Patients with elevated β-HCG levels believed to be due to end-stage renal disease may be enrolled if documented to not be pregnant;

      AND

   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.

4.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Laboratory Values

1. Absolute neutrophil count <2.0 x 10^9/L during screening.
2. Platelet count <120 x 10^9/L during screening.
3. Spot urine protein to creatinine ratio >4000 mg/g, or 4.0 g/g.
4. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5x ULN during screening.
5. Positive testing for tuberculosis (TB) during screening. Blood testing (e.g., QuantiFERON) is preferred but a purified protein derivative (PPD) skin test read within 48-72 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-1 (HIV-1) or HIV-2 infection by serology measured during screening.
7. Hepatitis B or C by serology (e.g. 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 SBP >160 mmHg or an average diastolic blood pressure (DBP) >100 mmHg during screening. Patients may be re-evaluated within 2 weeks, at the discretion of the investigator for this criterion if anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure being above these limits.
15. Planned coronary revascularization (PCI or CABG) or any other major surgical procedure.

16. Major cardiac surgical, non-cardiac surgical or major endoscopic procedure within the past 6 months prior to Randomization.
17. History of New York Heart Association Class IV congestive heart failure within 12-weeks prior to randomization.
18. Actively treated or active malignancy during the 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.
19. History of bone marrow or solid organ transplant or anticipated to receive an organ transplant during the time frame of the study.
20. Known allergy to the study drug or any of its ingredients.

Prior or Current Medications

21. Received any investigational drug within 30-days prior to screening visit.
22. Received a live vaccine product within 14 days of study drug administration (Day 1) or expect to receive live vaccine during the Treatment Period (receiving a live vaccine within 14 days prior to enrollment is allowed).
23. Treatment with a hypoxia-inducible factor (HIF) stabilizer (e.g., molidustat, roxadustat) or an erythropoietin-mimetic, e.g., erythropoietin alpha or beta, darbopoietin alpha, or continuous erythropoiesis receptor activator (CERA), within 6-weeks prior to randomization or during treatment period.
24. Expected to receive any investigational drug or any of the exclusionary drugs listed in Section 15.1 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 is (or equivalent) is permitted if dose has been stable for at least 4 weeks prior to screening, and no dose changes are planned during study participation.
26. Use of systemic antibiotics, systemic antivirals, or systemic antifungals during the screening period ("Systemic" is defined as oral or intravenous drugs that are absorbed into the circulation).
27. Requiring an indwelling catheter of any type.

General Exclusions

28. Currently breastfeeding.

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 Criteria for Discontinuation of Study Drug

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant shall remain in the study to be evaluated on all early termination and safety follow-up procedures per the Schedule of Assessments (SOA) in Section 5.3.9 and Section 5.6. Study drug may be prematurely discontinued for a number of reasons, including:

- An intercurrent illness at the discretion of the investigator;
- Any intolerable AE that cannot be ameliorated by appropriate medical intervention or that in the opinion of the Medical Monitor or Investigator would lead to undue risk if the patient were to continue on treatment;
- In the event of severe injection related reactions, anaphylaxis, or hypersensitivity (Section 8.2 and Section 4.5);
- If at any point during the study, ≥10% of subjects enrolled experience anaphylaxis, additional enrollment will stop in the study, and all patients in the study will discontinue receiving study drug (Section 8.2 and Section 4.4);
- Pregnancy;
- Organ transplantation or development of another indication for chronic immunosuppression;

Reasons for all withdrawals/discontinuations of Study Drug will be recorded, and the Medical Monitor should be informed of all such cases as they occur. Temporary discontinuation of study intervention and restarts may be performed per Section 4.5.

4.4 Anaphylaxis Study Stopping Rule

If at any point during the study ≥10% of participants experience an anaphylaxis 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, all randomized participants currently receiving study drug will immediately discontinue further study drug administration. The remaining study procedures and visits may be performed if deemed necessary by the Sponsor.

4.5 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 the participant 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.

4.6 Participant Discontinuation/Withdrawal from the Study

The following are descriptions of participant 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 participant may elect to withdraw consent to treatment at any time.
- Participants withdrawing their consent for all study procedures must be given the option to continue to give consent for passive follow-up (i.e., by means of chart review) for AEs.
- Participants discontinuing study drug treatment after receiving any amount of study drug should undergo all early termination and safety follow-up study procedures per the SOA (Section 5.3.9 and Section 5.6) unless the participant also explicitly withdraws consent for these procedures as mentioned above. The study drug has a long pharmacodynamic effect. Therefore, continued monitoring for pharmacodynamic effects and safety is prudent.

- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. Participation in the early termination and safety follow-up procedures will be evaluated on a case-by-case basis. If possible, participants should take part in the early termination and safety follow-up procedures in the SOA (Section 5.3.9 and Section 5.6).
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested. The investigator must document this in the site study records.

4.7 Lost-to-Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant 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 participant that it is important to adhere to the assigned visit schedule.
  - The site shall attempt to ascertain whether or not the participant wishes to and/or should continue in the study.
- Prior to a participant being deemed lost-to-follow-up, the investigator or designee must make every effort to regain contact with the participant. All attempts to regain contact with the participant must be recorded in the participant's medical record.

  If the participant continues to be unreachable, the participant will be considered to have withdrawn from the study.

4.8 Study Completion

Primary study completion is defined as the completion of the Week 24 visit, even if one or more interim visits or procedures was/were missed.

Completion of the Safety Follow-Up is defined by the completion of the Week 32 visit even if one or more interim visits or procedures was/were missed.

5 ENROLLMENT AND STUDY PROCEDURES

Table 2 presents the procedures and assessments at each of the scheduled visits. Details of each visit are provided in Section 5.1 through Section 5.6.

Table 2 SCHEDULE OF PROCEDURES

	Screening[1]		Treatment Period												Safety F/Up	
Visit Number	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**N/A**	**7**	**8**	**9**	**10**	**11/ET**	**12**	**13/ET**
Visit Day Window	**-14**	**-7**	**1**	**8**	**22**	**29-35**	**43-49**	**57-63**	**78-84**	**85-91**	**113-119**	**141-147**	**155-161**	**162-168**	**190-196**	**218-224**
Visit Window		**±2**		**±2**	**±2**											
Visit Week	**-2**	**-1**	**1**	**2**	**4**	**5**	**7**	**9**	**12**	**13**	**17**	**21**	**23**	**24/ET**	**28**	**32/ET**
ICF signed	X															
Medical History/Update		X	X													
Randomization			X													
Study drug administered (post-assessments)			X			X		X		X	X	X				
Concomitant and Prior Medications		X	X	X	X	X	X	X		X	X	X	X	X	X	X
Vital Signs[2]		X	X		X	X		X		X	X	X	X	X	X	X
BMI			X							X				X		
Hematology[3]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Lipids (fasting 8 hours)[4]		X	X							X			X	X	X	X
Chemistry[5]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Spot urine protein-creatinine ratio		X								X						
Urinalysis (including albumin) [6]			X							X			X	X		
Iron Indices[7]	X		X							X			X	X	X	X
Serum Hepcidin			X							X				X		
TMPRSS6 Genotype test	X															
Infectious Disease Screen[8]		X														
Special RBCs[9]			X							X				X	X	X
Screening (total) IL-6	X															
IL-6[10]			X		X	X		X		X	X	X	X	X	X	X
hs-CRP [11]	X		X		X	X		X		X	X	X	X	X	X	X
Serum Pregnancy, FSH [12]		X														
Ziltivekimab trough PK[13]			X	X	X	X	X	X		X	X	X	X	X	X	X
ADA[14]			X	X	X	X	X	X		X	X	X	X	X	X	X
12-lead ECG[15]		X												X		
CKD Biomarkers[16]		X	X							X			X	X		
NT-pro-BNP		X	X							X			X	X		
Lp(a), ApoB, ApoA1 (fasting 8 hours)[4]		X	X					X		X			X	X		

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Table 2 SCHEDULE OF PROCEDURES

	Screening[1]		Treatment Period												Safety F/Up	
Visit Number	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**N/A**	**7**	**8**	**9**	**10**	**11/ET**	**12**	**13/ET**
Visit Day Window	**-14**	**-7**	**1**	**8**	**22**	**29-35**	**43-49**	**57-63**	**78-84**	**85-91**	**113-119**	**141-147**	**155-161**	**162-168**	**190-196**	**218-224**
Visit Window		**±2**		**±2**	**±2**											
Visit Week	**-2**	**-1**	**1**	**2**	**4**	**5**	**7**	**9**	**12**	**13**	**17**	**21**	**23**	**24/ET**	**28**	**32/ET**
Lipid Profile by NMR spectroscopy (fasting 8 hours)[4]			X							X			X	X		
Cardiac Risk Biomarker[17]			X							X				X		
Storage samples for Exploratory Biomarkers and RNA Testing[18]		X								X				X		
DNA Testing (Stored Blood Samples)		X														
Limited Physical Examination[19]		X												X		
INR[20]			X	X	X	X	X	X		X	X	X	X	X		
Adverse Events			X	X	X	X	X	X		X	X	X	X	X	X	X
PROMIS® 13a and Fatigue Items[21]			X			X				X			X	X		
PROMIS® Sexual Interest Items[21]			X			X				X				X		
CARES (Corvidia ePRO)[22]		X			X				X				X	X		
PGIS[23]		X			X				X					X		
PGIC[24]						X				X				X		
Optum SF-36 v2®[25]			X			X				X			X	X		
EQ-5D-5L[26]			X			X				X				X		

ET = Early Termination; F/Up = Follow-up.

1. If a Screening laboratory (excluding hematology) result is outside inclusion criteria parameters screening may be extended up to one week to allow for retesting of lab test(s) that did not meet inclusion criteria.
2. 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 anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure). Whenever possible, vital signs will be obtained after at least 5 minutes resting in the supine position or, when necessary, in a semi-recumbent position. Vital signs will be done prior to ECG recordings.
3. Hematology: hemoglobin, hematocrit, reticulocyte count, red blood count (RBC) indices (e.g., mean corpuscular volume (MCV), red cell distribution width (RDW), platelets, white blood count (WBC), WBC differential.
4. Lipids and subfractions (fasting 8 hours): total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL), and triglycerides; Lp(a), ApoB, ApoA1.

5. Chemistry: sodium, potassium, chloride, bicarbonate (or CO2), calcium, phosphate, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN) creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, albumin, glucose and eGFR calculated by CKD-EPI Creatinine Equation (https://www.kidney.org/content/ckd-epi-creatinine-equation-2009).
6. At Weeks 1 and 24, a portion of urine will be stored frozen for future analysis.
7. Iron Indices: TSAT, ferritin, iron, total iron binding capacity (TIBC).
8. Infectious Disease Screen: HIV 1 and 2, Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis C antibody, mycobacterium tuberculosis test (e.g., QuantiFERON) is preferred, but a purified protein derivative (PPD) skin test read within 48-72 hours by a qualified healthcare professional can be performed. If the test comes back unable to perform analysis or indeterminate or confirmatory testing is required, the screening window is extended until central laboratory results are available. (https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm).
9. Special RBC: reticulocyte hemoglobin content (CHr).
10. IL-6: Interleukin-6. Pre-dose sampling.
11. hs-CRP: high-sensitivity C-reactive protein. Test can be repeated once prior to randomization visit. Results after screening will be blinded after the first dose.
12. Pregnancy: β-hCG; FSH: Follicle Stimulating Hormone.
13. On dosing Weeks 1, 5, 9, 13, 17, and 21, trough PK samples to be collected within approximately -0.5 h pre-dose. Single PK blood samples will also be collected on Weeks 2, 4, 7, 23, 24/ET, 28, and 32/ET around the same time as the pre-dose samples were collected on previous dosing visits.
14. On dosing weeks 1, 5, 9, 13, 17, and 21, ADA: Anti-drug antibodies specimens to be collected within approximately 0.5 h pre-dose.
15. Standard 12-lead ECG will be recorded in the supine position (or with the patient as flat as possible) after vital signs assessments. The ECG will be locally read by the Investigator.
16. Chronic Kidney Disease (CKD) Biomarkers: cystatin C and UACR.
17. Cardiac Risk marker: SSA, fibrinogen and ST2.
18. Exploratory storage samples will be two 5-ml tubes of plasma, two 5-ml tubes of serum, and two 5-mL tubes of whole blood (PBMC testing at Screening, Week 13 and Week 24).
19. Limited physical exam to include skin, oropharynx, lungs, heart, abdomen, extremities (including feet), and any areas suggested by symptoms, with particular attention to signs of infection. May be performed by a physician-investigator or mid-level provider. Record abnormal findings in the source documents.
20. INR performed by a local laboratory on Warfarin patients only.
21. PROMIS (Appendix B), to be done on subjects' device at the clinic PRIOR to dosing.
22. CARES Corvidia ePRO (Appendix D), 7 day at home assessment on subject's personal device; the questionnaire will be answered daily for 7 days prior to dose (Screening Day -7 to Day -1 prior to Dose 1 (Visit 1), Dose 2 (Visit 4), Dose 4 (Visit 7), and the last 2 weeks after Dose 6 (Visit 23-24).

    CARES: Daily recall

    (starts with Visit -1) = baseline average of the 7 consecutive assessments (Day -7 to Day -1) prior to Dose 1
    (starts with Visit 3) = end of month of Dose 1
    (no visit) = end of month of Dose 3
    (starts with Visit 10 and Visit 11) = starts 2 weeks after Dose 6
23. PGIS (Appendix E), to be done on subjects' device on the last day of CARES assessment.
24. PGIC (Appendix E), to be done on subjects' device at the clinic PRIOR to dosing.
25. Optum SF-36 v2® Health Survey (Appendix C), to be done on subjects' device at the clinic PRIOR to dosing.
26. EQ-5D-5L (Appendix F), to be done on subjects' device at the clinic PRIOR to dosing.

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After signing the ICF, patients should be registered into the electronic data capture system to obtain a patient identification number for the study.

5.1 Screening Visit Procedures (Up to 2 weeks, Days -14 to -7) – Initial Screening

Screening will be conducted in a stepwise manner. If a Screening laboratory result is outside inclusion criteria parameters screening may be extended up to one week to allow for retesting of lab test(s) that did not meet inclusion criteria.

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. The following will be performed according to Table 2.

- ICF signed
- Hematology
- Chemistry
- Iron Indices
- TMPRSS6 Genotype
- hs-CRP (may be repeated once up to randomization)
- Screening IL-6 (total)

5.2 Screening Visit Procedures (Week -1; Days -7 to -1) – Full Screening

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

The following list summarizes the procedures for Week -1. Please see Table 2 for full details.

- Medical History
- Concomitant and Prior Medications
- Vital Signs
- Hematology
- Lipids (fasting 8 hours)
- Chemistry

- Spot urine protein-creatinine ratio
- Infectious Disease Screen (If the test comes back unable to perform analysis or indeterminate or confirmatory testing is required, the screening window is extended until central laboratory results are available)
- Serum Pregnancy, FSH
- 12-lead ECG
- CKD Biomarkers
- NT-pro-BNP
- Lp(a), ApoB, ApoA1 (fasting 8 hours)
- Storage samples for Exploratory Biomarkers and RNA Testing (PBMC testing)
- DNA Testing – Stored Blood Samples
- Limited Physical Examination
- CARES Corvidia ePRO
- PGIS

The following sections summarize the procedures for the Treatment Period. Please see Table 2 for full details.

5.3 Treatment Period (Study Weeks 1 - 21)

Important: Study Visits during which Study Drug injections are required should be planned for the same day of the week so that Study Drug administration can occur on a schedule of every 28 days. See Section 6.1.1 for guidance on missed doses.

5.3.1 Visit 1, Week 1, Day 1 (Pre-Dose)

- Medical History (update if necessary)
- Randomization (may occur on Day -1 if needed)
- Concomitant and Prior Medications
- Vital Signs
- BMI
- Hematology
- Lipids (fasting 8 hours)

- Chemistry
- Urinalysis (including albumin); portion stored frozen
- Iron indices
- Serum hepcidin
- Special RBCs
- IL-6 (pre-dose)
- hs-CRP
- Ziltivekimab trough PK
- ADA (pre-dose)
- CKD Biomarkers
- NT-pro-BNP
- Lp(a), ApoB, ApoA1 (fasting 8 hours)
- Lipid profile by NMR spectroscopy (fasting 8 hours)
- Cardiac Biomarkers: SSA, fibrinogen and ST2
- Coagulation (INR): Patients on warfarin only
- Adverse Events
- PROMIS® 13a and Fatigue Items
- PROMIS® Sexual Interest Items
- Optum SF-36 v2® Health Survey
- EQ-5D-5L

5.3.2 Visit 1, Week 1, Day 1 (Dosing/Post-Dose)

Administration of the first dose of Study Drug will continue to define Study Day 1. Prepare the Study Drug prior to the anticipated time of administration (see Section 6.1.1 and Pharmacy Manual).

- Study Drug (after all assessments)

5.3.3 Visit 2, Week 2, Day 8

- Concomitant and Prior Medications
- Hematology
- Chemistry
- Ziltivekimab trough PK
- ADA
- Coagulation (INR): Patients on warfarin only
- Adverse Events

5.3.4 Visit 3, Week 4, Day 22

- Concomitant and Prior Medications
- Vital Signs
- Hematology
- Chemistry
- IL-6
- hs-CRP
- Ziltivekimab trough PK
- ADA (pre-dose)
- Coagulation (INR): Patients on warfarin only
- Adverse Events
- CARES Corvidia ePRO
- PGIS

5.3.5 Visit 4, Week 5

- Study drug administered (after all assessments)
- Concomitant and Prior Medications
- Vital Signs

- Hematology
- Chemistry
- IL-6 (pre-dose)
- hs-CRP
- Ziltivekimab trough PK
- ADA (pre-dose)
- Coagulation (INR): Patients on warfarin only
- Adverse events
- PROMIS® 13a and Fatigue Items
- PROMIS® Sexual Interest Items
- PGIC
- Optum SF-36 v2® Health Survey
- EQ-5D-5L

5.3.6 Visit 5, Week 7

- Concomitant and Prior Medications
- Hematology
- Chemistry
- Ziltivekimab trough PK
- ADA
- Coagulation (INR): Patients on warfarin only
- Adverse Events

5.3.7 Visits 6 through 9, Weeks 9 through 21

- Concomitant and Prior Medications (not Week 12)
- Vital Signs (not Week 12)
- BMI (Week 13 only)

- Hematology (not Week 12)
- Lipids (fasting 8 hours; Week 13 only)
- Chemistry (not Week 12)
- Spot urine protein-creatinine ratio (Week 13 only)
- Urinalysis (including albumin) (Week 13 only)
- Iron Indices (Week 13 only)
- Serum hepcidin (Week 13 only)
- Special RBCs (Week 13 only)
- IL-6 (pre-dose) (not Week 12)
- hs-CRP (not Week 12)
- Ziltivekimab trough PK (not Week 12)
- ADA (pre-dose) (not Week 12)
- CKD Biomarkers (Week 13 only)
- NT-pro-BNP (Week 13 only)
- Lp(a), ApoB, ApoA1 (fasting 8 hours; Weeks 9 and 13 only)
- Lipid profile by NMR spectroscopy (fasting 8 hours; Week 13 only)
- Cardiac Risk Biomarkers: SSA, fibrinogen and ST2 (Week 13 only)
- Storage samples for Exploratory Biomarkers and RNA Testing (Week 13 only)
- Coagulation (INR): Patients on warfarin only (not Week 12)
- Adverse Events (not Week 12)
- PROMIS® 13a and Fatigue Items (Week 13 only)
- PROMIS® Sexual Interest Items (Week 13 only)
- CARES Corvidia ePRO (Week 12 only)
- PGIS (Week 12 only)
- PGIC (Week 13 only)
- EQ-5D-5L (Week 13 only)
- Optum SF-36 v2 (Week 13 only)

5.3.8 Visits 6 through 9, Weeks 9 through Week 21 (Dosing/Post-Dose)

- Study Drug (after all assessments) (not Week 12)

5.3.9 Visit 10, Week 23 and Visit 11, Week 24/ET

- Concomitant and Prior Medications
- Vital Signs
- BMI (Week 24 only)
- Hematology
- Lipids (fasting 8 hours)
- Chemistry
- Urinalysis (including albumin); portion stored frozen at Week 24 only
- Iron Indices
- Serum hepcidin (Week 24 only)
- Special RBCs (Week 24 only)
- IL-6
- hs-CRP
- Ziltivekimab trough PK
- ADA
- 12-lead ECG (Week 24 only)
- CKD Biomarkers
- NT-pro-BNP
- Lp(a), ApoB, ApoA1 (fasting 8 hours)
- Lipid profile by NMR spectroscopy (fasting 8 hours)
- Cardiac Biomarker: SSA, fibrinogen and ST2 (Week 24 only)
- Storage samples for Exploratory Biomarkers and RNA Testing (Week 24 only)
- Limited Physical Examination (Week 24 only)

- Coagulation (INR): Patients on warfarin only
- Adverse Events
- PROMIS® 13a and Fatigue Items
- PROMIS® Sexual Interest Items (Week 24 only)
- CARES (Corvidia ePRO) [2 weeks after Week 21 (Dose 6) for 14 consecutive days]
- PGIS (Week 24 only)
- PGIC (Week 24 only)
- Optum SF-36 v2®
- EQ-5D-5L (Week 24 only)

5.4 Safety Follow-Up Visits 12 and 13 Procedures (Study Weeks 28 and 32)

- Concomitant and Prior Medications
- Vital Signs
- Hematology
- Lipids (fasting 8 hours)
- Chemistry
- Iron Indices
- Special RBCs
- IL-6
- hs-CRP
- Ziltivekimab trough PK
- ADA
- Adverse Events

5.5 Unscheduled Visit

Additional clinical visits may be scheduled at the Investigators' discretion in order to follow or evaluate AEs. The reason for a given unscheduled visit will be recorded.

The following must be performed at any unscheduled visit occurring prior to Week 32:

- Record adverse events
- Record any medication changes.

5.6 Early Termination Visit

There are two possible types of Early Termination visits:

Early Termination Visit 1 (ET-1): Randomized patients terminating from the study prematurely prior to Study Week 24 should undergo an Early Termination Visit during which Week 24 procedures are performed.

Early Termination Visit 2 (ET-2): Randomized patients terminating from the study prematurely after Study Week 24 visit, but before Week 32 should undergo an early termination visit during which Week 32 procedures are performed.

Criteria for discontinuation of Study Drug can be found in Section 4.3.

Patients may be withdrawn from the study for a number of reasons, including those outlined below:

- Patients withdrawing their consent for all study procedures. Patients must be given the option to continue to give consent for passive follow-up (i.e. by means of chart review) for adverse events through Study Week 21.
- Discontinuation of the study by the Sponsor.

6 DRUG SUPPLIES AND DOSING

6.1.1 Dosing and Administration

The dose of Ziltivekimab for subcutaneous (SC) injection must be prepared using aseptic techniques. Drug Product is presented as a single use vial and any unused portion must be discarded.

Ziltivekimab is supplied as a liquid for injection.

The rationale for the planned doses in the study is described in Section 3.5.4. Details on the dosing and administration are provided in Table 3, and the composition for Ziltivekimab for injection and amount per mL are provided in Table 4.

Personnel responsible for study drug preparation should have an appropriate background (i.e., physician, pharmacist, pharmacy technician, nurse, or other personnel approved by the Sponsor) and has been appropriately trained. Please see Pharmacy Manual for full details. The final required volume of Ziltivekimab is provided in Table 3.

Please see the Pharmacy Manual for instructions on preparing and administering the Study Drug and storage of prepared Study Drug.

Special Situations

Patients who miss a dose of Study Drug may receive the missed Study Drug up to 15 days later.

If the missed dose cannot be administered within this time frame, the dose should be considered “missed” and the next dose administered at the next study visit as planned.

In the above special situations, please ensure that blood testing and PK sampling that is timed with the administered dose must be adhered to.

Table 3 Planned Ziltivekimab Doses and Administered Volumes

	Dose Cohort 1	Dose Cohort 2	Dose Cohort 3	Dose Cohort 4
Intervention Name	Ziltivekimab	Ziltivekimab	Ziltivekimab	PBO
Type	Active Drug	Active Drug	Active Drug	Comparator
Dose	7.5 mg	15 mg	30 mg	N/A
Dose Administration	7.5 mg in 1 mL injection	15 mg in 1 mL injection	30 mg in 1 mL injection	1 mL PBO injections\
Route of Administration	SC injections	SC injections	SC injections	SC injections
Frequency	Every 28 days per SOA	Every 28 days per SOA	Every 28 days per SOA	Every 28 days per SOA

Abbreviations: PBO = placebo; SC = subcutaneous; SOA = schedule of activities

The date and time of administration of Study Drug must be recorded in the appropriate sections of the CRFs.

6.1.2 Storage

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

6.1.3 Formulation and Packaging

Table 4 Composition for Ziltivekimab for Injection, Amount per mL (7.5 mg/Vial, 15 mg/Vial, 30 mg/Vial, and Placebo)

Component	Amount per mL (7.5 mg vial)	Amount per mL (15 mg vial)	Amount per mL (30 mg vial)	Amount per mL (Placebo vial)
Ziltivekimab	7.5 mg	15 mg	30 mg	0 mg
Trehalose dihydrate	50.00 mg	50.00 mg	50.00 mg	50.00 mg
L-Arginine monohydrochloride	14.75 mg	14.75 mg	14.75 mg	14.75 mg
L-Methionine	1.49 mg	1.49 mg	1.49 mg	1.49 mg
L-Histidine	1.55 mg	1.55 mg	1.55 mg	1.55 mg
L-Histidine mono-hydrochloride monohydrate	2.10 mg	2.10 mg	2.10 mg	2.10 mg
Polysorbate 80	0.70 mg	0.70 mg	0.70 mg	0.70 mg
Water for Injection	q.s. to 1.0 mL	q.s. to 1.0 mL	q.s. to 1.0 mL	q.s. to 1.0 mL

Abbreviations: q.s. = quantum satis

6.2 Drug Accountability and Compliance

The dispensing pharmacist or designated qualified individual will write the date dispensed, dose dispensed, and the patient's identification number, and initials 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 Therapeutics. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to Corvidia Therapeutics. All records will be retained as noted in Section 13.5.

7 PRIOR AND CONCOMITANT MEDICATIONS AND TREATMENTS

7.1 Prior Medications and Treatments

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

7.2 Concomitant Medications and Treatments

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

Systemic immunosuppressive drugs (i.e., such as cyclosporine, tacrolimus, sirolimus, mycophenolate, oral and intravenous glucocorticoids other than prednisone [or equivalent] up to a dose of 5 mg per day) may not be prescribed at any time during Study. Topical use (e.g., 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 (e.g., less than 5 consecutive days) for managing acute illnesses is also not restricted.

Narrow therapeutic window medications that are influenced by CYP enzymatic pathways (See list in Appendix A) may not be prescribed at any time during Study.

- Warfarin is permitted, but the INR must be monitored closely and, at minimum, according to the protocol Schedule of Events (see Table 2).

8 MANAGEMENT OF SPECIFIC ADVERSE EVENTS

8.1 Serious Infections

Study drug treatments should be withheld if patients experience a serious infection until the infection is believed to have completely resolved. The Investigator should contact the Medical Monitor to discuss whether the patient should return to Study Drug treatment.

8.2 Injection-Related Reactions, Hypersensitivity, and Anaphylaxis

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:

- 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 during prior Study Drug administrations, antihistamines and/or acetaminophen may be administered prophylactically prior to subsequent injections, at the discretion of the Investigator.
- In patients who experience severe injection-related reactions, anaphylaxis, or hypersensitivity (see definition and grading below):
- 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
- Obtain a blood sample for the presence of anti-drug antibodies

The patient should remain in the study for continued follow-up, but should receive no further Study Drug.

9 ADVERSE EVENT REPORTING

9.1 Adverse Event Definitions

An AE is any undesirable event or any untoward medical occurrence that occurs to 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 [e.g., an increase in severity or frequency of pre-existing abnormality or disorder]);
- All reactions from Study Drug, abuse of drug, withdrawal phenomena, sensitivity or toxicity to Study Drug;
- Apparently unrelated illnesses;
- Injuries or accidents (e.g., 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, physiological testing or physical examination;
- Abnormal laboratory findings considered by the Investigator to be clinically significant. In general, an abnormal laboratory value should not be recorded as an adverse event unless:
    - It is associated with clinical signs or symptoms,
    - Requires an intervention, results in a serious adverse event, or
    - 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 (e.g., "increased white blood cell count"). When recording an adverse event resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

9.2 Serious Adverse Event Definition

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, (i.e., 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 for 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 (e.g., 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;
- 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 myocardial infarction); 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 adverse event 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.

9.3 Adverse Events of Special Interest

The following adverse events of special interest must be reported to the Sponsor within 24 hours of the Investigator's awareness, even if not meeting the definition of a serious adverse event:

- Serious infections.
- Severe injection-related reactions.
- Gastrointestinal perforations.
- Hypersensitivity reaction during study drug administration.
- Anaphylaxis occurring at any time, even if considered unrelated to the study drug. A CRF for the collection of the details of such reactions will be available in the EDC.
- Neutrophil <500/mm^3 (severe), or neutrophil <1000/mm^3 (severe) with evidence of concurrent infection. These events will be separately summarized by treatment group and dose.
- Thrombocytopenia (platelet count <50,000/mm^3 (severe)) or platelet count <75,000/mm^3 (moderate) with evidence of concurrent TIMI major bleeding. These events will be separately summarized by treatment group and dose.
- Malignancies
- Description of additional safety assessments by treatment group and dose: vital signs, ECG, clinical laboratory, and anti-drug antibodies (binding and neutralizing).

9.4 Assessment of Causal Relationship

The causal association of AEs to Study Drug administration should be determined as follows:

The following categories should be used in the causality assessment of suspected adverse reactions:

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.

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 Probable, Possible, or Unlikely.

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

9.5 Assessment of Severity

The Investigator must determine the severity of the event or laboratory value according to Table 5 (refer to laboratory manual for guidance); severity describes the intensity of the adverse event or lab value.

Table 5 Severity Assessment for AEs and Abnormal Laboratory Values

Mild	Awareness of sign or symptom, but easily tolerated; lab value mildly outside normal reference range but not clinically significant
Moderate	Discomfort enough to cause interference with normal daily activities; lab value moderately outside normal reference range and clinically significant
Severe	Inability to perform normal daily activities; lab value severely outside normal reference range and clinically significant

9.6 Adverse Event Reporting

The AE reporting period starts with randomization and continues through the Week 32 study visit. 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 CRF. 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 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 CRF.

9.7 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] by completing the SAE Form in the EDC system. Any pertinent source documents 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 by the Investigator when any additional relevant information about the event becomes known to the Investigator, or as requested by [redacted] or Corvidia Therapeutics.

SAE and Pregnancy Reporting Contact Information

[redacted]
Telephone: [redacted]
Facsimile: [redacted]
e-mail: [redacted]

Hypersensitivity reactions (see Section 8.2) occurring during the Study Drug injection and anaphylaxis occurring anytime during Weeks 1 – 21 of the study should be reported in the EDC as adverse or serious adverse events on the AE and SAE CRFs within 24 hours of the site's awareness of the event. Please submit as much information as is available with the initial report.

Corvidia Therapeutics 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 Investigator's Brochure.

9.8 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 a Pregnancy Form and faxing or emailing it to [redacted] (see Section 9.7). 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 the abnormal fetal outcome on an SAE form.

10 STUDY ASSESSMENTS

10.1 Pharmacodynamic Assessments

10.1.1 CKD symptoms, Fatigue, and Health-Related Quality of Life

CKD symptoms, fatigue, and health-related quality of life will be assessed with the PROMIS Fatigue 13a short form and selected items from the PROMIS fatigue item bank (Appendix B), Optum SF-36 v2® Health Survey PCS, MCS, and domain scores (Appendix C), PROMIS interest in sexual activity item (Appendix B), the Corvidia ePRO (Appendix D), the patient global impression of severity (PGIS) and the patient global impression of change (PGIC) (Appendix E), and the EQ-5D-5L (Appendix F).

10.1.2 Laboratory Assessments

Evaluation of hs-CRP and hemoglobin are direct measure of IL-6 function. Serum albumin is also closely negatively correlated with inflammation. Key hematologic and iron metabolism assessments include Chr, TSAT, TIBC, ferritin, serum iron, and hepcidin.

Biomarkers of inflammation and cardiovascular risk include serum SSA, fibrinogen, NT-pro-BNP and ST2, which were chosen based on the documented detrimental effects of IL-6, and beneficial effects of anti-IL-6 therapies, on inflammation and on cardiac structure and function.

Biomarkers for CKD will be evaluated including cystatin C, creatinine, and urine albumin-to-creatinine ratio (UACR).

10.2 Safety Assessments (other than Adverse Events)

10.2.1 Vital Signs

Vital signs include temperature, respiratory rate, heart rate, and blood pressure. Whenever possible, vital signs will be obtained after at least 5 minutes resting in the supine position or, when necessary, in a semi-recumbent position. Vital signs will be done prior to ECG recordings.

10.2.2 12-lead ECG

At specified time points, standard 12-lead ECG will be recorded in the supine position (or with the patient as flat as possible) after vital signs assessments. The ECG will be locally read by the Investigator.

10.2.3 Physical Examination

Scheduled (limited) physical exams must include at a minimum an examination of the skin, oropharynx, lungs, heart, abdomen, extremities (including feet), and any areas suggested by symptoms, with particular attention to signs of infection.

10.2.4 Clinical Laboratory Testing

Details on the collection, processing, storage, and shipment of central lab samples are contained in the Laboratory Manual. Coagulation: INR (only for patients on warfarin) will be performed at the Local Laboratory.

11 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

The study design and objectives are described in Sections 2.0 and 3.0, respectively. Details of all planned analyses are provided in the Statistical Analysis Plan (SAP).

11.1 Sample Size

The primary efficacy endpoint is percent change from baseline in hs-CRP (average of the hs-CRP value prior to randomization and Day 1) to Week 13 between each active group and placebo. Based on the observed treatment difference in percent change from baseline in hs-CRP of -60.74% between combined COR-001-01 active groups 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 54 per group yields more than 99% power with 2-sided alpha=0.05. Taking into consideration the dropout rate of 10% by the end of the study, a sample size of 60 per group is planned for this study

Approximately 240 patients (60 per group) will be randomized.

11.2 Randomization

Approximately 240 patients will be randomized 1:1:1:1 to Ziltivekimab Dose #1 (7.5 mg), Ziltivekimab Dose #2 (15 mg) or Ziltivekimab Dose #3 (30 mg) or Placebo as they became eligible to proceed with dosing on Day 1. Patient randomization will be stratified by baseline hemoglobin (≥11 or <11 g/dL) and CKD stage (3, 4 or 5). Approximately 240 patients will be randomized 1:1:1:1 (60 per group) into the trial.

11.3 General Statistical Considerations and Definitions

11.3.1 General 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, quartiles (Q1 and Q3), minimum (min) and maximum (max) values. Analysis of categorical variables will include frequency and percentage.

11.3.2 Analysis Populations

Intent-to-Treat (ITT) analysis population: all patients randomized.

The ITT analysis populations will be the primary population for the analyses of disposition and baseline data and efficacy endpoints.

Per-Protocol analysis population: all patients randomized who completed the study and did not incur a significant protocol violation

For the ITT analysis populations and per-protocol populations, treatment classification will be based on the randomized treatment.

Pharmacokinetics (PK) analysis population: all patients randomized and who received at least one dose of Test or Reference product and who had at least one post-dose PK blood sample

Safety analysis population: all patients randomized and who received at least one dose of Test or Reference product.

For the PK analysis population and safety population, treatment classification will be based on the treatment actually received.

11.3.3 Analysis Windows and Baseline

If data are collected by visit, the data will be analyzed by visit based on the protocol-planned visits. If multiple records are collected for a visit, the latest record will be used for the summary for that visit.

The observational period for the study will start from informed consent and end with study completion (see Section 4.4 for the definition of study completion). Any event occurring after the defined observational period, even if collected on the CRF, may not be included in the planned statistical analysis. However, all data, including that reported after the defined observational period, will be included in the patient data listings.

For evaluations that are collected at multiple occasions prior to initiation of Study Drug, the latest evaluation will be considered the "Baseline" evaluation for analysis, unless otherwise specified.

11.3.4 Missing Data Handling

Unless otherwise specified, missing data will not be imputed and the analyses will be based on observed data only.

11.4 Statistical Analyses

11.4.1 Demographic and Background Characteristics

Patient demographics and baseline characteristics will be summarized by treatment group using the ITT, per-protocol, and safety populations

11.4.2 Study Drug and Concomitant Medications

Summaries of prior (pre-baseline) medications and concomitant (baseline or later) medications will be provided by treatment group using the safety population. Prior medications are defined as medications given before the first dose of study drug. Concomitant medications are defined as medications taken before and continuing after first

dose of study drug or initiated after first dose of study drug. Medications will be coded with World Health Organization (WHO) Drug Dictionary. Patients will be counted only once by medication class or name.

11.4.3 Efficacy Analysis

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

A mixed model for repeated measures (MMRM) will be used to evaluate change or percent change from baseline. The model will include variables for baseline hemoglobin ($\geq$ 11 or $<$ 11 g/dL), CKD Stage (3, 4 or 5), treatment group, visit and treatment group-by-visit interaction as categorical fixed effects, baseline value and baseline-by-visit interaction will be included as covariates. The least squares means for each dose, the least squares mean differences from placebo along with the associated 95% confidence intervals (CIs) and p-values will be presented. If the normality assumption is not met, a nonparametric test will be selected for efficacy analysis. Details of normality test and nonparametric test will be provided in the Statistical Analysis Plan.

An unstructured covariance matrix will be used to model the within-subject correlation. The Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. The analysis will be performed based on all observed post-baseline scores without any imputation of missing data. In the case when the MMRM fails to converge using an unstructured covariance matrix in any stage, a less stringent covariance matrix (e.g., autoregressive 1) will be used.

Sensitivity analyses will be conducted to explore the robustness of the result for primary efficacy endpoint based on MMRM. Full details will be pre-specified in SAP and documented prior to database lock of the study.

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

11.4.4 Efficacy Variables

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

11.4.4.1 Primary

- Difference in percent change in hs-CRP levels from Baseline (average of the hs-CRP value prior to randomization and Day 1) to Week 13 between each active group and placebo.

11.4.4.2 Secondary

- Difference in change in SAA from Baseline to Week 13 between each active group and placebo.
- Difference in percent change in fibrinogen from Baseline to Week 13 between each active group and placebo.

11.4.4.3 Exploratory

- Difference in percent change in hs-CRP levels from Baseline to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in percent change in serum NT-pro-BNP from Baseline (average of the NT-pro-BNP value prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change in SAA from Baseline to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in percent change in fibrinogen from Baseline to End of Treatment (Week 24) between each active group and placebo.
- Difference in change in hemoglobin from Baseline (average of the two most recent hemoglobin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change in serum albumin from Baseline (average of the two most recent serum albumin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Proportion of patients achieving hs-CRP response at Week 13 and to End of Treatment (Weeks 23 through 24), defined as hs-CRP <2.0 mg/L in each active group and placebo.
- Difference in change in ST2 from Baseline to Week 13 and to End of Treatment (Week 24) between each active group and placebo.
- Difference in percent change in Lp(a) from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.

- Difference in percent change in LDL-C, triglycerides, ApoB, ApoA1, ApoB/ApoA1, and lipid profile by NMR spectroscopy from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of creatinine based eGFR and cystatin C-based eGFR from Baseline to Week 13 and to the End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of UACR from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of the total fatigue score (PROMIS Fatigue 13a short form and selected items from the PROMIS Fatigue item bank) from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of the PROMIS interest in sexual activity item from Baseline to Week 13 and to End of Treatment (Week 24) between each active group and placebo.
- Difference in change of the Corvidia ePRO items from Baseline to Week 12 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of the PGIS index from Baseline to Week 12 and to End of Treatment (Week 24) between each active group and placebo.
- Descriptive analyses of the PGIC index at Weeks 5, 13 and End of Treatment (Week 24) in each active group and placebo.
- Difference in change of the Optum SF-36 v2® Health Survey physical component summary (PCS), mental component summary (MCS) and domain scores from baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change of the EQ-5D-5L index from Baseline to Week 12 and to End of Treatment (Week 24) between each active group and placebo.
- Evaluation of the psychometric properties of the PROMIS Fatigue 13a short form and selected items from the PROMIS Fatigue item bank and the Corvidia ePRO items in CKD patients – to be described in a PRO psychometric analysis plan.
- Descriptive analyses by dose and treatment may be conducted on samples stored for analysis of exploratory biomarkers, genomic and transcriptomic analysis.
- Difference in change in TSAT from Baseline to peak level, Week 13 and End of Treatment (Weeks 23 through 24), between each active group and placebo.

- Difference in change in CHr from Baseline to peak level, Week 13 and to End of Treatment (Week 24) between each active group and placebo.
- Difference in change in TIBC from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change in serum ferritin from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change in serum iron from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo.
- Difference in change in serum hepcidin from Baseline to Week 13 and to End of Treatment (Week 24) between each active group and placebo.
- Difference in percent change in serum NT-pro-BNP from Baseline to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo in patients with baseline NT-pro-BNP > 250 pg/mL.
- Difference in change in hemoglobin from Baseline (average of the two most recent hemoglobin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo in patients with baseline hemoglobin < 11 g/dL.
- Difference in change in serum albumin from Baseline (average of the two most recent serum albumin values prior to randomization and Day 1) to Week 13 and to End of Treatment (Weeks 23 through 24) between each active group and placebo in patients with baseline albumin < 4.0 g/dL.

For the above efficacy variables, the observed values, changes from baseline, or percent changes from baseline (as applicable) will be summarized by treatment group using descriptive statistics using ITT.

The PROMIS Fatigue 13a short form contains 13 items that assess symptoms and impacts of fatigue (Appendix B). The total score of the PROMIS Fatigue 13a short form and selected items from the PROMIS fatigue item bank will be calculated as a raw score based on the average of the items. The observed value and change from baseline in total fatigue score will be summarized by treatment at each visit.

The PROMIS Sexual Function and Satisfaction (PROMIS SexFS) is a customizable self-reported set of measures that include 79 items in 11 domains, for the purpose of this protocol we are only using 1 item: interest in sexual activity, lubrication, vaginal discomfort, erectile function, global satisfaction with sex life, orgasm, anal discomfort, therapeutic aids, sexual activities, interfering factors, and screener questions. The PROMIS evaluations are to be

done on subjects' device at the clinic PRIOR to dosing. The observed value and the change from baseline will be summarized by treatment at each visit.

The Optum SF-36 v2® Health Survey is perhaps the most widely used health-related quality of life (HRQoL) survey instrument in the world today (Hays 2001). It is comprised of 36 items that assess eight health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions (Appendix C). Physical and mental health summary scores are also derived from the eight Optum SF-36 scales. The PCS, MCS, and domain scores will only be analyzed descriptively. The observed value and change from baseline in total Optum SF-36 v2® Health Survey score will be summarized by treatment. The Optum evaluations are to be done on subjects' device at the clinic PRIOR to dosing.

The CARES Corvidia ePRO is a new PRO instrument under development (Appendix D). It consists of 19 symptom items, with a 24-hour recall, asking patients to report their worst level of that symptom in the past 24 hours on a numeric rating scale from 0 (no symptom) to 10 (symptom as bad as I can imagine).

Data will be collected at home on subject's personal device or one provided by Corvidia; the questionnaire will be answered daily for 7 days prior to dose (Screening Day -7 to Day -1 prior to Dose 1 (Visit 1), Dose 2 (Visit 4), Dose 4 (Visit 7), and the last 2 weeks after Dose 6 (Visit 23-24). For each item, weekly scores will be derived as the average of the 7 consecutive daily scores as follows:

Baseline = average of Day -7 to Day -1

Visit 4 = average of Day 22 to Day 28

Visit 7 = average of Day 78 to Day 84

If more than 4 daily scores out of the 7 days (>50%) within the weekly period are missing, then the score is set to missing.

A bi-weekly score (the End of Treatment) will also be derived as the average of Day 155 to Day 168. If more than 8 daily scores out of the 14 days (>50%) within the bi-weekly period are missing, then the score is set to missing.

Psychometric analyses will be conducted using the trial data to assess the psychometric properties of the CARES Corvidia ePRO instrument. The structural validity of CARES Corvidia ePRO instrument will be evaluated by means of exploratory factor analysis. A total summary scale or set of scales will be proposed in light of the factor loadings as well as clinical and conceptual considerations. Additional details will be described in the PAP. The score(s) developed as psychometrically sound will be used to evaluate efficacy.

Summary measures of compliance at each analysis visit will be derived among those patients who are expected to have PRO assessments. The completion rate will be defined as the total number of actual completed diary entries divided by the expected number of diary entries in a given time period (total number of days X number of expected patients).

The observed value and change from baseline on the developed scores will be summarized by treatment at each analysis visit.

The Patients' Global Impression of Change (PGIC) scale and the Patients' Global Impression of Severity (PGIS) scale represent clinically relevant tools to assess perceived impact of disease management. The PGIC evaluates overall health status as perceived by the patient in a seven-point, single-item scale ranging from 'very much worse' to ‘no changes’ to 'very much improved’. The PGIS is a 5-point scale (from no symptoms to very severe symptoms) and patients are asked to rate their overall severity of symptoms in the present (e.g., at each visit). The PGIC and PGIS are the most commonly used anchor based method of assessing clinically important change and severity in which the external judgment of meaningful change is made by the patient (Appendix E). The PGIC and PGIS evaluations will be done on subjects’ device at the clinic PRIOR to dosing. Descriptive statistics (counts and percentages) for each response option at each scheduled visit for both PGIC and PGIS (separately) will be provided. A stacked column chart showing the distribution of responses at each scheduled visit will also be provided.

The EurQol-5D-5L (EQ-5D-5L) is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (Appendix F). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. EQ-5D is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics, and in face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

The EQ-5D-5L is to be done on a subject’s device at the clinic PRIOR to dosing. EQ-5D-5L consists of two parts:

- EQ-5D-5L descriptive system
- Visual Analog Scale (VAS) with instant recall of “how you feel today”; scale goes from 0-100, where 100 means the best health you can imagine and 0, the worst one.

The EQ-5D-5L descriptive system includes the basic domains common to each generic health status measure: mobility, self-care, usual activities, pain/discomfort and

anxiety/depression. The instrument includes one single question per domain. For each question, there are 5 levels of responses, corresponding to increasing levels of impairment (no problems, slight problems, moderate problems, severe problems, and extreme problems), and coded 1 to 5.

Only descriptive analyses of the EQ-5D-5L results will be presented. Number and percentage of patients with each of five levels (no problems, slight problems, moderate problems, severe problems, and extreme problems) of response in each domain will be presented by treatment and visit. The observed value and change from baseline on the EQ-5D-5L VAS score will be summarized by treatment at each analysis visit.

Additional exploratory analyses of the PROs collected in the study will be described in the PROSAP.

11.4.4.4 Multiple Comparisons Procedure for Primary Efficacy and Secondary Endpoints

The overall familywise error rate (FWER) will be controlled at $\alpha = 0.05$ using the sequential testing procedure for the primary efficacy endpoint comparing between the three dose levels of Ziltivekimab vs. placebo. The high dose (30 mg) will be compared with placebo at the beginning. If significant then the middle dose (15 mg) will be compared with placebo. If the middle dose is significant, then the low dose (7.5 mg) will be compared with placebo. The procedure stops whenever a nonsignificant test occurs.

Secondary endpoints are not included in the multiplicity control.

11.4.5 Safety Analysis

11.4.5.1 Adverse Events

The adverse event verbatim descriptions (investigator terms from the CRF) will be classified into medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to primary System Organ Class (SOC) and preferred term (PT) using MedDRA, Version 21.0.

Treatment emergent adverse events (TEAEs) are defined as AEs that initiated or worsened on or after the date of first dose of study drug up to the end of safety-follow-up. For AEs occurring on the first dosing day, if the start time cannot be ascertained, the event will be counted as treatment-emergent.

Safety events of special interest (Section 9.3) will be summarized by dose group and treatment assignment.

An overview of AEs will be provided including counts and percentages of subjects with the following:

- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs (overall and by maximum severity)
- Any TEAEs of special interest (overall and by maximum severity)
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to discontinuation of study
- Any AEs leading to death
- Any severe hematologic AEs (see Section 11.4.5.7)
- Any severe non-hematologic AEs

The number and percentage of patients reporting TEAEs and SAEs for each preferred term will be tabulated by system-organ class, by system- organ class and severity, and by system-organ class and relationship to Study Drug. If more than one event occurred with the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to study drug, respectively.

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

11.4.5.2 Laboratory Tests

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

11.4.5.3 Vital Signs

Vital signs and change from baseline in vital signs will be summarized descriptively at each visit by treatment group. The number and percentage of patients with exceeding pre-defined absolute and relative threshold values will be summarized according to Table 6.

When calculating the percentages for the criterion related to a threshold, the numerator will be the number of subjects with normal baseline with respect to the specific criterion and at least 1 post-baseline outlier value within the analysis period; and the denominator will be the number of subjects with a baseline and at least 1 post-baseline assessment within the analysis period.

Table 6 Pre-defined Threshold Value for Vital Signs

Parameter	Criteria
Systolic Blood Pressure (SBP)	>25% mmHg increased or decreased from baseline
SBP	>160 mmHg
SBP	<90 mmHg
Heart Rate (HR)	>100 beats per minute
HR	<50 beats per minute
Respiration Rate	>24 breaths per minute
BMI	>10% increased from baseline
BMI	>10% decreased from baseline

11.4.5.4 12-lead ECG

ECG interpretation (normal vs. abnormal) will be summarized using frequency and percentage at each visit by treatment group. ECG intervals (PR, QT, HR, and QTcF) will be summarized descriptively at each visit. The number and percentage of patients with exceeding pre-defined absolute and relative threshold values will be summarized (Table 7).

When calculating the percentages for the criterion related to a threshold, the numerator will be the number of subjects with normal baseline with respect to the specific criterion and at least 1 post-baseline outlier value within the analysis period; and the denominator will be the number of subjects with a baseline and at least 1 post-baseline assessment within the analysis period.

Table 7 Pre-defined Threshold Value for ECG

Parameter	Criteria
PR Interval	>200 msec
QTcF	>450 msec
QTcF	>480 msec
QTcF	>500 msec
QTcF	Increase from baseline >30 msec
QTcF	Increase from baseline >60 msec

11.4.5.5 Physical Examination

Physical examination clinically significant new or worsening findings will be reported as adverse events and will therefore be summarized as described for adverse events.

11.4.5.6 Antibodies to Ziltivekimab

The immunogenic potential of Ziltivekimab will be assessed by summarizing the number and percentage of patients who develop detectable anti-drug antibodies (ADA). Anti-drug antibody titers will be summarized descriptively for ADA positive samples and the impact of ADA on PK will be assessed if data allows.

11.4.5.7 Bleeding Events

Bleeding events will be classified using the TIMI Bleeding Classification in Table 8.

Table 8 TIMI Bleeding Classification

Parameter	Criteria
Major	Intracranial hemorrhage or a ≥5 g/dl decrease in the hemoglobin concentration or a ≥15% absolute decrease in the hematocrit
Minor	Observed blood loss: ≥3 g/dl decrease in the hemoglobin concentration or ≥10% decrease in the hematocrit. No observed blood loss: ≥4 g/dl decrease in the hemoglobin concentration or ≥12% decrease in the hematocrit
Minimal	Any clinically overt sign of hemorrhage (including imaging) that is associated with a <3 g/dl decrease in the hemoglobin concentration or <9% decrease in the hematocrit
All TIMI definitions take into account blood transfusions, so that hemoglobin and hematocrit values are adjusted by 1 g/dl or 3%, respectively, for each unit of blood transfused. Therefore, the true change in hemoglobin or hematocrit if there has been an intervening transfusion between two blood measurements is calculated as follows: Δ Hemoglobin = [baseline Hgb − post-transfusion Hgb] + [number of transfused units]; Δ Hematocrit = [baseline Hct − post-transfusion Hct] + [number of transfused units × 3].	
TIMI = Thrombolysis In Myocardial Infarction. Source: Rao 2006	

11.4.6 Pharmacokinetic Analysis and Pharmacokinetic/Pharmacodynamic Analysis

11.4.6.1 Pharmacokinetic Data

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A 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 (e.g., n, arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum, median, maximum, geometric mean, and geometric CV (GCV).

For IL-6, results of PK parameters such as C_{max}, AUC, and $T_{1/2}$ will be summarized by dose group.

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

The data from this study may be used in combination with data from other studies to develop a population PK model. If performed, the plan for and results of such analysis will be documented separately.

Pharmacokinetic analysis will be performed separately.

11.4.6.2 Pharmacokinetic/Pharmacodynamic Analysis

Pharmacokinetic-pharmacodynamic (PK-PD) model parameters will be derived using plasma IL-6 levels to describe target engagement, with clinically meaningful PD variables that may include one or more of the following: C-reactive protein, serum amyloid A, transferrin saturation, hemoglobin, reticulocyte hemoglobin content, or reticulocyte count. The specific model parameters to be estimated will be determined based on review of the observed data. The PD endpoints 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 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: individual observed and percent change from baseline serum concentration-time curves for each patient on linear scale; arithmetic mean serum concentration-time curves by dose group on linear scale.

11.4.7 Exploratory Analyses of Efficacy and Safety Endpoints Based on Baseline Hemoglobin (≥11 or <11 g/dL).

Exploratory analyses may be performed for the primary and secondary efficacy endpoints with a stratified analysis by baseline hemoglobin (≥11 or <11 g/dL) and CKD stage (3, 4 or 5).

11.5 Interim Analyses

Interim analyses will not be conducted.

12 STUDY COMMITTEES

12.1 Clinical Events Committee

An independent external Clinical Events Committee (CEC) will not be established based on the low current event rates in this ongoing trial.

12.2 Safety Assessment Committee (SAC)

A Safety Assessment Committee (SAC) will not be required because the study will be unblinded after 13 weeks for the primary analysis, and all safety data will be reviewed at that time by Sponsor including any potential changes to the ziltivekimab development program if necessary. At the 13-week analysis, only a small internal group of staff at Corvidia and the CRO who are uninvolved with running the study will know the results. The sites, Corvidia and CRO study teams, [redacted] study team, CRAs, Investigators and patients will remain blinded to treatment for the duration of the trial.

13 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

13.1 Institutional Review Board or Independent Ethics Committee

The protocol and informed consent for this study must be reviewed and approved by an appropriate IRB or IEC before patients are enrolled in the study. It is the responsibility of the Investigator to assure that the study is conducted in accordance with current country and Local Regulations, International Conference on Harmonisation (ICH), GCP, and the Declaration of Helsinki. A letter, documenting the approval that specifically identifies the protocol by number and title as well as the Investigator, must be received by Corvidia Therapeutics before initiation of the study. Amendments to the protocol will be patient to the same requirements as the original protocol.

After the completion or termination of the study, the Investigator will submit a report to the IRB or IEC.

13.2 Informed Consent

Each potential subject must be provided with oral and written information from the investigator (or other study staff who are conducting the informed consent interview) to allow for an informed decision about participation in the clinical investigation, facilitating the potential subject's comprehension of the information, providing adequate opportunity for the potential subject to ask questions and to consider whether to participate, obtaining the potential subject's voluntary agreement to participate and continuing to provide information as the clinical investigation progresses or as the subject or situations requires. The process must provide sufficient time for subjects to consider the information and providing time and opportunity for the subjects to ask questions and have those questions answered. The investigator (or other study staff who are conducting the informed consent interview) and the subject should exchange information and discuss the contents of the informed consent. This process must occur under circumstances that minimize the possibility of coercion or undue influence. Each patient must be provided with oral and written information describing the nature and duration of the study and must sign a written ICF in a language in which the patient is fluent before study specific procedures are conducted. The signed and dated ICF will be retained with the study records. Each patient will also be given a copy of their signed ICF.

13.3 Supplementary Documentation

Before initiation of the study, the Investigator must provide Corvidia Therapeutics with the following documents (copies of which must be maintained by the Investigator):

1. Curriculum vitae of the Investigator and any sub-Investigators listed on the 1572 form;

2. A signed copy of the IRB or IEC approval notice for protocol and informed consent;
3. A copy of the IRB or IEC approved ICF;
4. Laboratory certification with a list of normal values for laboratory tests that will be conducted at local laboratories;
5. Completed financial disclosure form for the Investigator and any sub Investigators listed on the 1572 form.

13.4 Data Reporting and Case Report Forms

Data for each patient will be entered into the CRF and verified by the Investigator. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient's clinical status.

The Investigator or designated representative should complete the CRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. CRF data will be processed in a US 21 Code of Federal Regulations (CFR) Part 11-compliant system.

13.5 Retention of Data

U.S. Federal regulations require that a copy of records (e.g., laboratory data slips, source documents, test article disbursement records), which support case records of this study, must be retained in the files of the responsible Investigator for a minimum of 2 years after notification by the Sponsor that the FDA has approved a marketing application for the drug and indication being investigated, or the investigation has been terminated.

13.6 Deviation from the Protocol

The Investigator will not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard, and then notify the Corvidia Therapeutics Medical Monitor and the IRB or IEC immediately regarding the type of emergency and course of action taken. Any action in this regard will be recorded on the appropriate CRF. Any other changes or deviations in the protocol will be made as an amendment to the protocol and must be approved by Corvidia Therapeutics and the IRB or IEC — before the changes or deviations are implemented. Corvidia Therapeutics will not assume any responsibility or liability for any deviation or change.

13.7 Study Monitoring

The Investigator will allow representatives of Corvidia Therapeutics to periodically audit (at mutually convenient times before, during, and after the study has been completed) all CRFs and relevant portions of office, clinical, and laboratory records for each patient. Appropriate source documents such as a record of the patient's medical history and concomitant medications from the patient's physician must be available to confirm eligibility for the study. The monitoring visits provide Corvidia Therapeutics with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of CRFs; assure that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records.

13.8 Drug Accountability

The Investigator must maintain accurate records of the amounts and dates Study Drugs were received from Corvidia Therapeutics and dispensed to the patients, including the remaining volume after dose administration. All drug supplies must be accounted for at the termination of the study and a written explanation provided for any discrepancies. All partially used or unused drug supplies will be destroyed at the site, in accordance with approved written procedures, or returned to Corvidia Therapeutics after written authorization is obtained from Corvidia Therapeutics. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned. All records will be retained as noted in Section 13.5.

13.9 Disclosure of Data

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Patient confidentiality will be further assured by utilizing patient identification code numbers to correspond to treatment data in the computer files. The study personnel, employees of the regulatory agencies, including the U.S. FDA and the study sponsor, Corvidia Therapeutics, and its agents will need to review patient medical records in order to accurately record information for this study. If results of this study are reported in medical journals or at meetings, the patient's identity will remain confidential.

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15 APPENDICES

15.1 Appendix A Exclusionary Drugs

The following medications are metabolized by CYP450 enzymatic pathways and have a narrow therapeutic window. The use of these medications from one day prior to Randomization (Day -1) through Study Week 24 is prohibited.

digoxin

theophylline

terfenadine

tizanidine

quinidine

phenytoin and its derivatives

taxane chemotherapeutic agents

cyclosporine

mTOR inhibitors (e.g., sirolimus, tacrolimus)

ergot alkaloids

antipsychotic medications (specifically pimozide, thioridazine)

fentanyl and derivatives (e.g., alfentanil and sufentanil)

15.2 Appendix B PROMIS® (Patient-Reported Outcomes Measurement Information System)

PROMIS Items

PROMIS Short Form v1.0 – Fatigue 13a

During the past 7 days……..	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel fatigued	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I feel weak all over	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I feel listless (“washed out”)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I feel tired	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I have trouble starting things because I am tired	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I have trouble finishing things because I am tired	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I have energy	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I am able to do my usual activities	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I need to sleep during the day	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I am too tired to eat	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I need help doing my usual activities	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I am frustrated by being too tired to do the things I want to do	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
I have to limit my social activity because I am tired	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

PROMIS items (Item identifier in bold)

FATEXP36: How exhausted were you on average?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
FATEXP43: How physically drained were you on average?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
FATIMP52: To what degree did your fatigue make you feel less alert?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

During the past 30 days……..	Not at all	A little bit	Somewhat	Quite a bit	Very much
SFINT101: How interested have you been in sexual activity?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

Protocol Amendment COR-001-02_ProtAmend_V5_23Dec2019 | EX6018 -4779

15.3 Appendix C Optum SF-36 v2® Health Survey

SF-36v2® Health Survey Single-Item Standard Recall for Handheld Device

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
	Your Health and Well-Being						
	This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please select the one response that best describes your answer.						
SF36v2_GH1	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor	
SF36v2_HT	Compared to one year ago, how would you rate your health in general now?	Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago	
	The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?						
SF36v2_PF01	Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF02	Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF03	Does your health now limit you in lifting or carrying groceries? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF04	Does your health now limit you in climbing several flights of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF05	Does your health now limit you in climbing one flight of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF06	Does your health now limit you in bending, kneeling, or stooping? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF07	Does your health now limit you in walking more than a mile? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF08	Does your health now limit you in walking several hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF09	Does your health now limit you in walking one hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF10	Does your health now limit you in bathing or dressing yourself? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?						

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(SF-36v2® Health Survey Standard, United States (English))

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
SF36v2_RP1	During the past 4 weeks, how much of the time have you cut down on the amount of time you spent on work or other activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RP2	During the past 4 weeks, how much of the time have you accomplished less than you would like as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RP3	During the past 4 weeks, how much of the time were you limited in the kind of work or other activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RP4	During the past 4 weeks, how much of the time have you had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?						
SF36v2_RE1	During the past 4 weeks, how much of the time have you cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RE2	During the past 4 weeks, how much of the time have you accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RE3	During the past 4 weeks, how much of the time have you done work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_SF1	During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Not at all	Slightly	Moderately	Quite a bit	Extremely	
SF36v2_BP1	How much bodily pain have you had during the past 4 weeks?	None	Very mild	Mild	Moderate	Severe	Very severe
SF36v2_BP2	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A little bit	Moderately	Quite a bit	Extremely	
	These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.						

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Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
SF36v2_VT1	How much of the time during the past 4 weeks did you feel full of life?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH1	How much of the time during the past 4 weeks have you been very nervous?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH2	How much of the time during the past 4 weeks have you felt so down in the dumps that nothing could cheer you up?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH3	How much of the time during the past 4 weeks have you felt calm and peaceful?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_VT2	How much of the time during the past 4 weeks did you have a lot of energy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH4	How much of the time during the past 4 weeks have you felt downhearted and depressed?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_VT3	How much of the time during the past 4 weeks did you feel worn out?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH5	How much of the time during the past 4 weeks have you been happy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_VT4	How much of the time during the past 4 weeks did you feel tired?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_SF2	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
	How TRUE or FALSE is each of the following statements for you?						
SF36v2_GH2	I seem to get sick a little easier than other people.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
SF36v2_GH3	I am as healthy as anybody I know.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
SF36v2_GH4	I expect my health to get worse.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
SF36v2_GH5	My health is excellent.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
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SAMPLE

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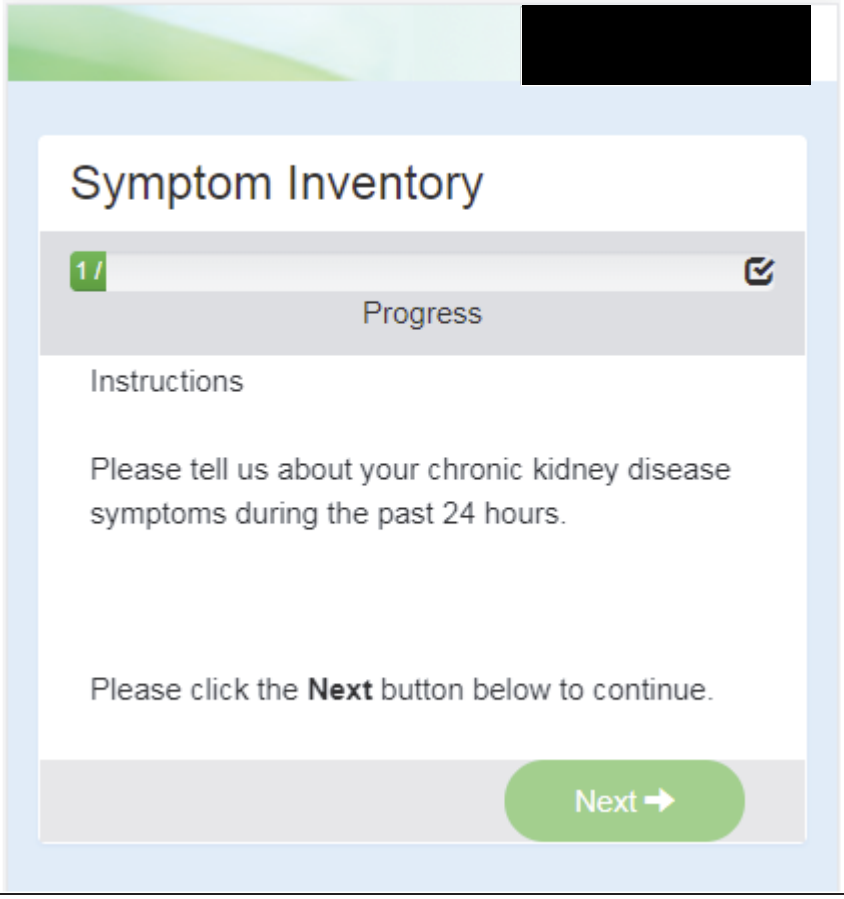
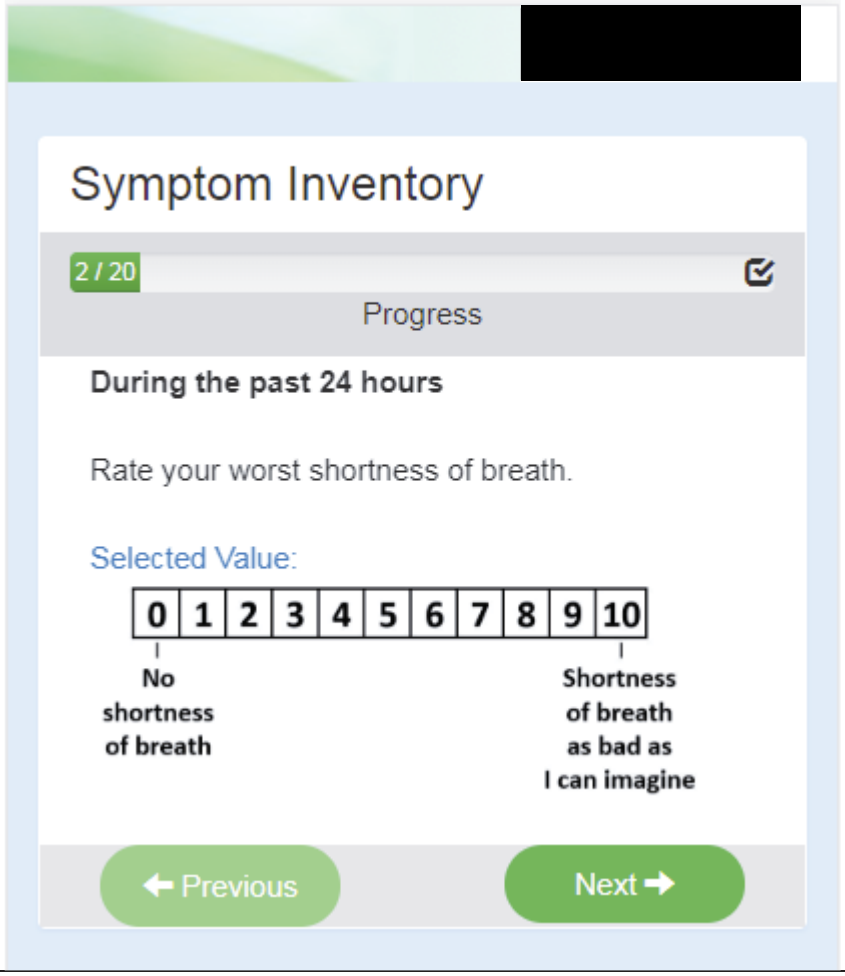
15.4 Appendix D Corvidia ePRO

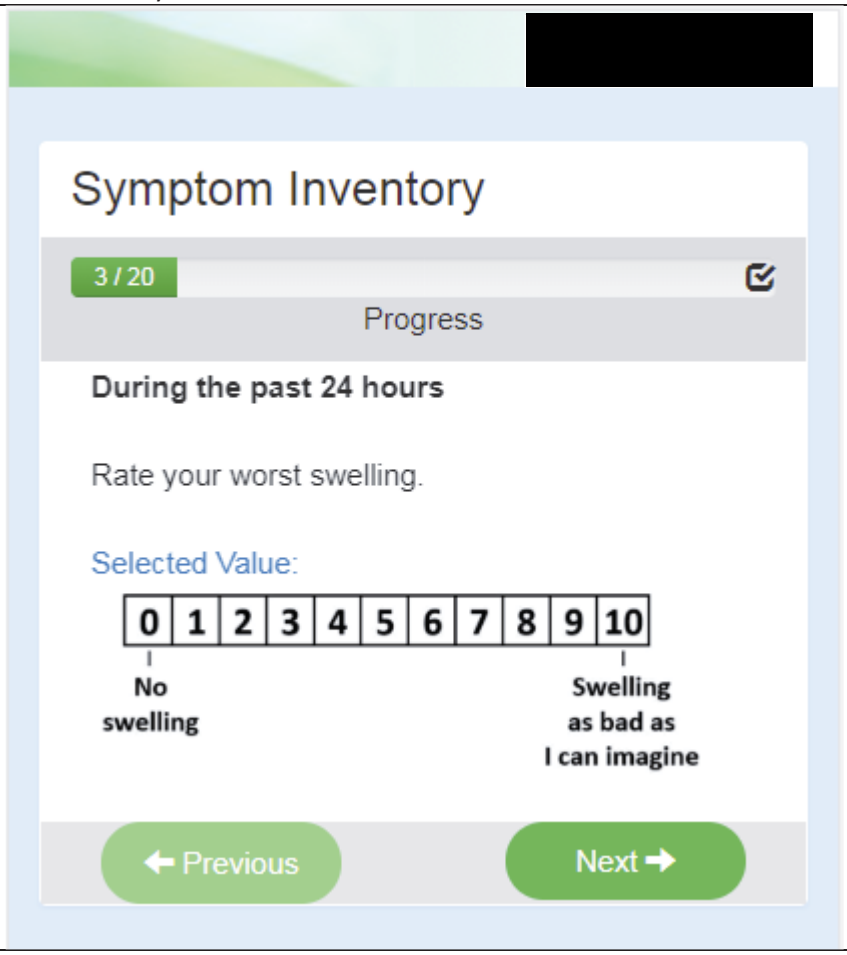
Symptom Inventory



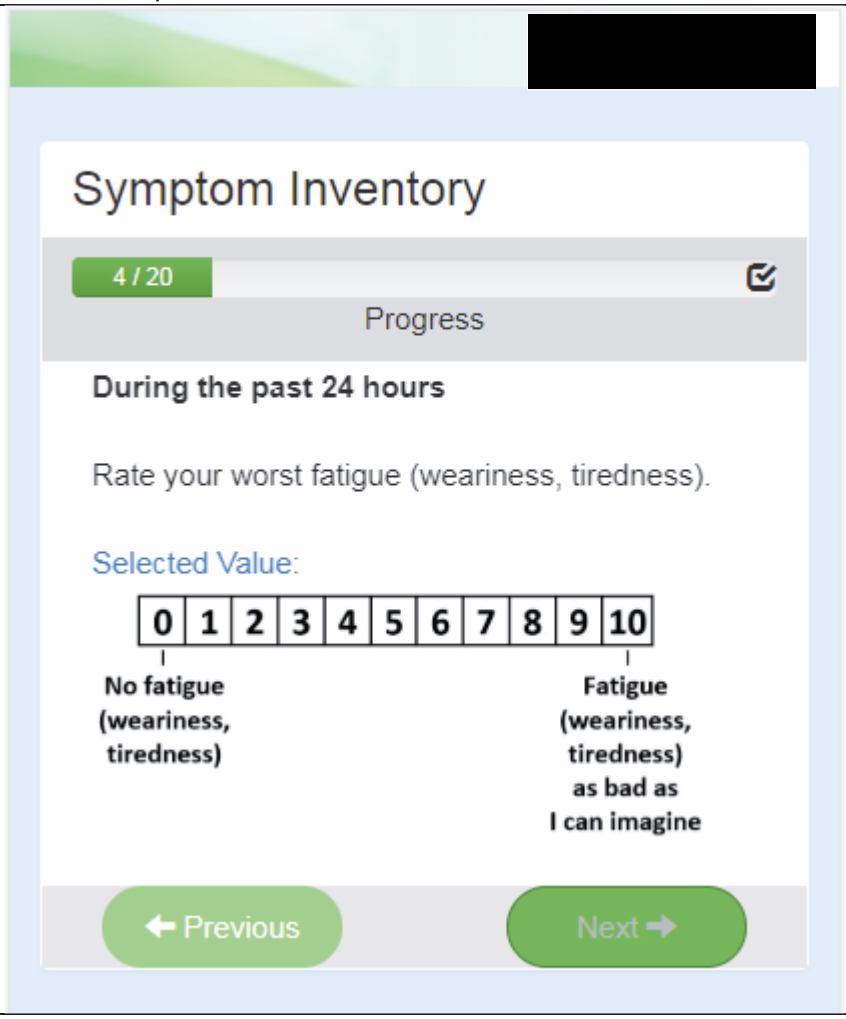
Symptom Inventory



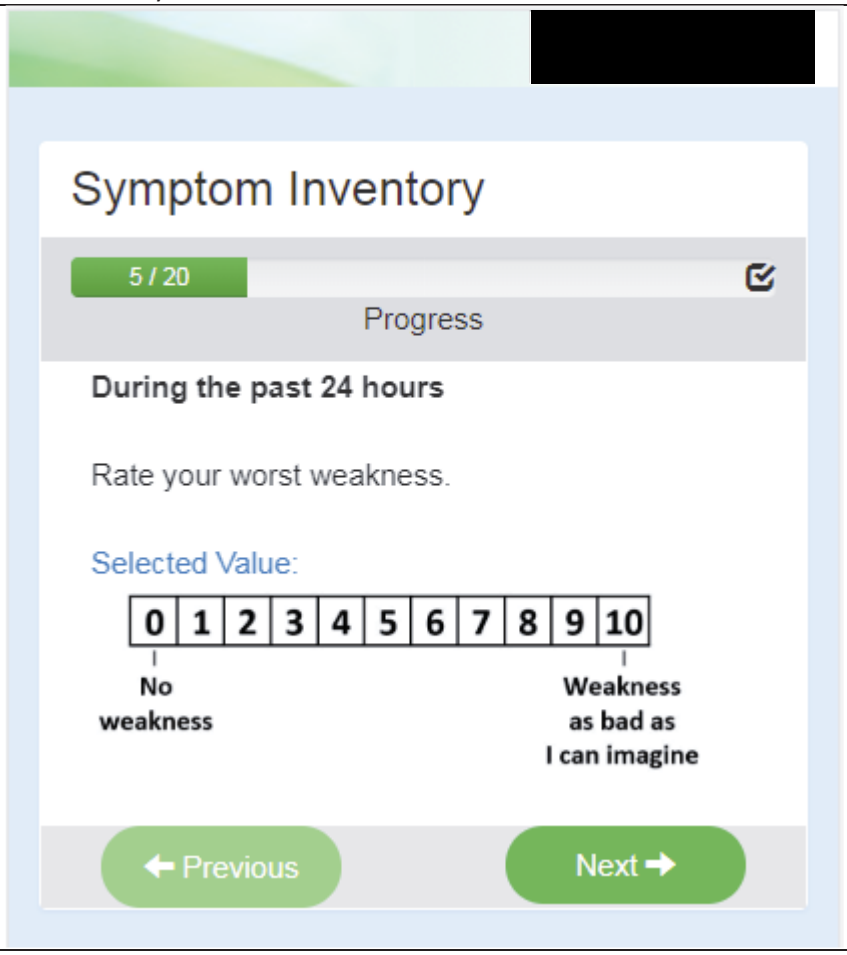
Symptom Inventory



Symptom Inventory



Symptom Inventory



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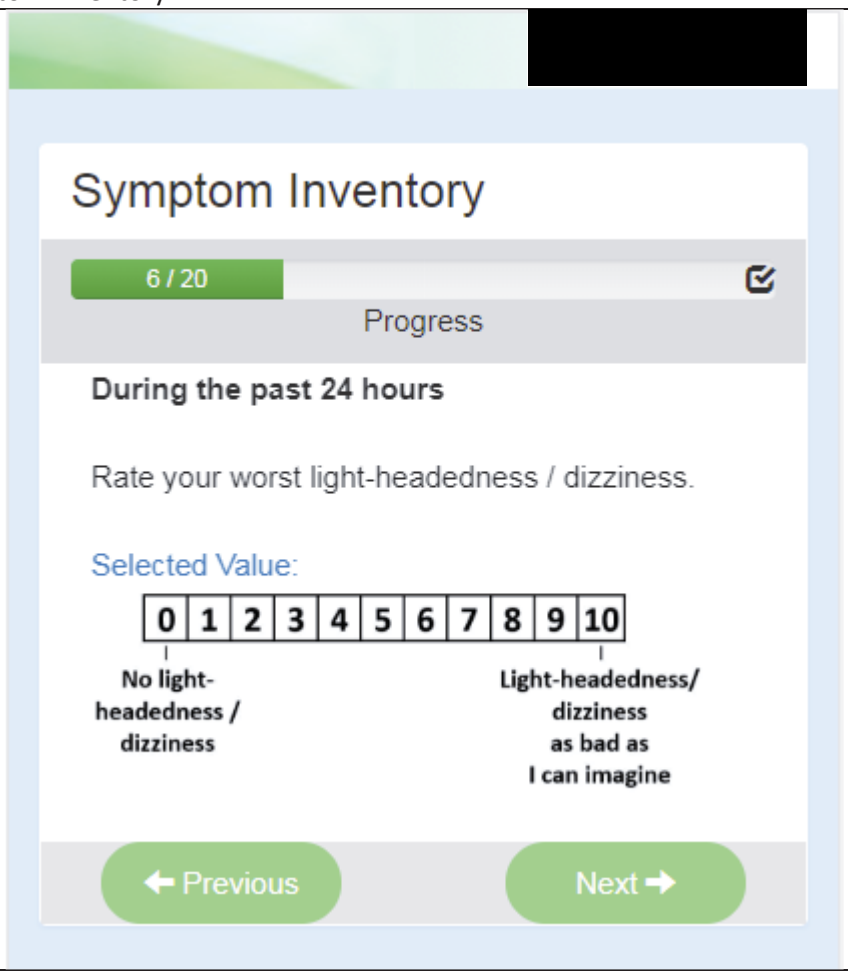

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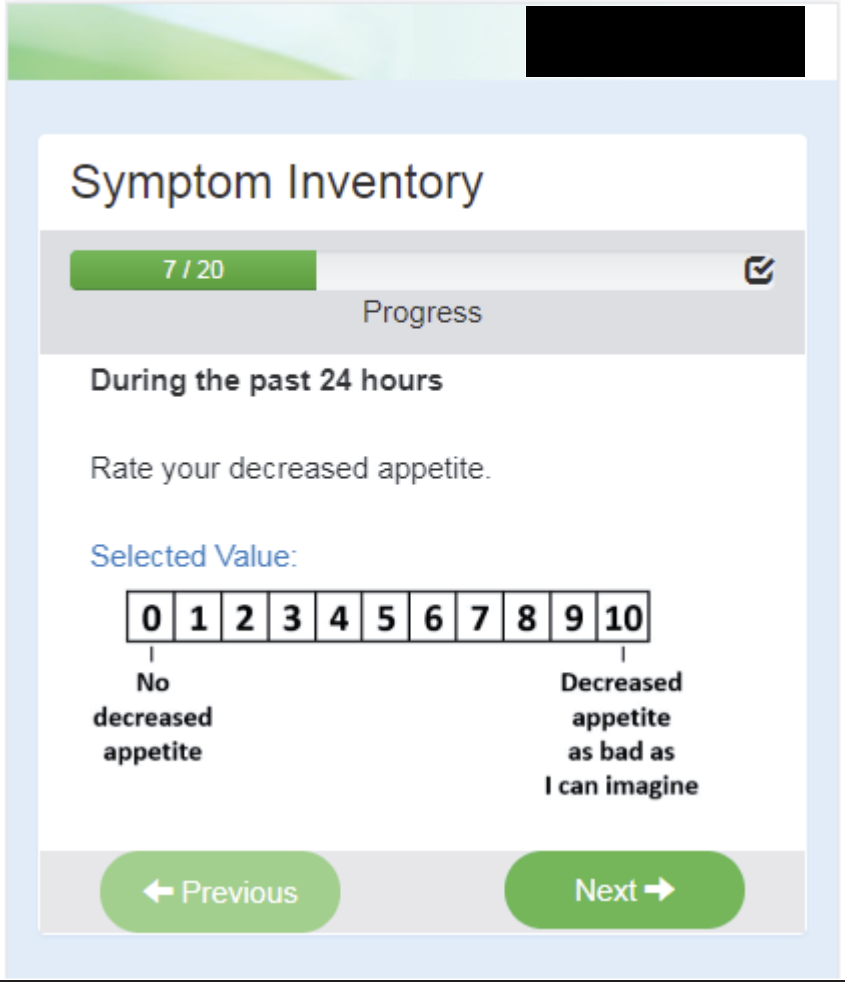

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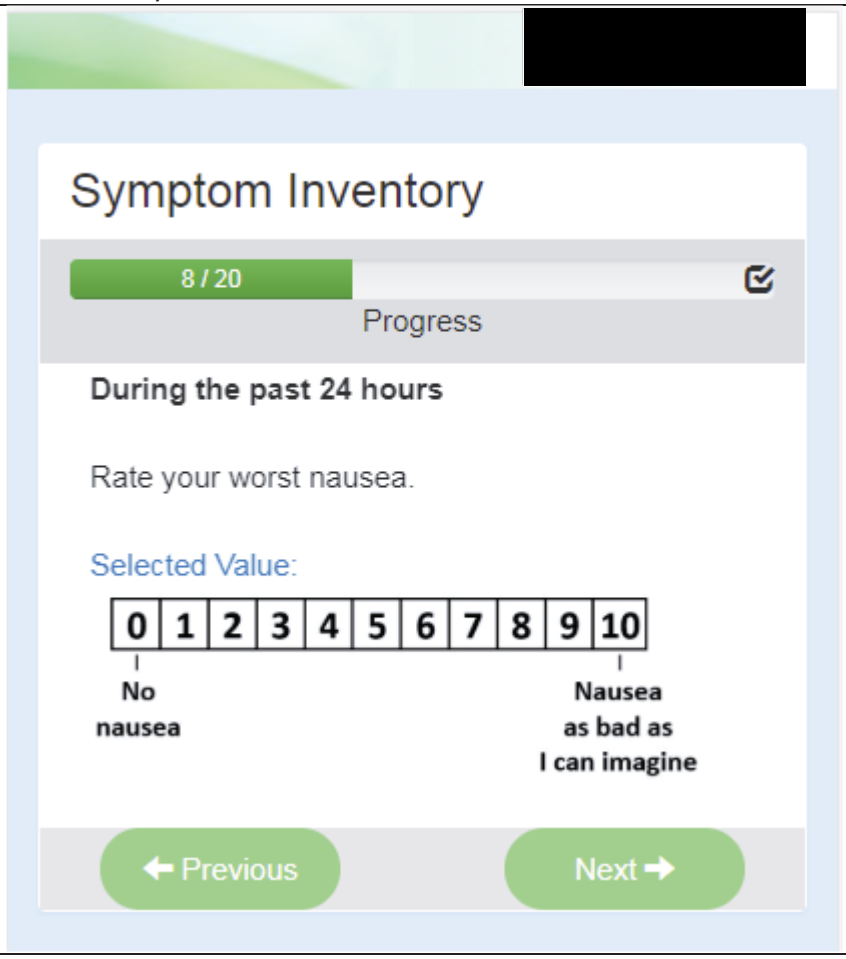

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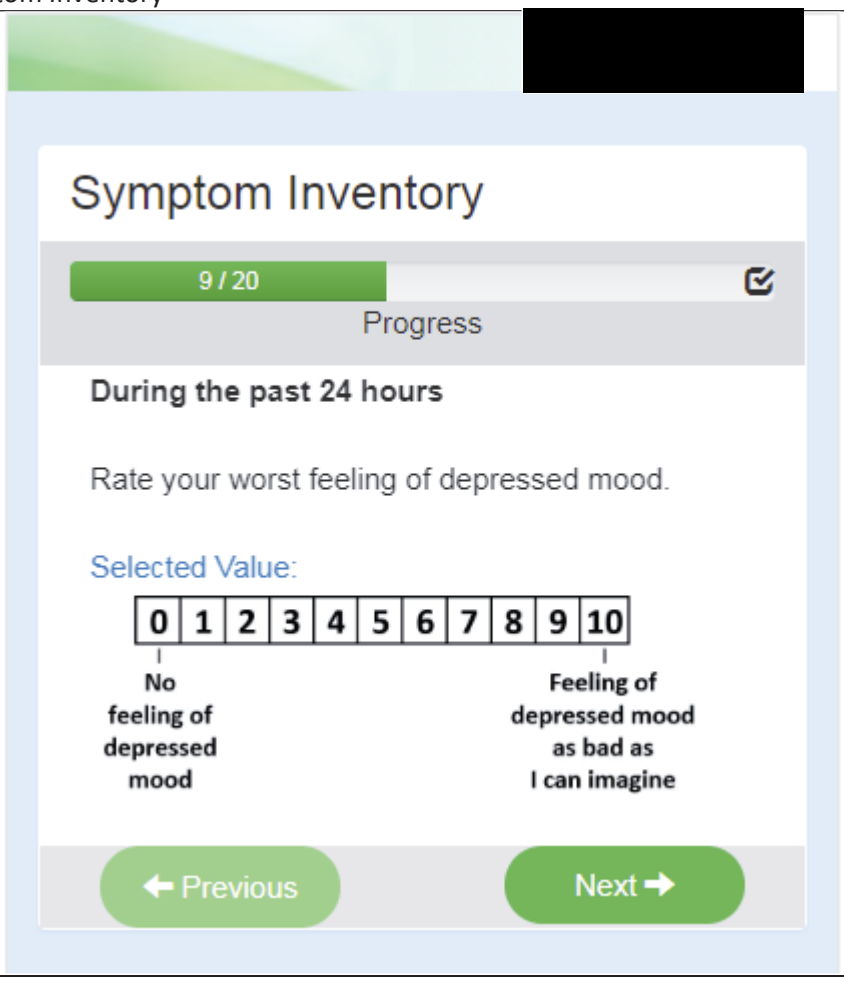

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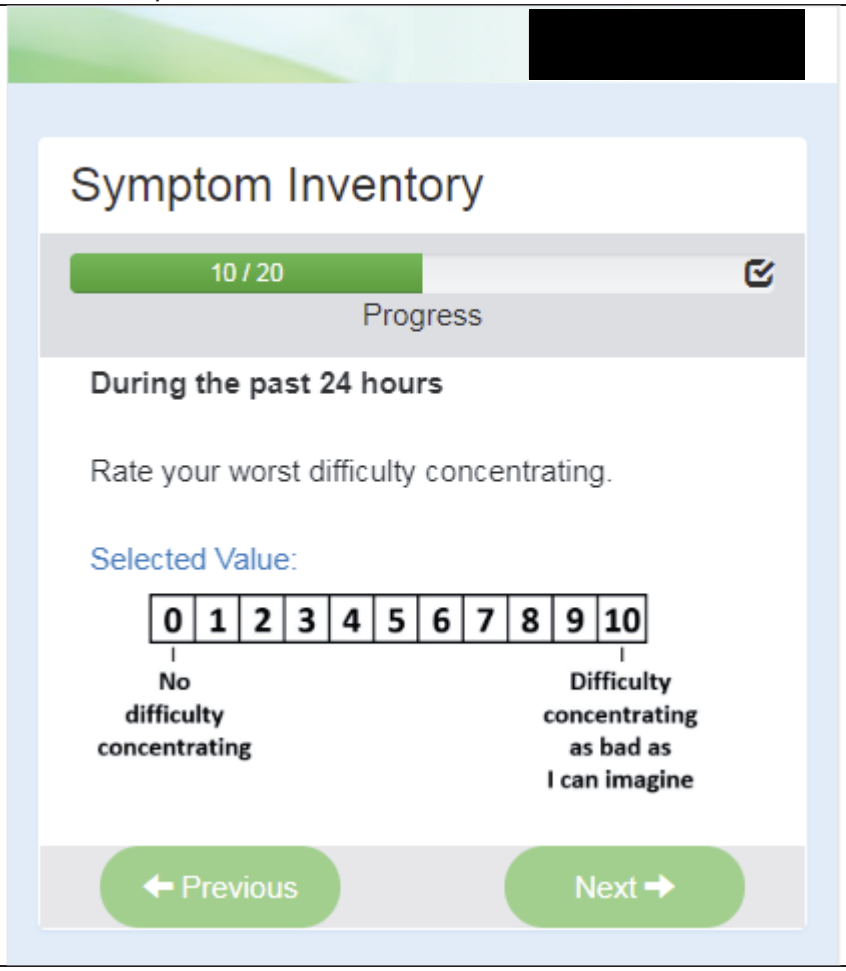

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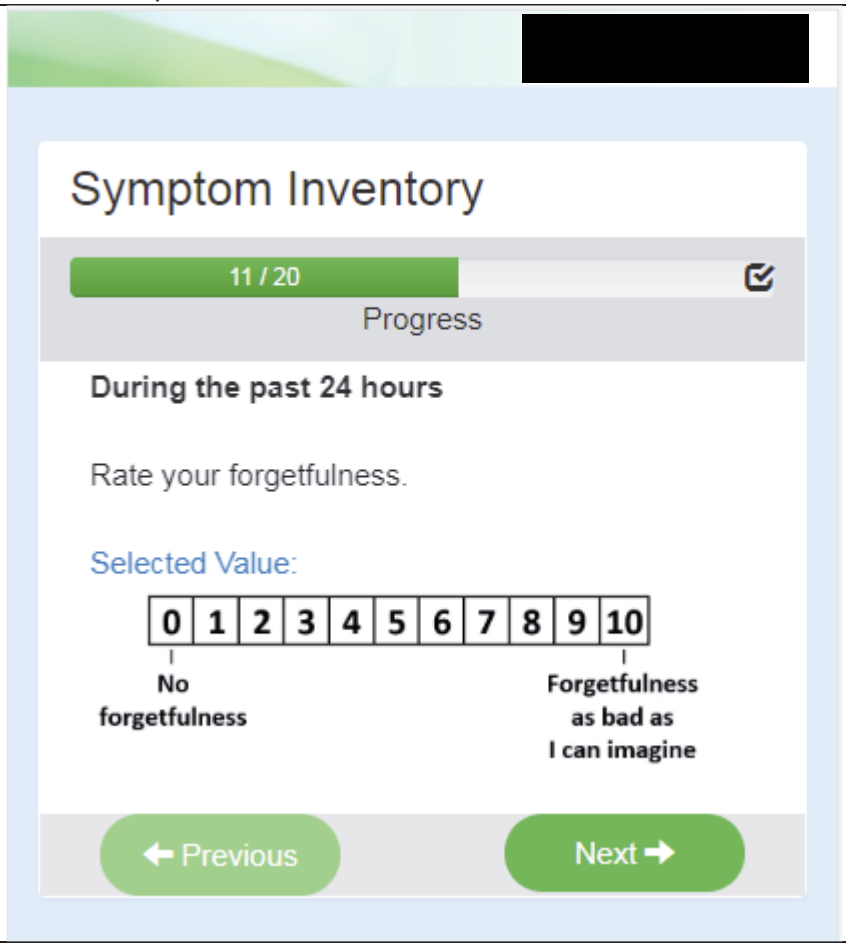

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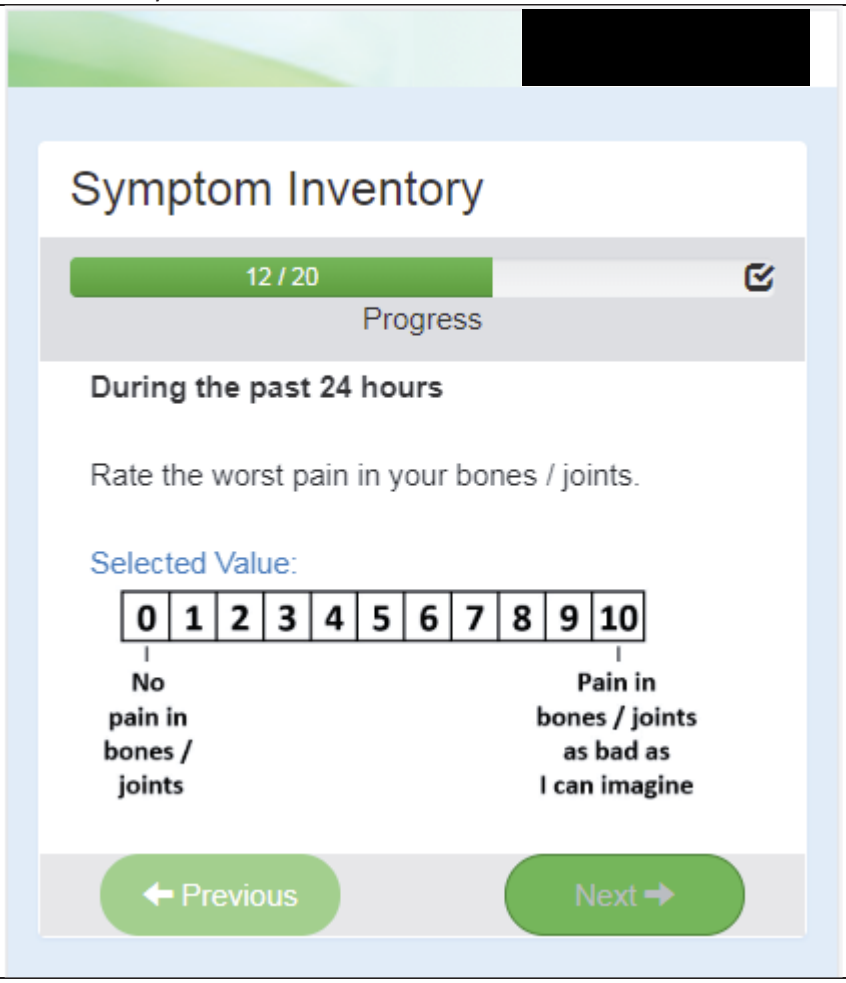

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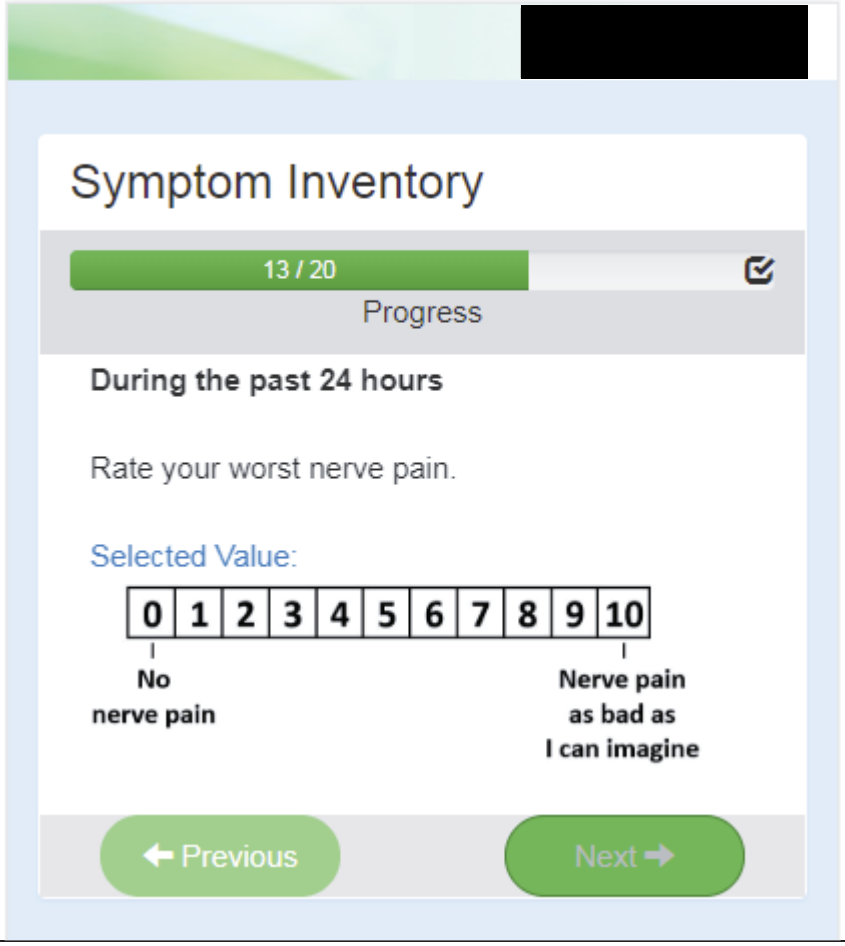

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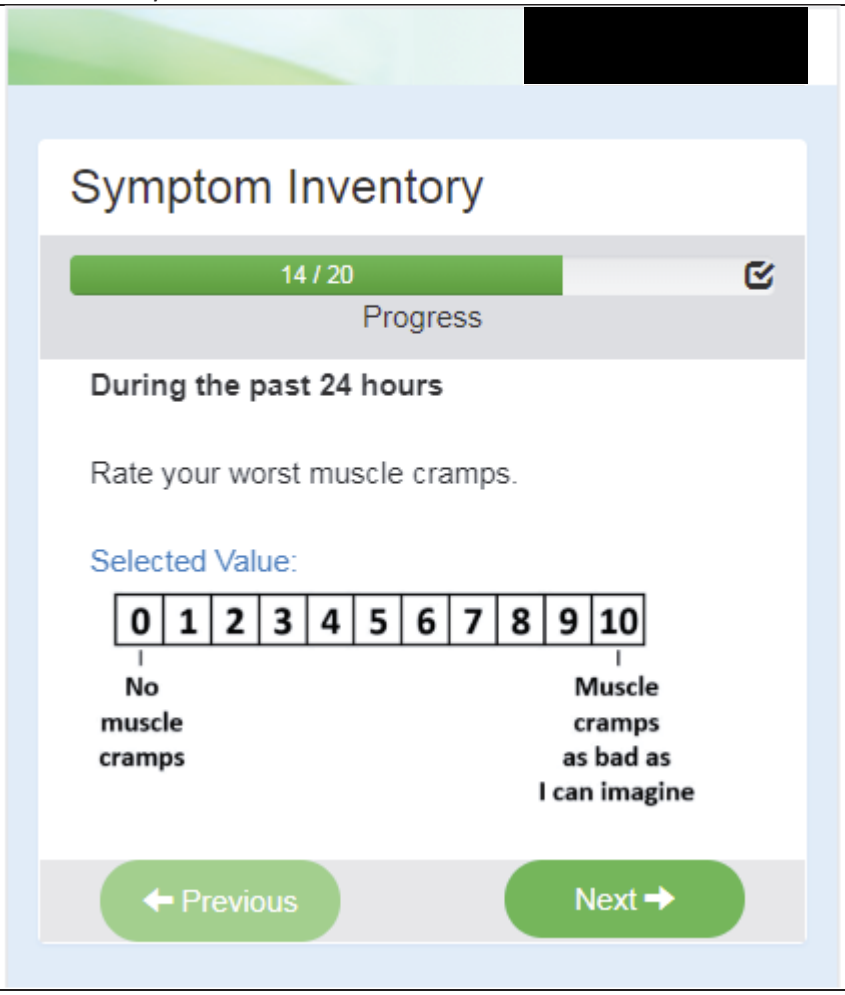

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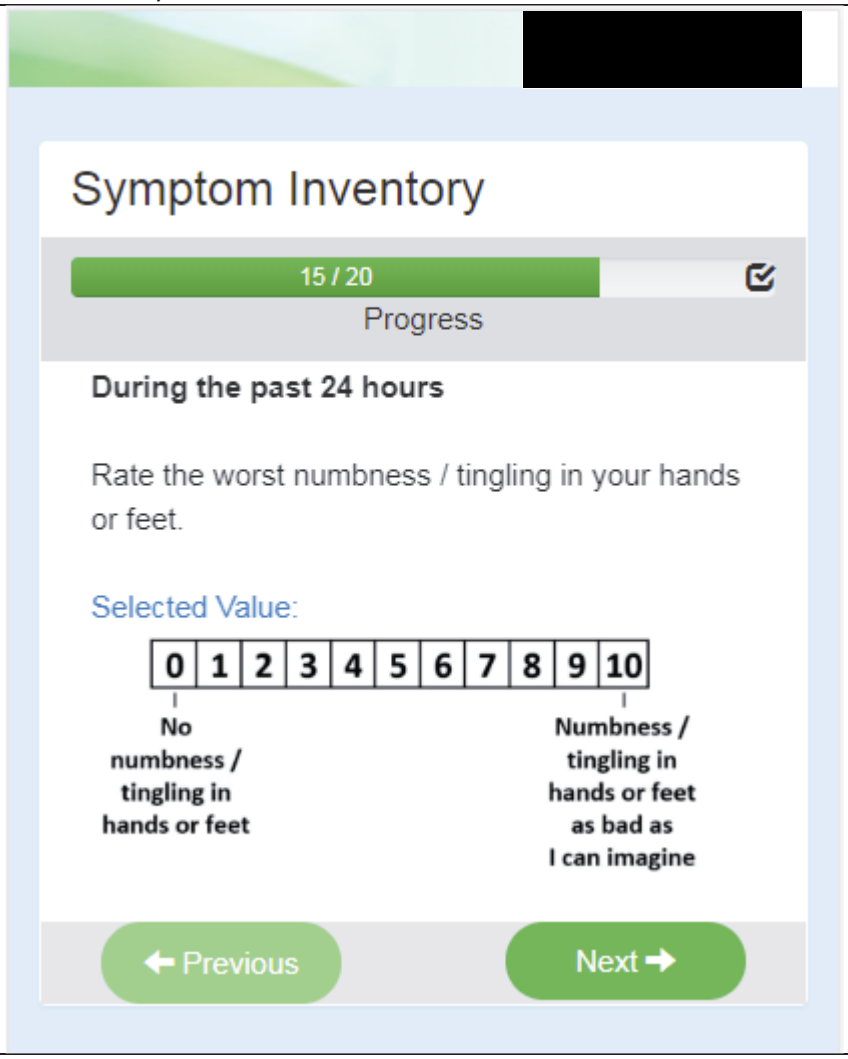

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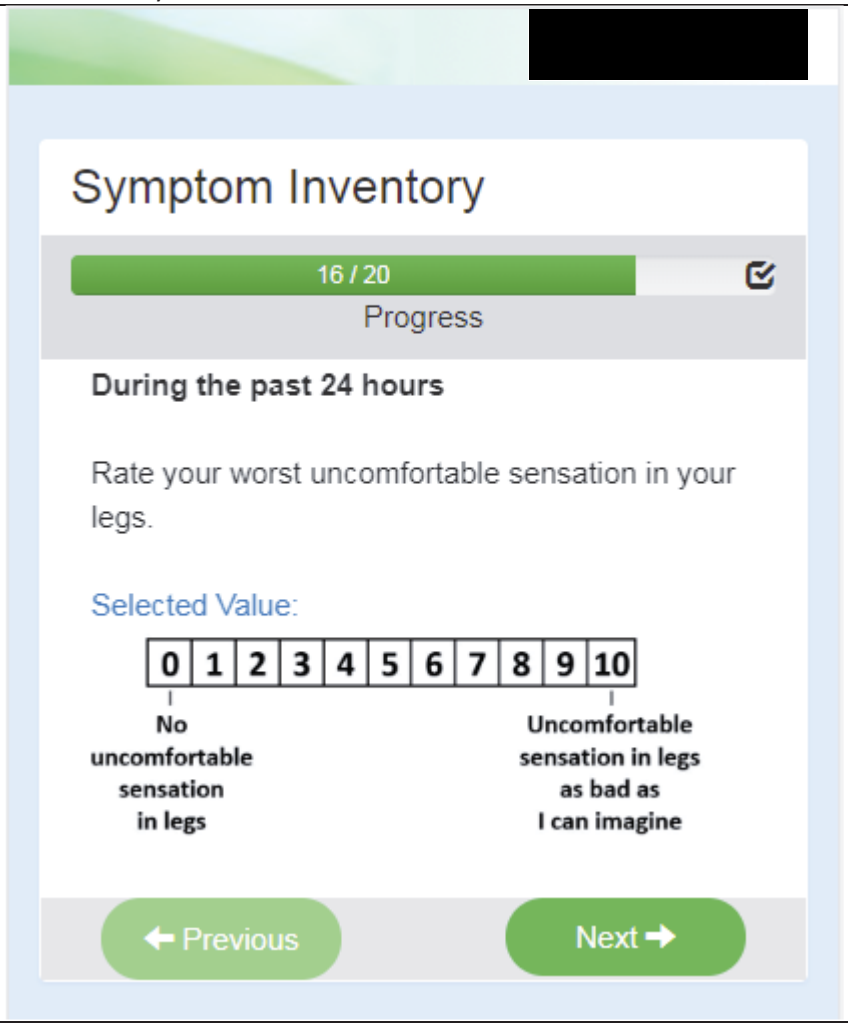
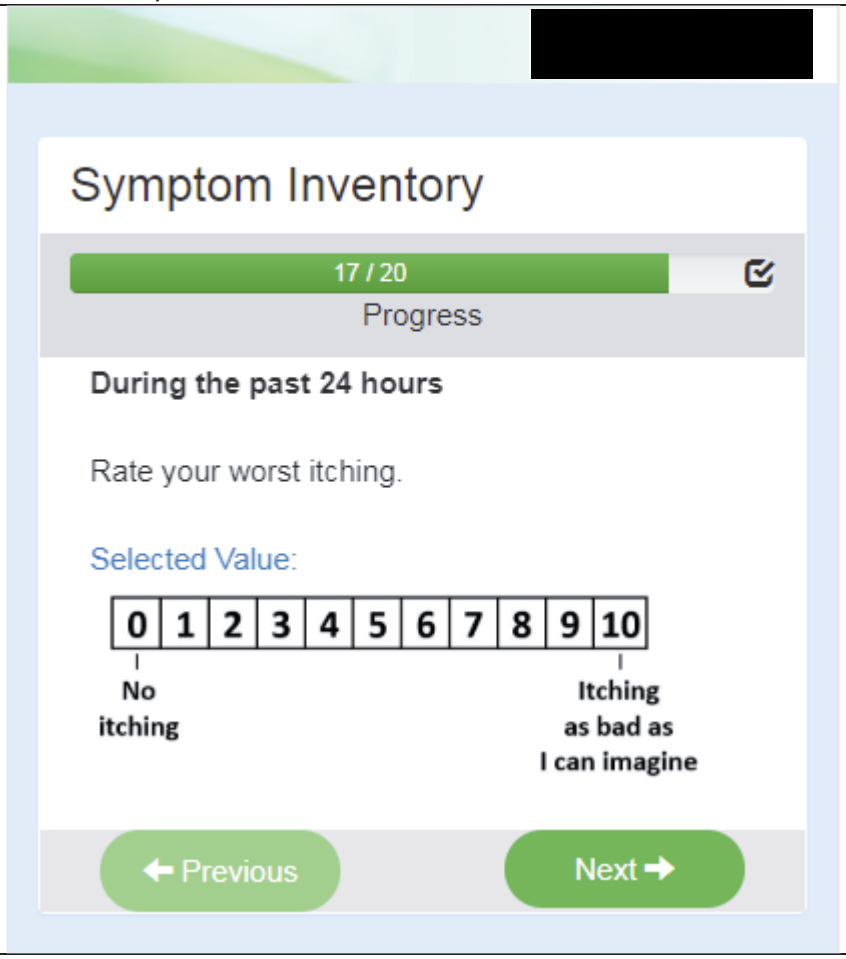


Symptom Inventory



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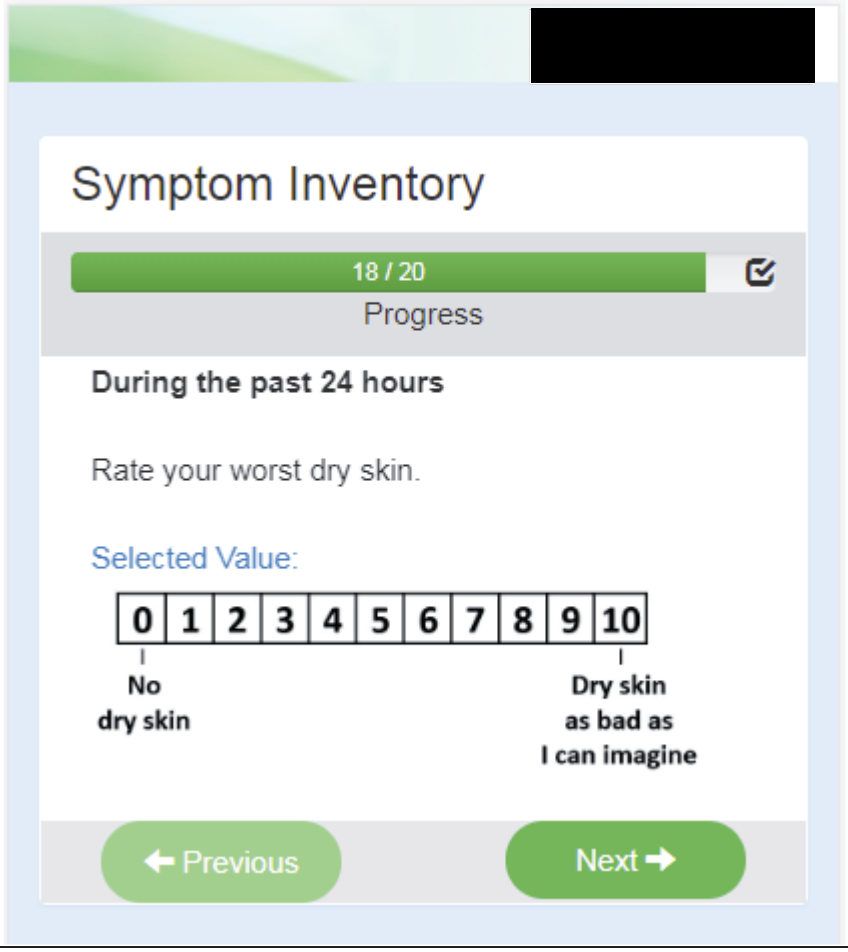

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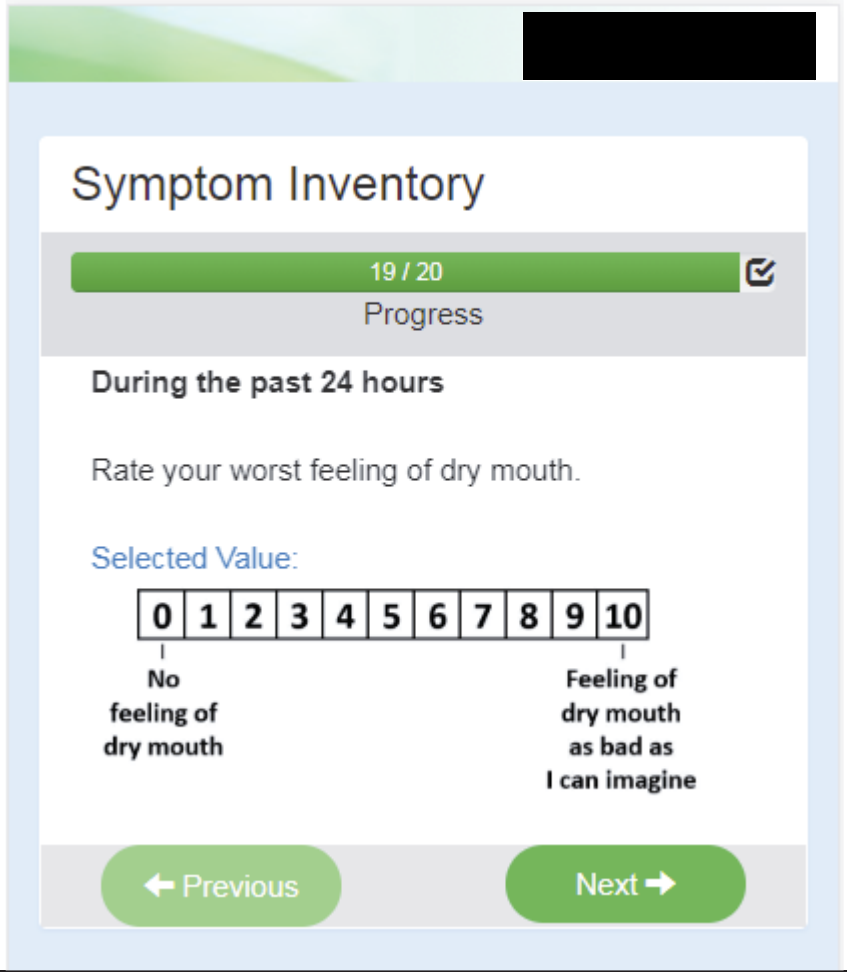

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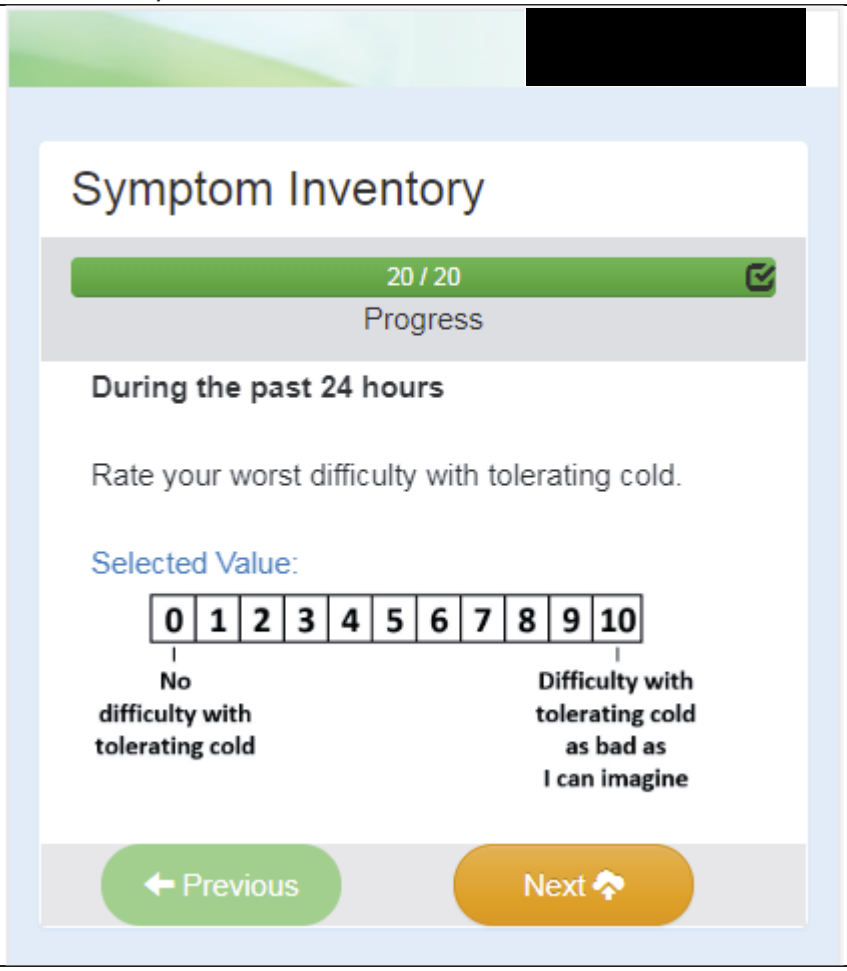
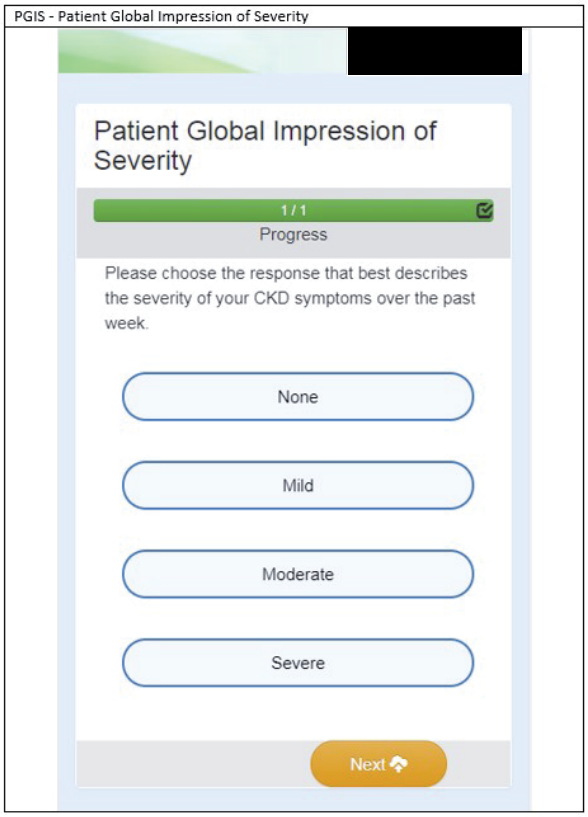
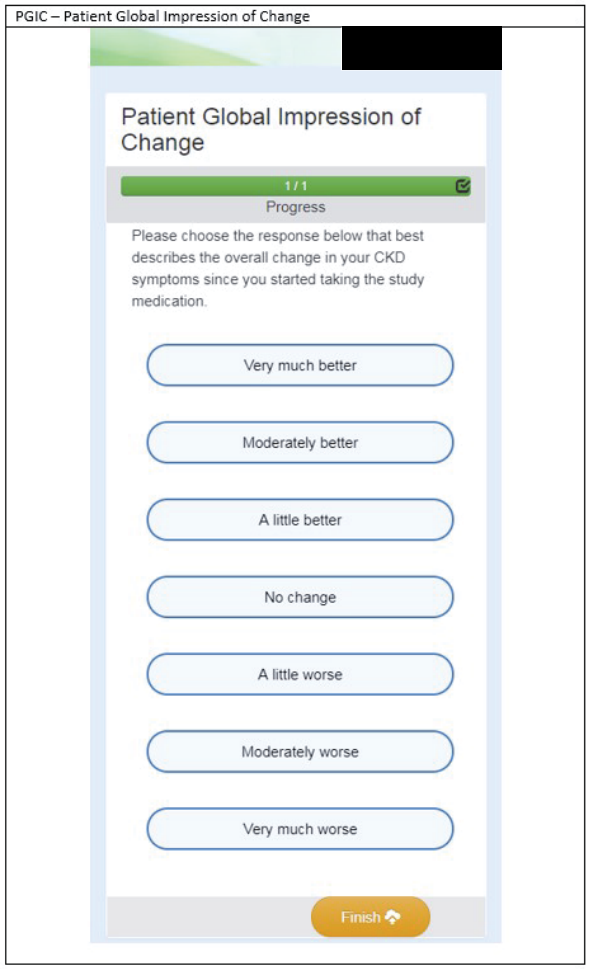


15.5 Appendix E PGIS and PGIC

PGIS - Patient Global Impression of Severity



PGIC – Patient Global Impression of Change



15.6 Appendix F EurQol-5D-5L (EQ-5D-5L)

EQ-5D-5L	
EQ-5D-5L PDA version	
English (USA)	Country (Language)
Health Questionnaire **English version for the USA**	Health Questionnaire Version (Target Language) Version (English)
On the following screens please tap the statement that best describes your health TODAY.	Instruction
Your mobility TODAY	**Mobility**
I have no problems walking	MB1
I have slight problems walking	MB2
I have moderate problems walking	MB3
I have severe problems walking	MB4
I am unable to walk	MB5
Your self-care TODAY	**Self-care**
I have no problems washing or dressing myself	SC1
I have slight problems washing or dressing myself	SC2
I have moderate problems washing or dressing myself	SC3
I have severe problems washing or dressing myself	SC4
I am unable to wash or dress myself	SC5
Your usual activities TODAY (*e.g. work, study, housework, family or leisure activities*)	**Usual Activities**
I have no problems doing my usual activities	UA1
I have slight problems doing my usual activities	UA2
I have moderate problems doing my usual activities	UA3
I have severe problems doing my usual activities	UA4
I am unable to do my usual activities	UA5
Your pain / discomfort TODAY	**Pain / Discomfort**
I have no pain or discomfort	PD1
I have slight pain or discomfort	PD2
I have moderate pain or discomfort	PD3
I have severe pain or discomfort	PD4
I have extreme pain or discomfort	PD5
Your anxiety / depression TODAY	**Anxiety / Depression**
I am not anxious or depressed	AD1
I am slightly anxious or depressed	AD2
I am moderately anxious or depressed	AD3
I am severely anxious or depressed	AD4
I am extremely anxious or depressed	AD5
We would like to know how good or bad your health is TODAY.	Vas Line 1
On the next screen you will see a scale numbered 0 to 100.	Vas Line 2
100 means the best health you can imagine.	Vas Line 3
0 means the worst health you can imagine.	Vas Line 4
Please tap on the scale to indicate how your health is TODAY.	Vas Line 5
The best health you can imagine	Top Scale
The worst health you can imagine	Bottom Scale
YOUR HEALTH TODAY	Box Health

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Disclaimer: *This is a preview of the EQ-5D instrument. It demonstrates the text, questions and response options included in this version. This preview does not represent the final product and should not be used as an official EQ-5D instrument.*

15.7 Appendix G Guidance on Contraception

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

a) Women of childbearing potential must be using a method of contraception, that is "highly effective" (i.e., <1% failure rate)

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 (FSH) level (i.e., >40 mIU/mL) at Screening;

AND

b) Postmenopausal • All female patients of childbearing potential must have a documented negative pregnancy test result at Screening. Patients with elevated β-HCG levels believed to be due to end-stage renal disease may be enrolled if documented to not be pregnant.

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 (i.e., less than 1 percent per year) when used consistently and correctly, and include the following:

- Surgical sterilization at least 6 months before Study Drug administration
- Implants
- LNG and Copper T IUDs
- Sexual abstinence

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

- Injectable hormone depots
- Oral contraceptive pill
- Hormone patch
- Vaginal ring

Periodic abstinence (e.g., 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 FDA M3(R2).