TOUR006-C01 Protocol

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

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

Protocol Number: TOUR006-C01

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Compound name: pacibekitug

Study Phase: 2

Sponsor Name: Tourmaline Bio, Inc.

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Signed by:
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PPD

Date

PPD

Medical monitor name and contact information will be provided separately.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
CCI	[redacted]
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
BP	blood pressure
CFR	Code of Federal Regulations
CCI	[redacted]
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HbA1c	hemoglobin A1c

Abbreviation	Definition
HIV	human immunodeficiency virus
HR	heart rate
hs-CRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committees
IgG	immunoglobulin G
IL	interleukin
IL-6R	interleukin 6 receptor
IRB	Institutional Review Board
LDL-C	low-density lipoprotein-cholesterol
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
mITT	modified intent-to-treat
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
q#d	once every # days (eg, q30d = once every 30 days)
QTL	quality tolerance limit
RR	respiratory rate
SAE	serious adverse event

Abbreviation	**Definition**
SAP	Statistical Analysis Plan
SC	subcutaneous
SMC	Safety Monitoring Committee
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UPCR	urinary protein-to-creatinine ratio
WHO	World Health Organization
WOCBP	women of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

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

Rationale:

Despite the availability of medical therapies to reduce cardiovascular risk in atherosclerotic cardiovascular disease (ASCVD), the overall disease burden remains high. And even in patients managed intensively, a sizable subset of individuals with ASCVD continue to suffer from a high risk of major cardiovascular events (MACE). Thus, there still remains significant unmet need for therapies that target additional risk factors for ASCVD, particularly inflammation.

Interleukin (IL)-6 has been implicated as a promising drug target for addressing this persistent risk of MACE in ASCVD, with human evidence spanning epidemiologic data and genetic analyses (Ridker & Rane, 2021). Such evidence includes the observation across numerous studies for a strong association between cardiovascular risk and elevated IL-6 levels as well as elevated levels of high-sensitivity C-reactive protein (hs-CRP), a well-established marker of IL-6 pathway activation. In addition, subgroup analyses from Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) found that canakinumab, a monoclonal antibody (mAb) targeting IL-1β and yielding partial inhibition of IL-6 upregulation, substantially decreased the risk of cardiovascular events in the subgroups of patients achieving higher reductions in IL-6 levels and hs-CRP (Lorenzatti & Servato, 2018; Ridker et al, 2018). Given the body of evidence supporting the therapeutic potential of IL-6 blockade and the high unmet medical need, TOUR006, also known as pacibekitug, is being developed towards an aim of meaningfully reducing the risk for MACE.

This study will determine whether various dosing regimens of TOUR006, a neutralizing mAb that binds to soluble IL-6, can decrease hs-CRP levels in participants with elevated cardiovascular risk (identified in this study as an elevated hs-CRP and a diagnosis of chronic kidney disease [CKD]). Key outcome measures include levels of hs-CRP CCI [redacted] The pharmacokinetics (PK), safety and tolerability of TOUR006 will also be examined.

Objectives and Endpoints:

Objective	*Endpoint*
Primary	
• Evaluate the effects of TOUR006 compared with placebo on hs-CRP	• Time-averaged percent change from baseline in hs-CRP through Day 90
Key Secondary	
• Evaluate the effects of TOUR006 compared with placebo on hs-CRP	• Percent of participants with time-averaged hs-CRP <2 mg/L through Day 90
Additional Secondary	
• Evaluate the effects of TOUR006 compared with placebo on hs-CRP	• Change from baseline in hs-CRP through Day 180
• Evaluate the pharmacokinetics of TOUR006	• Serum drug concentrations of TOUR006 at Baseline and after 30, 60, 90, 120, 150, and 180 days of treatment • Serum drug concentrations of TOUR006 at 240, 300, and 365 days
Safety	
• Evaluate the safety and tolerability of TOUR006 in participants with elevated cardiovascular risk and CKD	• Proportion of participants with AEs, SAEs, severe AEs, and AEs leading to discontinuation • Description and frequency of AEs of special interest by treatment group • Description of additional safety assessments by treatment group and dose, eg, vital signs, electrocardiogram, and anti-drug antibodies
CCI	
[redacted]	[redacted]

AE=adverse event; CKD=chronic kidney disease; hs-CRP=high sensitivity C-reactive protein CCI
CCI SAE=serious adverse event

Overall Design:

This is a randomized, double-blind, placebo-controlled Phase 2 study to evaluate the PD, pharmacokinetics (PK), and safety of TOUR006 at 3 dosing regimens in participants with elevated cardiovascular risk (identified as an elevated hs-CRP and a diagnosis of CKD).

Participants will undergo a Screening Period of up to 14 days to determine eligibility and those who meet all inclusion criteria and no exclusion criteria will be randomized 1:1:1:1 to 1 of 3 dosing regimens of TOUR006 or placebo (see treatment arms below). To mitigate against imbalances in background safety risk from CKD, participants will be stratified by CKD status to ensure balanced randomization. The treatment arms are as follows:

- Arm A: TOUR006 50 mg administered subcutaneously (SC) every 90 days
- Arm B: TOUR006 25 mg administered SC every 90 days
- Arm C: TOUR006 15 mg administered SC every 30 days
- Placebo: administered SC every 30 days

Approximately 120 participants (30 per treatment arm) will be randomized. After the Screening Period, randomized participants will be dosed every 30 days with TOUR006 or placebo (participants in Arms A and B will receive placebo at Study Days 30, 60, 120, and 150 to align with the 30-day dosing regimen). The end of the treatment period is Study Day 180, after which participants will be followed for safety until Study Day 365. The primary endpoint is the time-averaged percent change from baseline in hs-CRP through Day 90. The primary evaluation will occur after the last participant has their Day 90 assessments.

Inclusion Criteria:

Participants must meet all of the following criteria to participate in the study:

1) Age ≥18 years at time of informed consent form (ICF) signature.
2) Serum hs-CRP level ≥2.0 mg/L and <15 mg/L at the Screening visit and/or at the Pre-screening visit (optional), if the Pre-screening visit occurs within 4 weeks of the Screening visit.
    - Note that hs-CRP testing is not required at the Screening visit if the above criteria for the Pre-screening hs-CRP test are met. However, if hs-CRP testing is performed at the Screening visit, the Screening hs-CRP value must be ≥2.0 mg/L and <15 mg/L to meet this inclusion criterion.
    - Screening patients with ASCVD, diabetes mellitus, metabolic syndrome, obesity, and/or current smoking may increase the chances of identifying patients with hs-CRP ≥2.0 mg/L.

3) Diagnosis of chronic kidney disease, not anticipated to require dialysis during the course of the study, and either:

   - Estimated glomerular filtration rate (eGFR) ≥15 and <60 mL/min/1.73 m^2 at the Screening visit corresponding to stage G3 or G4 (KDIGO 2012), *or*
   - Spot urinary protein-to-creatinine ratio (UPCR) ≥200 mg/g and eGFR ≥60 mL/min/1.73m^2 at the Screening visit.

   Estimated glomerular filtration rate will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (Section 10.6). Screening patients with prior documented proteinuria or albuminuria by quantitative testing or urinary dipstick or patients with long-standing diabetes mellitus and/or hypertension may increase the chances of identifying patients with UPCR ≥200 mg/g at Screening. Note that severe proteinuria (UPCR>3000 mg/g) remains an exclusion criterion (EC #4).

4) Received coronavirus disease 2019 (COVID-19) vaccine (completed the primary series and/or received one bivalent vaccination) at least 30 days prior to the Screening visit, per participant verbal attestation. Primary series is defined as 1 dose of the adenovirus vector vaccine Ad26.COV2 (Janssen/Johnson & Johnson) OR 2 doses of an mRNA vaccine (BNT162b2, Pfizer BioNTech or mRNA-1273, Moderna) OR 2 doses of a protein-based vaccine (NVX-CoV2373, Novavax). Bivalent vaccine (designed to protect against both the original virus that causes COVID-19 and the Omicron variants) is defined as an updated (2023-2024 formula) Pfizer-BioNTech vaccine OR an updated (2023-2024 formula) Moderna vaccine OR an updated (2023-2024 formula) Novavax.

5) Agreement to comply with the following contraception and reproduction restrictions:

   - Male participants must be surgically sterile or, if sexually active with a female partner of childbearing potential must also agree to use a condom for the duration of the study and for 4 months after the last dose of study drug.

   - Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at the Screening visit and negative urine pregnancy test at the randomization visit and must agree to use at least 1 acceptable method (see Section 10.4.2) of contraception throughout the study and for 32 weeks after the last dose of study drug. For the purposes of this study, WOCBP are defined as postmenarchal women who are not surgically sterile (presence of ovaries, uterus, and either fallopian tube) AND not definitively postmenopausal, defined as absence of menses for 24 consecutive months before the Screening visit.

Exclusion Criteria:

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

Laboratory Values

1) Hemoglobin values <9.0 g/dL at the Screening visit.

2) Absolute neutrophil count < 2,000/µL at the Screening visit.

3) Platelet count < 120,000/µL at the Screening visit.

4) Spot urine protein to creatinine ratio >3000 mg/g (3.0 g/g) at the Screening visit.

5) Serum albumin <3.0 g/dL at the Screening visit.

6) Serum total immunoglobulin gamma (IgG) <700 mg/dL at the Screening visit.

7) Uncontrolled diabetes with hemoglobin A1c (HbA1c) >9% at the Screening visit.

8) Low density lipoprotein-cholesterol (LDL-C) ≥190 mg/dL at the Screening visit.

9) Triglycerides ≥500 mg/dL at the Screening visit.

10) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 × upper limit of normal (ULN) at the Screening visit.

11) Total bilirubin >1.5 x upper limit of normal at the Screening visit in the absence of Gilbert syndrome. In participants with Gilbert syndrome, total bilirubin >2.0 x upper limit of normal is the exclusionary threshold.

12) INR outside the therapeutic range (eg, INR 2.0-3.0 for nonvalvular atrial fibrillation) at the Screening visit for participants treated with warfarin.

13) Positive or indeterminate result from QuantiFERON®-TB Gold test at Screening without evaluation and completion of a standard course of therapy meeting World Health Organization (WHO) or local guidelines. For indeterminate test results, retesting may be considered (see Section 5.4).

14) Evidence of human immunodeficiency virus (HIV)-1 or HIV-2 infection by serology at the Screening visit.

15) Evidence of hepatitis B or C by serology (eg, hepatitis B surface antigen positive, or hepatitis C antibody and RNA positive) at Screening. To accommodate reflex testing, the screening period may be increased from up to 14 days to up to 21 days.

Medical Conditions or Diseases

16) Clinical evidence or suspicion of active infection at the Screening or Baseline visit. Treated and/or indolent cutaneous infections, such as isolated cutaneous warts or non-severe tinea pedis, are not exclusionary.

17) Current or recent COVID-19 infection defined as positive result of SARS-CoV-2 test at the Screening visit obtained using point-of-care testing and/or known COVID-19 infection within 30 days prior to the Baseline visit.

18) Serious infection (an infection requiring hospitalization and/or IV antibiotic, IV antifungal, or IV antiviral treatment and/or having a clinical presentation that is viewed by the investigator as consistent with a serious infection) within 6 months before Screening or more than 1 such episode within 18 months prior to the Baseline visit.

19) History (prior or current) of a serious opportunistic infection (ie, not localized thrush due to corticosteroid therapy) within 18 months prior to the Baseline visit.

20) Participants with indwelling urinary or IV catheters at the Screening or Baseline visit.

21) Known history of immunodeficiency (genetic or acquired, such as acquired immunodeficiency syndrome, common variable immunodeficiency, etc.).

22) Active systemic lupus erythematosus and/or systemic lupus erythematosus requiring treatment within 1 year prior to the Baseline visit.

23) History of bone marrow or solid organ transplant or anticipated to receive a bone marrow or solid organ transplant during study participation.

24) History of gastrointestinal (GI) ulceration (with the exception of oral aphthous ulcers) or GI perforation within 12 months prior to the Baseline visit.

25) History of active diverticulitis, active inflammatory bowel disease, or GI abscess within 12 months prior to the Baseline visit.

26) History of GI bleeding (not including hemorrhoidal bleed) requiring hospitalization and/or transfusion within 6 months prior to the Baseline visit.

27) New York Heart Association Class III or IV congestive heart failure and/or hospitalization for heart failure exacerbation within 6 months prior to the Baseline visit.

28) Acute coronary syndrome, stroke, transient ischemic attack, or other thrombotic or thromboembolic event, or arterial revascularization procedure within 6 months prior to the Baseline visit.

29) Untreated clinically significant arrhythmia within 6 months of the Baseline visit, including atrial fibrillation with uncontrolled ventricular rate (>120 bpm) at the Screening or Baseline visit.

30) Uncontrolled hypertension, defined as a systolic blood pressure (BP) >160 mmHg and/or diastolic BP >100 mmHg based on an average of two measurements at the Screening visit.

31) Diagnosis of protein-losing enteropathy.

32) Diagnosis of cachexia and/or unintended weight loss of ≥5% within 3 months prior to the Baseline visit.

33) Active cancer and/or cancer requiring treatment within 1 year prior to the Baseline visit or expected to require treatment during the course of the study. The following are not considered exclusionary: excised basal cell or squamous cell carcinoma of the skin; carcinoma in situ such as cervical or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis; low-risk prostate cancer (Gleason score 6 or less and prostate specific antigen < 10 mg/mL).

34) Active uncontrolled or untreated neuropsychological disorder including seizures within 5 years prior to the Baseline visit, psychosis, or severe cognitive impairment.

35) History of alcohol abuse or other substance use disorder within 1 year prior to the Baseline visit.

36) Known allergy to the study drug or any of its ingredients.

Prior or Current Medications

37) Initiation or discontinuation of a statin, bempedoic acid, icosapent ethyl, GLP-1 receptor agonist, or SGLT2 inhibitor within 4 weeks of the Screening or Baseline visit. A change in dose of any of these medications is not exclusionary.

38) Any previous treatment with an immunomodulatory or immunosuppressive agent, including but not limited to systemic corticosteroids, anti-cytokine therapy (eg, other IL-6 inhibitor [siltuximab, tocilizumab, sarilumab, satralziumab], TNF inhibitor [adalimumab, etanercept, etc], IL-17 inhibitor [secukinumab, ixekizumab, etc], IL-23 inhibitor [guselkumab, risankizumab, etc], other IL inhibitor), methotrexate, azathioprine, mercaptopurine, mycophenolate mofetil, montelukast, or colchicine, within 5 half-lives of the drug (or 3 months, whichever is longer) prior to the Baseline visit 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.

39) Use of systemic antibiotics, antivirals, or antifungals within 14 days prior to the Baseline visit. Systemic is defined as oral or IV drugs that are absorbed into the circulation. Participants who received prophylactic antibiotics may be considered for enrollment after discussion with the medical monitor.

40) Received a live (attenuated) vaccine within 4 weeks prior to the Baseline visit.

41) Received an investigational drug within 30 days (or 5 half-lives of the investigational drug administered, whichever is longer) prior to the Baseline visit.

42) Expected to receive any of the prohibited concomitant treatments/interventions specified in the protocol (Section 6.9) during the Treatment Period or Safety Follow-Up Period.

General Exclusions

43) Currently breastfeeding at the Screening or the Baseline visit.

44) Scheduled, planned, or anticipated surgery, major procedure, or hospitalization that could potentially occur during participation in the study. Participants scheduled for a very low risk surgery (eg, cataract surgery) may be permissible after discussion with the medical monitor.

45) Life expectancy anticipated to be <2 years from the Baseline visit.

46) 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 the study are:

- Treatment Arm A (TOUR006 50 mg administered SC every 90 days)
    - Participants will receive TOUR006 50 mg injections on Baseline and Day 90 visits; matching placebo injections will be administered on Study Days 30, 60, 120, and 150.
    - Total cumulative TOUR006 dose: 100 mg
- Treatment Arm B (TOUR006 25 mg administered SC every 90 days)
    - Participants will receive TOUR006 25 mg injections on Baseline and Day 90 visits; matching placebo injections will be administered on Study Days 30, 60, 120, and 150.
    - Total cumulative TOUR006 dose: 50 mg
- Treatment Arm C (TOUR006 15 mg administered SC every 30 days)
    - Participants will receive TOUR006 15 mg injections on Baseline and Day 30, 60, 90, 120, and 150 visits.
    - Total cumulative TOUR006 dose: 90 mg

Placebo, Dose, and Mode of Administration:

Matched placebo injections will be administered SC every 30 days (Visits 1-6) in the placebo group. Participants in Treatment Arms A and B will receive placebo injections as described above.

Number of Participants:

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

Study Centers

Approximately 50 sites in the US.

Statistical Methods:

The Statistical Analysis Plan (SAP) will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP text will be finalized before the primary analysis is conducted. No changes to the SAP can be made after unblinding for the primary analysis.

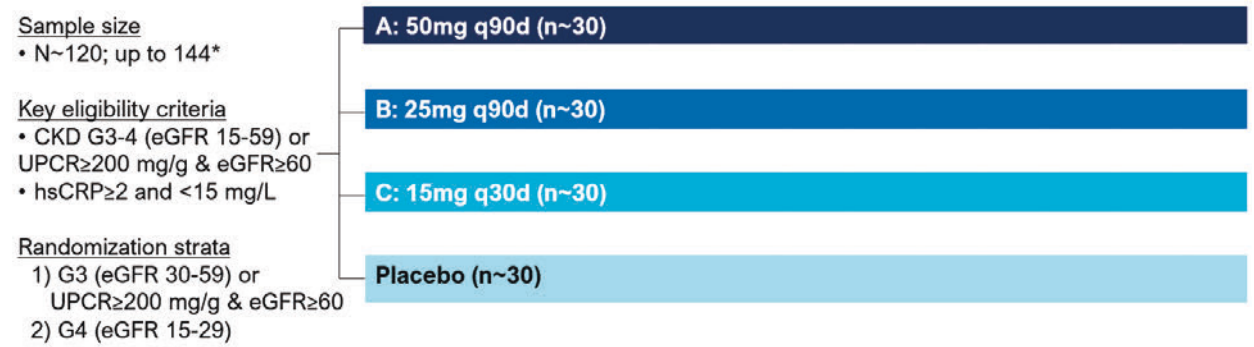
Summary statistics will be presented by treatment arm. Continuous and ordinal variables will be summarized by the number of participants (n), mean, standard deviation (SD), median (IQR), minimum, and maximum for actual values and change from baseline. The quartiles (Q1 and Q3) may be presented as well. Binary and categorical variables will be summarized for each treatment arm by presenting the number and percentage of participants in the categories. Pharmacodynamic endpoints will be analyzed using modified intent-to-treat (mITT) and per protocol populations. Safety endpoints will be analyzed using the safety population. Inclusion into these analytical populations will require at least one dose of study medication. mITT will additionally require at least one post-baseline hs-CRP assessment. Details will be provided in the SAP.

Data Monitoring Committees:

No external Data and Safety Monitoring Board has been appointed for this study. The sponsor's internal safety monitoring committee will monitor the study for safety findings throughout the study

1.2 Study Schema

Figure 1: TOUR006-C01 Study Schema



Screening Period	Treatment Period							Safety Follow-up Period		
Up to 14d (up to 21d if retest)	BL	30	60	90	120	150	180	240	300	365
hs-CRP	X	X	X	X	X	X	X	X	X	X
Study drug injection	X	X	X	X	X	X				

*See Section 9.8 Sample Size Determination
Abbreviations: BL = Baseline; CKD = chronic kidney disease; D/d = day; eGFR = estimated glomerular filtration rate; hs-CRP = high sensitivity C-reactive protein; q30d = every 30 days; q90d = every 90 days; UPCR = urine protein-to-creatinine ratio

1.3 Schedule of Activities (SoA)

	Optional Pre-screening[1]	Screening[2]	Treatment Period							Safety Follow-Up		
Visit Number	-2	-1	1/BL[4]	2[4]	3	4	5	6	7	8	9	10
Visit Day	-56 to -1	Up to 14 days (If retest, up to 21 days)	0	30	60	90	120	150	180	240	300	365
Visit Window (days)				+7/-3	+7/-3	+7/-3	+7/-3	+7/-3	±7	±14	±14	±14
Visit Month			0	1	2	3	4	5	6	8	10	12/EOS
Optional Pre-screening ICF signed	X											
Informed consent signed		X										
Inclusion/exclusion criteria		X	X									
Randomization			X									
Study drug administration (after assessments)			X[3,4]	X[3,4,5]	X[3,5]	X[3,5]	X[3,5]	X[3,5]				
Clinical assessments												
SARS-CoV-2 test (point-of-care)		X										
Medical history		X	X									
Concomitant & prior medications and procedures		X	X	X	X	X	X	X	X	X	X	X
Vital signs[6]		X	X	X	X	X	X	X	X	X	X	X
Height, weight, and BMI			X			X			X			X
Physical examination[7]		X	X			X			X			X
ECG[8]		X	X			X			X			X
AE assessment[9]	X	X	X	X	X	X	X	X	X	X	X	X

	Optional Pre-screening[1]	Screening[2]	Treatment Period							Safety Follow-Up		
Visit Number	-2	-1	1/BL[4]	2[4]	3	4	5	6	7	8	9	10
Visit Day	-56 to -1	Up to 14 days (If retest, up to 21 days)	1	30	60	90	120	150	180	240	300	365
Visit Window (days)				+7/-3	+7/-3	+7/-3	+7/-3	+7/-3	±7	±14	±14	±14
Visit Month			0	1	2	3	4	5	6	8	10	12/EOS
Laboratory Assessments (blood)												
hs-CRP[10]	X[1]	X[1]	X	X	X	X	X	X	X	X	X	X
CCI												
Pregnancy test, serum (WOCBP)[11]		X										
HBV, HCV, HIV tests[12]		X										
QuantiFERON-TB test		X										
Hemoglobin A1c		X										
IgG		X										
Chemistry & eGFR (CKD-EPI)[13]		X	X	X	X	X	X	X	X	X	X	X
Hematology[14]		X	X	X	X	X	X	X	X	X	X	X
INR (if on warfarin)[15]		X	X	X	X	X	X	X	X	X	X	X
Lipids[16]		X	X			X			X			X
CCI												
Additional PD biomarkers[18]			X	X	X	X	X	X	X	X	X	X
TOUR006 PK[19]			X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies[20]			X	X	X	X	X	X	X	X	X	X

	Optional Pre-screening[1]	Screening[2]	Treatment Period							Safety Follow-Up		
Visit Number	-2	-1	1/BL[4]	2[4]	3	4	5	6	7	8	9	10
Visit Day	-56 to -1	Up to 14 days (If retest, up to 21 days)	1	30	60	90	120	150	180	240	300	365
Visit Window (days)				+7/-3	+7/-3	+7/-3	+7/-3	+7/-3	±7	±14	±14	±14
Visit Month			0	1	2	3	4	5	6	8	10	12/EOS
CCI												
Laboratory Assessments (urine)												
Urine pregnancy test, local (WOCBP)[24]			X	X	X	X	X	X	X	X	X	X
Urine protein, creatinine, UPCR (spot)		X							X			X
Urine albumin (spot)			X						X			X
Urinalysis[25]		X							X			X

Abbreviations: AE = adverse event; BL = Baseline Visit; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high sensitivity C-reactive protein; IgG = immunoglobulin gamma; CCI INR = international normalized ratio; PK = pharmacokinetic; TB = tuberculosis; WOCBP = women of childbearing potential; UPCR = urine protein-creatinine ratio

Note: Unscheduled visits/assessments will be performed as needed at the discretion of the investigator.
Note: All scheduled laboratory assessments will be performed centrally except for SARS-CoV-2 testing and urine pregnancy testing.
Note: Blinded laboratory results: hs-CRP, CCI laboratory results will be provided to sites for the Screening and Randomization visits (Visit 1/BL), but will be blinded after Visit 1. Pharmacokinetic data (TOUR006 levels) and anti-drug antibody levels will also be blinded.

1. Optional pre-screening visit: An optional pre-screening visit to obtain a blood sample to evaluate hs-CRP is recommended. This pre-screening visit should only be performed after i) investigator review of the patient's charts to preliminarily assess patient eligibility, and ii) patient signing of the pre-screening informed consent form. The pre-screening hs-CRP test will be performed by the central laboratory. If the pre-screening hs-CRP value is ≥2 mg/L and <15 mg/L

and the pre-screening visit is within 4 weeks of the screening visit, the pre-screening hs-CRP value may be used to support inclusion criterion #2, and hs-CRP testing is not required at the screening visit. If the optional pre-screening visit is used, screening may occur as soon as the pre-screening hs-CRP value has been reviewed by the investigator. See Section 5.3.
2. Screening Period: Note that fasting is not required for Screening assessments. Laboratory tests and blood pressure measurements may be repeated once to assess for eligibility if initial values are slightly out of range. To accommodate retesting, the screening period may be increased from up to 14 days to up to 21 days. See Section 5.3.
3. After study drug has been administered, participants must remain at the study site for at least 1 hour for AE monitoring.
4. Post-dose safety contact: Within 7 days after study drug administration on BL and Day 30 visits, the site must inquire (through email, text, or phone call) whether the participant has experienced any subacute AEs or hypersensitivity reactions following dosing. The site should make at least 2 attempts to contact the participant within 7 days post dose administration. If there is any such reaction or AE, the site must collect applicable information as needed as an AE, and the investigator must determine whether further monitoring and/or safety intervention is warranted for the safety of the participant.
5. Study drug administration should occur no more than 3 days earlier than the nominally scheduled dosing visit and no more than 7 days later than nominally scheduled dosing visit. Study drug will be injected after pre-dose vital signs, physical examination, ECG recording, and blood sample collection are performed.
6. Vital signs include temperature, respiratory rate, heart rate, and blood pressure. Vital signs should be obtained after at least 5 minutes in the sitting position or, when necessary, in a semi-recumbent position. Vital signs will be collected prior to blood sample collection, ECG recording, and study drug administration. At study drug dosing visits, vital signs will be obtained prior to study drug injection and twice after injection. Post-dose vital signs will be obtained 15 minutes (±10 minutes) and 45 minutes (± 15 minutes) after study drug administration.
7. Physical examinations will include assessments of the skin, oropharynx, lungs, heart, abdomen, and extremities. In addition, care should be taken to assess any abnormalities that may be present as indicated by symptoms reported by the participant, the participant's medical history, AEs, or other findings, with particular attention to signs of infection. Physical examinations will be performed by a medically qualified individual such as a licensed physician, physician's assistant, or a registered nurse practitioner.
8. Standard 12-lead ECGs will be recorded in the supine position (or with the participant as flat as possible) after vital signs assessments and after the participant has been resting for at least 5 minutes. The ECGs will be locally read by the investigator.
9. Only procedure-related AEs will be collected at Pre-Screening (optional) and Screening visits.
10. hs-CRP CCI sampling to be acquired prior to dosing.
11. Pregnancy test, serum: For participants who are WOCBP, serum β-human chorionic gonadotropin (β-HCG) will be performed at the Screening visit. Additional testing may be conducted per local requirements. For the purposes of this study, WOCBP are defined as postmenarchal women who are not surgically sterile (presence of ovaries, uterus, and either fallopian tube) AND not definitively postmenopausal, defined as absence of menses for 24 consecutive months before the Screening visit.
12. HBV, HCV, HIV tests: hepatitis B surface antigen (HbsAg), hepatitis C antibody (HCVAb), HCV RNA (reflex testing if HCVAb positive), human immunodeficiency virus (HIV)-1 and HIV-2 antibody.
13. Chemistry and eGFR (CKD-EPI): alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, direct bilirubin, gamma-glutamyl transferase, glucose, phosphate, potassium, sodium, total bilirubin, total protein. eGFR calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Section 10.6).
14. Hematology: hematocrit, hemoglobin, red blood cell indices (mean corpuscular hemoglobin, mean corpuscular volume, red blood cell count, red cell distribution width, reticulocyte count), platelet count, white blood cell count, white blood cell differential (basophils, eosinophils, immature forms, lymphocytes, monocytes, neutrophils)
15. INR will be evaluated among participants treated with warfarin and should be collected in a coagulation tube.

16. Lipids: For the measurement of lipids at visits noted in the SoA, except at Screening, participants will fast (nothing to eat or drink except water) for at least 10 hours prior to fasting lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol [direct]).

CCI [redacted]

19. On dosing visits (BL and Day30, 60, 90, 120, and 150 visits), PK samples to be collected pre-dose. PK blood samples will also be collected on Study Days 180, 240, 300, and 365 at approximately the same time as the pre-dose samples were collected on previous dosing visits.
20. On dosing visits (BL and Day30, 60, 90, 120, and 150 visits), ADA specimens to be collected pre-dose. ADA blood samples will also be collected on Study Days 180, 240, 300, and 365 at approximately the same time as the pre-dose samples were collected on previous dosing visits.

CCI [redacted]

24. Urine pregnancy test (WOCBP): For participants who are WOCBP, urine pregnancy testing will be performed and confirmed negative prior to study drug injection. Additional testing may be conducted per local requirements. For the purposes of this study, WOCBP are defined as postmenarchal women who are not surgically sterile (presence of ovaries, uterus, and either fallopian tube) AND not definitively postmenopausal, defined as absence of menses for 24 consecutive months before the Screening visit.
25. Urinalysis: Dipstick measurements for glucose, heme, ketones, leukocyte esterase, nitrite, and protein will be performed. Microscopy will also be assessed as a reflex if the dipstick is abnormal.

2 INTRODUCTION

2.1 Background and Study Rationale

2.1.1 Overview of ASCVD and Unmet Medical Need

In the US, atherosclerotic cardiovascular disease (ASCVD) is a major, if not the leading, cause of death across gender, race, and ethnicity. In 2020, approximately 550,000 adults in the US died due to coronary heart disease or stroke (Tsao et al., 2023). Atherosclerotic cardiovascular disease involves the narrowing of arteries as plaque builds up on the vessel walls. Arterial plaques can rupture and result in thrombosis, leading to myocardial infarction, stroke, and/or occlusion in other peripheral arteries, leading to vascular complications.

Despite the availability of medical therapies to reduce cardiovascular risk in ASCVD, the overall disease burden remains high. Even among patients optimally managed with lifestyle modifications and pharmacologic therapy, a sizable population with established ASCVD or with multiple risk factors for ASCVD continue to suffer from a high risk of major cardiovascular events (MACE). Thus, there remains a significant unmet need for therapies which target additional risk factors for ASCVD, particularly inflammation.

2.1.2 Therapeutic Rationale for TOUR006 in ASCVD

Interleukin (IL) 6 is a pleiotropic cytokine that belongs to the family of glycoprotein 130 receptor ligands and is produced by many cell types, including T lymphocytes, fibroblasts, and monocytes (Kishimoto, 1989). IL-6 is produced constitutively at low levels and is readily induced by infectious stimuli or inflammatory cytokines. IL-6 is involved in an array of host defense mechanisms and plays a key role in mediating inflammation. The importance of IL-6 in inflammatory conditions was initially demonstrated in rheumatoid arthritis, and currently there are several FDA-approved mAb drugs that target either IL-6 or interleukin 6 receptor (IL-6R) for the treatment of various inflammatory conditions. IL-6 signaling prompts hepatocytes to produce C-reactive protein (CRP), which can serve as an informative biomarker for various inflammatory conditions.

IL-6 has been identified as a promising drug target for addressing this residual inflammatory risk of MACE in ASCVD, with human evidence spanning epidemiologic data and genetic analyses (Ridker & Rane, 2021). Such evidence includes the observation across numerous studies that a strong association exists between cardiovascular risk and elevated IL-6 levels as well as elevated levels of high sensitivity C-reactive protein (hs-CRP), a well-established marker of IL-6 pathway activation (Ridker & Rane, 2021).

High levels of CRP are a known risk factor for ASCVD, nearly tripling the risk of MACE occurrence in 1 study (Ridker et al., 2000). Additionally, hs-CRP levels ≥2.0 mg/L are listed as a risk-enhancing factor alongside elevated low-density lipoprotein-cholesterol (LDL-C) by the American College of Cardiology and American Heart Association (Arnett et al., 2019). Of note, LDL-C and CRP reductions were equal predictors of statin therapeutic benefit in the Pravastatin

or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) study (Ridker et al., 2005).

Subgroup analyses from CANTOS found that canakinumab, a mAb targeting IL-1β and yielding partial inhibition of IL-6 upregulation, substantially decreased the risk of cardiovascular events in the subgroups of patients achieving higher reductions in IL-6 and hs-CRP levels (Lorenzatti & Servato, 2018; Ridker, Everett, et al., 2017). In addition, blockade of IL-6 itself has also been shown to decrease hs-CRP levels after 12 weeks of treatment in the Trial to Evaluate Reduction in Inflammation in Patients With Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition (RESCUE), which was a randomized, double-blind, placebo-controlled study of ziltivekimab, a fully human mAb directed against the IL-6 ligand, with reductions in median hs-CRP levels of 77% to 92% for the ziltivekimab groups and 4% for the placebo group. Dose-dependent reductions in additional biomarkers, including fibrinogen, serum amyloid A, haptoglobin, secretory phospholipase A2, and lipoprotein(a), were also seen, thus reinforcing that inhibition of IL-6 could provide a mechanism to decrease pro-atherothrombotic inflammation (Ridker et al., 2021).

TOUR006 is a neutralizing mAb that binds to soluble IL-6 to inhibit downstream IL-6 signaling and thereby has an impact on inflammation as demonstrated by a reduction in the PD marker, CRP. The available treatments for ASCVD do not target the underlying IL-6 pathway known to drive disease progression; thus, a treatment targeting the inflammatory component of ASCVD could provide a new mechanism for providing therapeutic benefits to patients at high risk for MACE.

A detailed description of the chemistry, pharmacology, development history, efficacy, and safety of TOUR006 is provided in the Investigator's Brochure (IB).

2.2 Benefit/Risk Assessment

2.2.1 Risk Assessment

Table 1: TOUR006 in ASCVD Risk Assessment Summary

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks (potential and observed) associated with anti IL-6/IL-6R class and/or TOUR006 (eg, serious infections; GI perforation and abscess; laboratory abnormalities including neutropenia, thrombocytopenia, elevated liver enzymes, and lipid abnormalities; hypersensitivity reactions	Clinical trial and postmarketing data from other IL-6 and IL-6R inhibitors. Refer to IB Section 6.	[redacted]

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
including anaphylaxis; thromboembolic events)		[redacted]
For 1 of the 4 treatment arms, participants will receive placebo rather than treatment with TOUR006	Placebo comparison supports a robust evaluation of the pharmacodynamics and safety of the investigational agent.	[redacted]
Injection site reaction	CCI [redacted]	CCI [redacted]

Abbreviations: AE=adverse event; ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; GI=gastrointestinal; CCI [redacted]; IL-6=interleukin 6; IL-6R=interleukin 6 receptor; SC=subcutaneous; CCI [redacted]

2.2.2 Benefit Assessment

Most participants will receive active study drug (TOUR006) during the course of the study, which may provide benefit to participants' ASCVD. Meaningful effects in participant outcomes may include reductions in markers of inflammation, including, but not limited to, hs-CRP. All participants will receive medical evaluations related to their general health and disease.

2.2.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants involved in this study, the potential risks identified in association with TOUR006 are justified by the potential benefits that may be afforded to participants with chronic kidney disease (CKD) and ASCVD. In addition, this study will offer important scientific information and insights relevant to evaluating the PD and safety of a novel agent aimed at addressing an unmet medical need for patients with ASCVD.

3 OBJECTIVES AND ENDPOINTS

Objective	*Endpoint*
Primary	
• Evaluate the effects of TOUR006 compared with placebo on hs-CRP	• Time-averaged percent change from baseline in hs-CRP through Day 90
Key Secondary	
• Evaluate the effects of TOUR006 compared with placebo on hs-CRP	• Percent of participants with time-averaged hs-CRP <2 mg/L through Day 90
Additional Secondary	
• Evaluate the effects of TOUR006 compared with placebo on hs-CRP	• Change from baseline in hs-CRP through Day 180
• Evaluate the pharmacokinetics of TOUR006	• Serum drug concentrations of TOUR006 at Baseline and after 30, 60, 90, 120, 150, and 180 days of treatment • Serum drug concentrations of TOUR006 at 240, 300, and 365 days
Safety	
• Evaluate the safety and tolerability of TOUR006 in participants with elevated cardiovascular risk and CKD	• Proportion of participants with AEs, SAEs, severe AEs, and AEs leading to discontinuation • Description and frequency of AEs of special interest by treatment group • Description of additional safety assessments by treatment group and dose, eg, vital signs, electrocardiogram, and anti-drug antibodies
CCI	
[redacted]	[redacted]

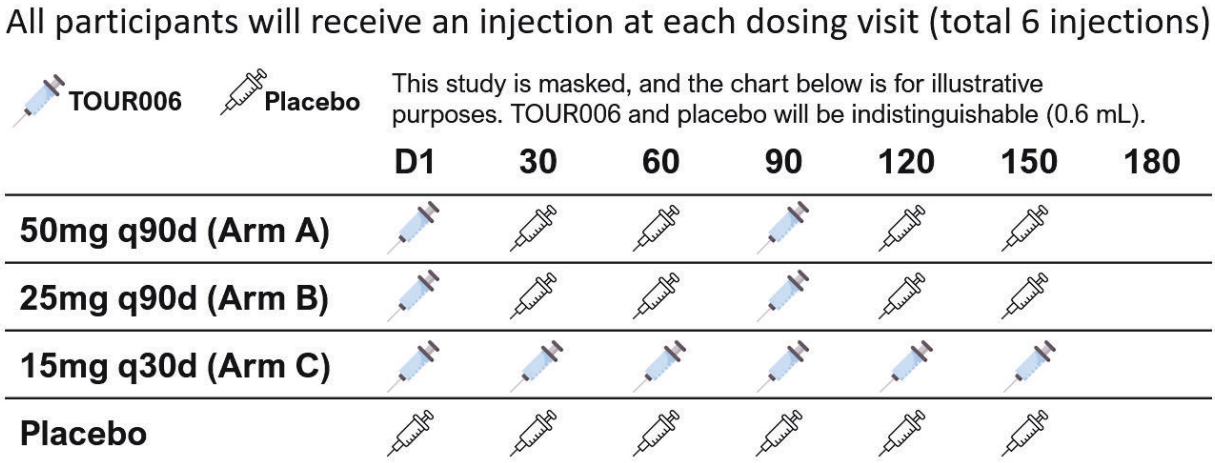
AE=adverse event; CKD=chronic kidney disease; hs-CRP=high sensitivity C-reactive protein; CCI [redacted]; SAE=serious adverse event

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled study to evaluate the PD, pharmacokinetics (PK), and safety (including immunogenicity) of 3 dosing regimens of subcutaneous (SC)-administered TOUR006 (50 mg once every 90 days [q90d], 25 mg q90d, and 15 mg q30d) versus placebo in participants with elevated cardiovascular risk (identified as an elevated hs-CRP and a diagnosis of CKD). The study aims to determine whether various dose levels and dosing regimens of TOUR006 can decrease hs-CRP levels following administration every 30 or 90 days. The study will consist of a 180-day treatment period and a 185-day follow-up period.

Figure 2: Dosing Regimen for TOUR006



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

Approximately 120 participants (30 per treatment arm) will be randomized 1:1:1:1 to one of 4 treatment arms. After the Screening Period, randomized participants will be dosed with TOUR006 at 50 mg q90d (Arm A), 25 mg q90d (Arm B), 15 mg q30d (Arm C), or placebo q30d. Participants in Arms A and B will receive TOUR006 on Baseline and Day 90 visits and placebo on Study Days 30, 60, 120, and 150 to maintain a q30d dosing schedule as for the Arm C and placebo groups. Participants will be followed until Study Day 365. The primary endpoint is the time-averaged percent change from baseline in hs-CRP through Day 90. The primary evaluation will occur after the last participant has their Day 90 assessments (see Section 3).

4.2 Study Design Rationale

4.2.1 Selection of Non-Safety Endpoints

The primary and secondary endpoints involve measurements of changes in hs-CRP levels from baseline. Large cardiovascular outcome studies have demonstrated that reductions in hs-CRP

were associated with improved outcomes, making hs-CRP an important predictor for therapeutic benefit, as discussed in Section 2.1.2.

As a dose-ranging study, the secondary endpoint to assess the PK of various dosages of TOUR006 will provide the first PK clinical data in participants with elevated cardiovascular risk (defined as an elevated hs-CRP and a diagnosis of CKD). CCI

CCI

CCI

4.2.3 Selection of Study Population

Elevated levels of hs-CRP represent a prominent risk factor for MACE, and this study aims to determine if IL-6 activation, measured by elevated hs-CRP levels (≥2 mg/L), can be reduced by treatment with TOUR006 to the target range (hs-CRP <2 mg/L). Accordingly, participants must have elevated hs-CRP levels (≥2.0 mg/L) in order to enroll in the study. In addition, this study will include participants with CKD, given that CKD is associated with a high risk for cardiovascular events and mortality due to ASCVD (reviewed in Liu et al., 2014). Moreover, inflammation plays an important role in the progression of not only ASCVD but also CKD, with involvement of the IL-1 to IL-6 pathway initiated by NLRP3 inflammasome activation in early

renal dysfunction, late kidney failure, diabetic nephropathy, IgA nephropathy, and crystal-mediated nephropathy (Ridker & Rane, 2021).

4.3 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SoA; Section 1.3) for the last participant in the study.

A participant is considered to have completed the study if the participant has completed all visits, including the last visit listed in the SoA (Section 1.3). A participant is considered to have completed the primary outcome if the participant has completed the Day 90 visit.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants must meet all of the following criteria to participate in the study:

1) Age ≥18 years at time of informed consent form (ICF) signature.

2) Serum hs-CRP level ≥2.0 mg/L and <15 mg/L at the Screening visit and/or at the Pre-screening visit (optional), if the Pre-screening visit occurs within 4 weeks of the Screening visit.

   - Note that hs-CRP testing is not required at the Screening visit if the above criteria for the Pre-screening hs-CRP test are met. However, if hs-CRP testing is performed at the Screening visit, the Screening hs-CRP value must be ≥2.0 mg/L and <15 mg/L to meet this inclusion criterion.

   - Screening patients with ASCVD, diabetes mellitus, metabolic syndrome, obesity, and/or current smoking may increase the chances of identifying patients with hs-CRP ≥2.0 mg/L.

3) Diagnosis of chronic kidney disease, not anticipated to require dialysis during the course of the study, and either:

   - Estimated glomerular filtration rate ≥15 and <60 mL/min/1.73 m^2 at the Screening visit corresponding to stage G3 or G4 (KDIGO 2012), *or*

   - Spot urinary protein-to-creatinine ratio (UPCR) ≥200 mg/g and estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2 at the Screening visit.

   Estimated glomerular filtration rate will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (Section 10.6). Screening patients with prior documented proteinuria or albuminuria by quantitative testing or urinary dipstick or patients with long-standing diabetes mellitus and/or hypertension may increase the chances of identifying patients with UPCR ≥200 mg/g at Screening. Note that severe proteinuria (UPCR>3000 mg/g) remains an exclusion criterion (EC #4).

4) Received coronavirus disease 2019 (COVID-19) vaccine (completed the primary series and/or received one bivalent vaccination) at least 30 days prior to the Screening visit, per participant verbal attestation. Primary series is defined as 1 dose of the adenovirus vector vaccine Ad26.COV2 (Janssen/Johnson & Johnson) OR 2 doses of an mRNA vaccine (BNT162b2, Pfizer BioNTech or mRNA-1273, Moderna) OR 2 doses of a protein-based vaccine (NVX-CoV2373, Novavax). Bivalent vaccine (designed to protect against both the original virus that causes COVID-19 and the Omicron variants) is defined as an

updated (2023-2024 formula) Pfizer-BioNTech vaccine OR an updated (2023-2024 formula) Moderna vaccine OR an updated (2023-2024 formula) Novavax.

5) Agreement to comply with the following contraception and reproduction restrictions:

- Male participants must be surgically sterile or, if sexually active with a female partner of childbearing potential must also agree to use a condom for the duration of the study and for 4 months after the last dose of study drug.

- Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at the Screening visit and negative urine pregnancy test at the randomization visit and must agree to use at least 1 acceptable method (see Section 10.4.2) of contraception throughout the study and for 32 weeks after the last dose of study drug. For the purposes of this study, WOCBP are defined as postmenarchal women who are not surgically sterile (presence of ovaries, uterus, and either fallopian tube) AND not definitively postmenopausal, defined as absence of menses for 24 consecutive months before the Screening visit.

5.2 Exclusion Criteria

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

Laboratory Values

1) Hemoglobin values <9.0 g/dL at the Screening visit.

2) Absolute neutrophil count < 2,000/µL at the Screening visit.

3) Platelet count < 120,000/µL at the Screening visit.

4) Spot urine protein to creatinine ratio >3000 mg/g (3.0 g/g) at the Screening visit.

5) Serum albumin <3.0 g/dL at the Screening visit.

6) Serum total immunoglobulin gamma (IgG) <700 mg/dL at the Screening visit.

7) Uncontrolled diabetes with hemoglobin A1c (HbA1c) >9% at the Screening visit.

8) Low density lipoprotein-cholesterol (LDL-C) ≥190 mg/dL at the Screening visit.

9) Triglycerides ≥500 mg/dL at the Screening visit.

10) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 × upper limit of normal (ULN) at the Screening visit.

11) Total bilirubin >1.5 x upper limit of normal at the Screening visit in the absence of Gilbert syndrome. In participants with Gilbert syndrome, total bilirubin >2.0 x upper limit of normal is the exclusionary threshold.

12) INR outside the therapeutic range (eg, INR 2.0-3.0 for nonvalvular atrial fibrillation) at the Screening visit for participants treated with warfarin.

13) Positive or indeterminate result from QuantiFERON®-TB Gold test at Screening without evaluation and completion of a standard course of therapy meeting World Health Organization (WHO) or local guidelines. For indeterminate test results, retesting may be considered (see Section 5.4).

14) Evidence of human immunodeficiency virus (HIV)-1 or HIV-2 infection by serology at the Screening visit.

15) Evidence of hepatitis B or C by serology (eg, hepatitis B surface antigen positive or hepatitis C antibody and RNA positive) at Screening. To accommodate reflex testing, the screening period may be increased from up to 14 days to up to 21 days.

Medical Conditions or Diseases

16) Clinical evidence or suspicion of active infection at the Screening or Baseline visit. Treated and/or indolent cutaneous infections, such as isolated cutaneous warts or non-severe tinea pedis, are not exclusionary.

17) Current or recent COVID-19 infection defined as positive result of SARS-CoV-2 test at the Screening visit obtained using point-of-care testing and/or known COVID-19 infection within 30 days prior to the Baseline visit.

18) Serious infection (an infection requiring hospitalization and/or IV antibiotic, IV antifungal, or IV antiviral treatment and/or having a clinical presentation that is viewed by the investigator as consistent with a serious infection) within 6 months before Screening or more than 1 such episode within 18 months prior to the Baseline visit.

19) History (prior or current) of a serious opportunistic infection (ie, not localized thrush due to corticosteroid therapy) within 18 months prior to the Baseline visit.

20) Participants with indwelling urinary or IV catheters at the Screening or Baseline visit.

21) Known history of immunodeficiency (genetic or acquired, such as acquired immunodeficiency syndrome, common variable immunodeficiency, etc.).

22) Active systemic lupus erythematosus and/or systemic lupus erythematosus requiring treatment within 1 year prior to the Baseline visit.

23) History of bone marrow or solid organ transplant or anticipated to receive a bone marrow or solid organ transplant during study participation.

24) History of gastrointestinal (GI) ulceration (with the exception of oral aphthous ulcers) or GI perforation within 12 months prior to the Baseline visit.

25) History of active diverticulitis, active inflammatory bowel disease, or GI abscess within 12 months prior to the Baseline visit.

26) History of GI bleeding (not including hemorrhoidal bleed) requiring hospitalization and/or transfusion within 6 months prior to the Baseline visit.

27) New York Heart Association Class III or IV congestive heart failure and/or hospitalization for heart failure exacerbation within 6 months prior to the Baseline visit.

28) Acute coronary syndrome, stroke, transient ischemic attack, or other thrombotic or thromboembolic event, or arterial revascularization procedure within 6 months prior to the Baseline visit.

29) Untreated clinically significant arrhythmia within 6 months of the Baseline visit, including atrial fibrillation with uncontrolled ventricular rate (>120 bpm) at the Screening or Baseline visit.

30) Uncontrolled hypertension, defined as a systolic BP >160 mmHg and/or diastolic BP >100 mmHg based on an average of two measurements at the Screening visit.

31) Diagnosis of protein-losing enteropathy.

32) Diagnosis of cachexia and/or unintended weight loss of $\geq$5% within 3 months prior to the Baseline visit.

33) Active cancer and/or cancer requiring treatment within 1 year prior to the Baseline visit or expected to require treatment during the course of the study. The following are not considered exclusionary: excised basal cell or squamous cell carcinoma of the skin; carcinoma in situ such as cervical or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis; low-risk prostate cancer (Gleason score 6 or less and prostate specific antigen <10 mg/mL).

34) Active uncontrolled or untreated neuropsychological disorder including seizures within 5 years prior to the Baseline visit, psychosis, or severe cognitive impairment.

35) History of alcohol abuse or other substance use disorder within 1 year prior to the Baseline visit.

36) Known allergy to the study drug or any of its ingredients.

Prior or Current Medications

37) Initiation or discontinuation of a statin, bempedoic acid, icosapent ethyl, GLP-1 receptor agonist, or SGLT2 inhibitor within 4 weeks of the Screening or Baseline visit. A change in dose of any of these medications is not exclusionary.

38) Any previous treatment with an immunomodulatory or immunosuppressive agent, including but not limited to systemic corticosteroids, anti-cytokine therapy (eg, other IL-6 inhibitor [siltuximab, tocilizumab, sarilumab, satralziumab], TNF inhibitor [adalimumab, etanercept, etc], IL-17 inhibitor [secukinumab, ixekizumab, etc], IL-23 inhibitor [guselkumab, risankizumab, etc], other IL inhibitor), methotrexate, azathioprine, mercaptopurine, mycophenolate mofetil, montelukast, or colchicine within 5 half-lives of the drug (or 3 months, whichever is longer) prior to the Baseline visitor 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.

39) Use of systemic antibiotics, antivirals, or antifungals within 14 days prior to the Baseline visit. Systemic is defined as oral or IV drugs that are absorbed into the circulation. Participants who received prophylactic antibiotics may be considered for enrollment after discussion with the medical monitor

40) Received a live (attenuated) vaccine within 4 weeks prior to the Baseline visit.

41) Received an investigational drug within 30 days (or 5 half-lives of the investigational drug administered, whichever is longer) prior to the Baseline visit.

42) Expected to receive any of the prohibited concomitant treatments/interventions specified in the protocol (Section 6.9) during the Treatment Period or Safety Follow-Up Period.

General Exclusions

43) Currently breastfeeding at the Screening or the Baseline visit.

44) Scheduled, planned, or anticipated surgery, major procedure, or hospitalization that could potentially occur during participation in the study. Participants scheduled for a very low risk surgery (eg, cataract surgery) may be permissible after discussion with the medical monitor.

45) Life expectancy anticipated to be <2 years from the Baseline visit.

46) 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.

5.3 Optional Pre-screening

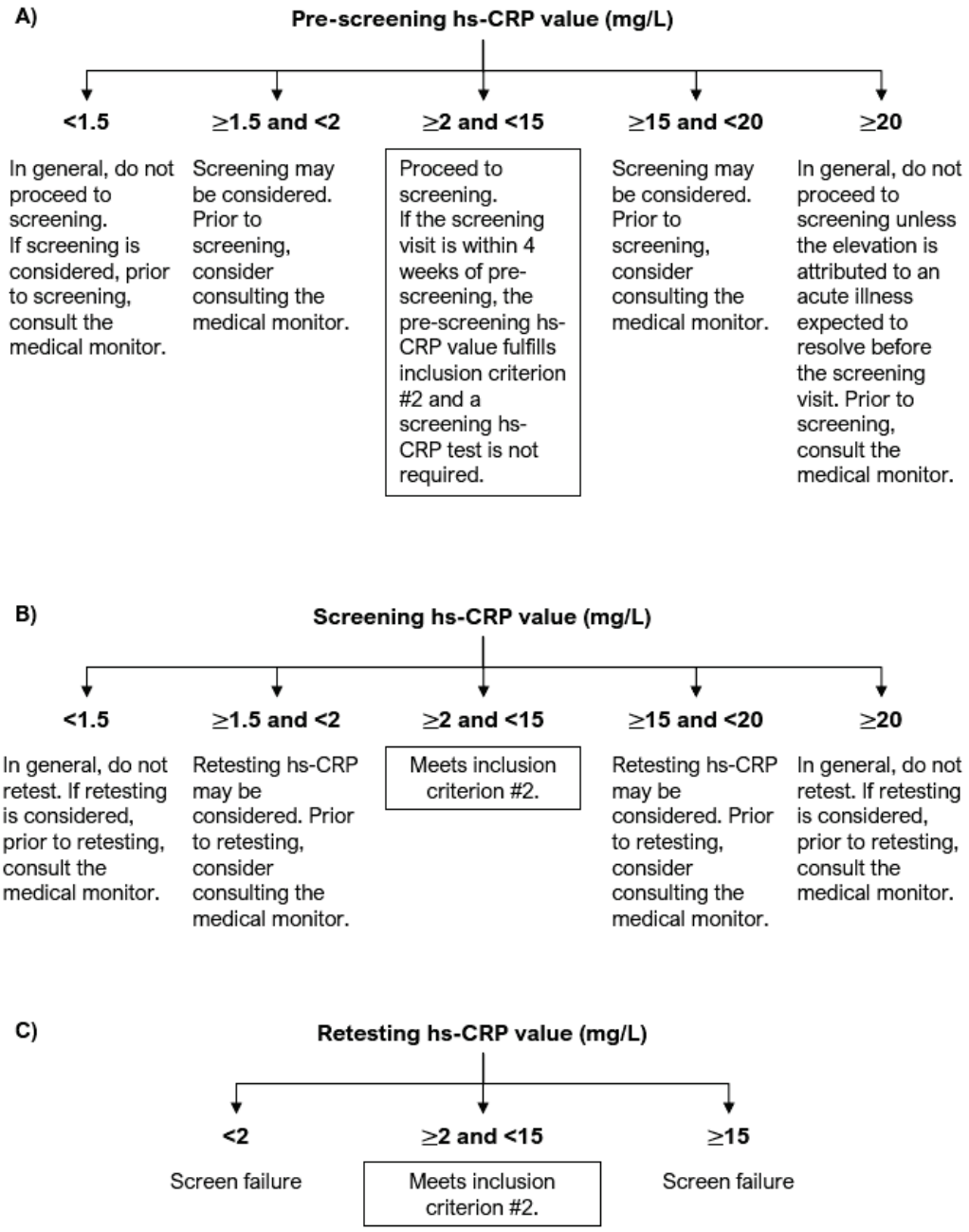
An optional pre-screening visit to obtain a blood sample to evaluate hs-CRP is recommended. This pre-screening visit should only be performed after i) investigator review of the patient's

charts to preliminarily assess patient eligibility, and ii) patient signing of the pre-screening informed consent form. The pre-screening hs-CRP test will be performed by the central laboratory.

If the pre-screening hs-CRP value is ≥2 mg/L and <15 mg/L and the pre-screening visit is within 4 weeks of the screening visit, the pre-screening hs-CRP value may be used to fulfill inclusion criterion #2, and hs-CRP testing is not required at the screening visit. Note that if a screening hs-CRP test is performed, then the value must be ≥2 mg/L and <15 mg/L to support inclusion criterion #2. See Figure 3 for guidance on the approach to hs-CRP values obtained at the pre-screening and screening visits and during retesting.

Optional pre-screening may be performed no more than once per study participant. If the optional pre-screening visit is used, screening may occur as soon as the pre-screening hs-CRP value has been assessed and reviewed by the investigator.

Figure 3: Approach to hs-CRP Test Results from Pre-screening, Screening, and Retesting



Abbreviations; hs-CRP = high sensitivity C-reactive protein

A) Pre-screening: The pre-screening visit is optional. Pre-screening may be performed no more than once per study participant. B) Screening: Note that if the pre-screening hs-CRP value is ≥2 and <15 mg/L and the screening visit occurs within 4 weeks of the pre-screening visit, the pre-screening hs-CRP value fulfills inclusion criterion #2 and a screening hs-CRP test is not required. However, if a screening hs-CRP test is performed, the screening hs-CRP value must be used to determine eligibility. C) Retesting: To accommodate retesting, the screening period may be increased from up to 14 days to up to 21 days.

5.4 Retesting

Laboratory tests and BP measurements may be repeated once to assess for eligibility at screening if initial values are only slightly out of range. To accommodate retesting, the screening period may be increased from up to 14 days to up to 21 days. In general, retesting of hs-CRP may be considered if the initial test is ≥1.5 mg/L. Prior to retesting, the investigator should consult with the medical monitor for any questions or concerns. See Figure 3 for guidance on the approach to hs-CRP values obtained at the pre-screening and screening visits and during retesting.

5.5 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the consolidated standards of reporting trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any procedure-related adverse event (AE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants must be assigned a new participant number. Screen failures may be allowed to rescreen for the study if both the investigator and the sponsor are in agreement regarding rescreening based on the likelihood of the participant satisfying all the eligibility criteria.

6 STUDY DRUG(S) AND CONCOMITANT THERAPY

Study drugs are all pre-specified, investigational medicinal products intended to be administered to the study participants during the study conduct.

6.1 Study Drugs Administered

Table 2: Study Drugs Administered

	TOUR006 50 mg	**TOUR006 25 mg**	**TOUR006 15 mg**	**Placebo**
Study Arm	Arm A	Arm B	Arm C	Placebo
Study Drug Name	TOUR006	TOUR006	TOUR006	Placebo
Study Drug Description	A fully human mAb of the IgG2 isotype. It binds with high affinity to human IL-6 and neutralizes its functions.	A fully human mAb of the IgG2 isotype. It binds with high affinity to human IL-6 and neutralizes its functions.	A fully human mAb of the IgG2 isotype. It binds with high affinity to human IL-6 and neutralizes its functions.	All excipients found in TOUR006 vial but without any active drug.
Type	Biologic	Biologic	Biologic	Non-active comparator
[redacted]				
Route of Administration	SC injection	SC injection	SC injection	SC injection
Arm Description	Participants will receive TOUR006 50 mg on Baseline and Day 90 visits; matching placebo injections will be administered on Study Days 30, 60, 120, and 150	Participants will receive TOUR006 25 mg on Baseline and Day 90 visits; matching placebo injections will be administered on Study Days 30, 60, 120, and 150	Participants will receive TOUR006 15 mg on Baseline and Day 30, 60, 90, 120, and 150 visits	Participants will receive matching placebo injections on Baseline and Day 30, 60, 90, 120, and 150 visits
Use	Experimental	Experimental	Experimental	Non-active comparator
IMP and NIMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study drug will be provided in vial. Each vial will be labeled as required per country requirement.	Study drug will be provided in vial. Each vial will be labeled as required per country requirement.	Study drug will be provided in vials. Each vial will be labeled as required per country requirement.	Study drug will be provided in vial. Each vial will be labeled as required per country requirement.

Former Name(s)	PF-04236921	PF-04236921	PF-04236921	Not applicable

Abbreviations: AxMP=auxiliary medicinal products; IgG2=immunoglobulin G2; IL=interleukin; IMP=investigational medicinal product; mAb=monoclonal antibody; NIMP=non investigational medicinal product; SC=subcutaneous; q30d=every 30 days; q90d=every 90 days.

6.2 Preparation/Handling/Storage/Accountability

Instructions for preparation of each SC dose of study drug will be provided to the unblinded, qualified staff member. Preparation and dispensing of the study drug will be handled by the site pharmacy. Instructions for safe handling of the study drug are provided in the Pharmacy manual.

The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study drug.

Only participants enrolled in the study may receive study drug, and only authorized site staff may supply, prepare, or administer study drug.

All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator or designee is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

6.3 Assignment to Study Drug

Table 3: Randomization Assignment

Type of Study	Study Assignment
Study using IWRS	Participants will be randomly assigned to a treatment arm after the investigator has verified eligibility. Participants will be randomly assigned 1:1:1:1 to receive TOUR006 (50 mg q90d, 25 mg q90d, or 15 mg q30d) SC or placebo. Randomization will be stratified by CKD status to one of two strata: • stage 3 [eGFR 30-59 mL/min/1.73m^2] *or* UPCR≥200 mg/g and eGFR ≥60 mL/min/1.73m^2 vs • stage 4 [15-29 mL/min/1.73m^2] using a centralized IWRS. Refer to the IWRS Quick Reference Guide for instructions on using the IWRS.

Abbreviations: CKD=chronic kidney disease; IWRS=Interactive Web Response System; SC=subcutaneous; UPCR=urinary protein-to-creatinine ratio.

6.4 Blinding

Table 4: Study Blinding

Type of Study	Blinding
Blinded study with unblinded third party who is dispensing study drug	The sponsor, participants, caregivers, investigators, and site personnel, with the exception of the unblinded, qualified staff member, will be blinded to treatment assignments. The site unblinded, qualified staff member will remain unblinded throughout the duration of the trial. If for any reason sponsor personnel need to be unblinded, the list of personnel and the reason for unblinding will be documented. Blinding of the participant and the investigator will remain in place throughout the duration of the study.

In the event of a suspected drug-related, serious, and unexpected adverse event (ie, suspected unexpected serious adverse reaction [SUSAR]), designated unblinded sponsor (or designee) personnel may provide a participant's treatment assignment for the purpose of regulatory authority reporting. If the serious adverse event (SAE) requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention information, may be sent to investigators in accordance with local regulations. Notification of the intervention information is only made known to those who require it for safety reporting and submission processes. All other individuals involved in the study, including the investigator, will remain blinded to the intervention information. Participants for whom the blinding is broken for this reason are not withdrawn from the study.

In case of an emergency including an SAE that may be considered drug-related, the investigator will determine (in consultation with the medical monitor, if possible, to do so in a timely fashion without undue delay that may adversely affect the participant's care) if unblinding of a participant's treatment assignment and obtaining the participant's treatment assignment from the IWRS is medically necessary to provide care. If a participant's treatment assignment is to be unblinded, the sponsor must be notified as soon as possible but no later than 24 hours after unblinding. The date and reason for unblinding must be recorded in the source documentation and electronic Case Report Form (eCRF), as applicable.

6.5 Study Drug Administration

Participants will be dosed at the study site and receive study drug directly from the investigator or a qualified designee, under medical supervision. Study drug will be administered after visit assessments are completed. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug. For details, see Section 8.1.6.

6.6 Dose Modification

Dose modification at the individual participant level will not be permitted in the study.

Dose reduction may be recommended by the Safety Monitoring Committee (SMC) at an aggregate level (eg, the dose level of a study arm) for safety reasons. Please refer to Section 7 for details on study drug discontinuation or interruption for individual participants.

6.7 Access to Study Drug after the End of the Study

Study drug will not be available to study participants following completion of the study. Study participants should follow the investigator or physician's advice for standard of care treatment.

6.8 Treatment of Overdose

An overdose is defined as a significant increase from the recommended/scheduled dosage for a product. Administration of investigational product for this study will be performed in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, any single administration of study drug that is at least 100 mg (2-fold higher than the planned highest dose of 50 mg) will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event the investigator becomes aware of an overdose, the investigator should:

- Contact the medical monitor within 24 hours.
- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study drug should be interrupted. The evaluation process should be completed before the next investigational product administration.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Any AE that emerges from the overdose should be managed by the investigator in accordance with standard of care.
- Obtain a plasma sample for PK analysis if requested by the medical monitor and/or sponsor, as determined on a case-by-case basis.
- Document the quantity of the excess dose.

6.9 Concomitant Therapy and Interventions

Concomitant therapies or interventional procedures that are medically indicated for any AEs the participant has during the trial or that are provided as part of standard care for the participant's medical conditions, are permitted at the discretion of the investigator and supersede any of the restrictions outlined in this protocol.

Any therapy (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 CYP450 Substrates with a Narrow Therapeutic Index

Inhibition of IL-6 signaling in the setting of an IL-6 driven inflammatory process may result in increased activity of some cytochrome P450 enzymes, possibly leading to increased metabolism and reducing the effectiveness of certain concomitant medications that are CYP450 substrates. The effects of TOUR006 on the expression of CYP enzymes and transporters is unknown. The effect of TOUR006 on CYP enzymes may be clinically relevant for CYP450 substrates with a narrow therapeutic index.

Exercise caution when study drug is co-administered with CYP3A4 substrate drugs where a decrease in effectiveness would be undesirable. CYP450 substrates with a narrow therapeutic index include: conivaptan, desipramine, dronedarone, imipramine, nortriptyline, phenytoin, quinidine, theophylline, tizanidine, tolvaptan, trimipramine, warfarin (Drug Interaction Database queried 25 Oct 2023).

Study participants treated with warfarin will undergo INR testing as specified in Section 1.3 with additional testing as clinically indicated.

6.9.2 Excluded Concomitant Therapies/Interventions

The following therapies/interventions are prohibited during participation in the study:

- Systemic (ie, oral or IV) corticosteroid use. Otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not prohibited.
- Agent that inhibits IL-6 (besides study drug), such as siltuximab, or inhibits the IL-6 receptor, such as tocilizumab, sarilumab, or satralizumab.
- Any treatment with an immunomodulatory or immunosuppressive agent, such as anti-cytokine therapy (eg, TNF inhibitor [adalimumab, etanercept, etc], IL-17 inhibitor [secukinumab, ixekizumab, etc], IL-23 inhibitor [guselkumab, risankizumab, etc], other IL inhibitor), methotrexate, azathioprine, mercaptopurine, mycophenolate mofetil, montelukast, or colchicine, etc.

- Use of any investigational agent for any condition.

- Any live (attenuated) vaccination. Examples of live (attenuated) vaccinations include but are not limited to the intranasal influenza vaccine and Zostavax (a shingles vaccine). The injected influenza vaccine and Shingrix (a shingles vaccine) are not live vaccines and are thus permitted.

7 DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.9.

7.1 Discontinuation of Study Drug

In rare instances, it may be necessary for a participant to permanently discontinue study drug. A participant may be withdrawn from the study drug at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Discontinuation of treatment does not represent withdrawal from the study. If study drug is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for safety and other outcomes. Study termination should happen only in cases of withdrawal of informed consent or lost-to-follow-up. Even if the study drug administration is discontinued, all effort should be made to keep the participant in the study until the scheduled end of the study.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing a reason).

If possible, this participant should undergo an unscheduled visit and obtain assessments as noted in the SoA for the end-of-study visit. The participant will be permanently discontinued from the study drug and the study at the time that the participant indicates a desire to withdraw.

Any SAE will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (Section 7.3).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, and the investigator must document this in the site study records.

Study participants will not be replaced.

7.3 Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study drug. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

7.4 Criteria for Early Study Termination

The sponsor may terminate the study at any time. Early study termination criteria may include, but are not limited to:

- A safety concern per a recommendation of the SMC;

- The quality or quantity of data recording is inaccurate or incomplete as assessed by the sponsor;

- There is poor adherence to the protocol and regulatory requirements;

- The incidence or severity of AEs indicates a potential health hazard to the participants;

- The sponsor initiates plans to modify or discontinue the development of the study drug.

In the event of sponsor decision to no longer supply the study drug, ample notification, whenever possible, will be provided so that appropriate adjustments to participant's treatment can be made.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

The maximum amount of blood collected from each participant over the duration of the study, excluding a pre-screening blood sample to evaluate hs-CRP or any extra assessments that may be required, will not exceed the volume referenced in the ICF.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

Baseline will be determined by the assessments obtained on Baseline visit and before administration of study drug.

8.1.1 Informed Consent

The investigator or a qualified designee (consistent with local regulations) must obtain documented consent from each potential participant/legal representative before participation in the study. A separate documented consent must be obtained prior to collection of a blood sample to evaluate hs-CRP during the optional pre-screening visit. A signed copy of the pre-screening ICF and study ICF must be given to the participant and the original must be placed in the participant's study source records.

8.1.2 Assignment of Participant Number

Each participant who signs the ICF, meets all eligibility criteria, and is assigned to study procedures will be assigned a unique participant number that will identify the participant throughout the study. Once a number has been assigned, it cannot be reassigned to another study participant.

8.1.3 Medical History

A medical history will be obtained by the investigator or a qualified designee at the screening visit and the Baseline visit. All active conditions and clinically relevant past conditions should be recorded, and any condition diagnosed that the investigator deems clinically significant.

8.1.4 Therapy and Interventions Review (Prior and Concomitant)

The investigator or a qualified designee should review the participant's prior treatment/intervention use to confirm eligibility based upon the inclusion (Section 5.1) and exclusion (Section 5.2) criteria. All treatments/interventions currently taken by the participant should be reviewed and recorded at all study visits.

8.1.5 Inclusion and Exclusion Criteria Review

All inclusion (Section 5.1) and exclusion criteria (Section 5.2) should be reviewed by the investigator at screening and the Baseline visit to ensure that the participant qualifies for the study.

CCI [redacted]

8.2 Blinded Laboratory Results

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. The following labs will be blinded to the study team and site staff after the Randomization visit until unblinding of the clinical database,

and will not be reported to sites: hs-CRP, IL-6, fibrinogen, serum amyloid A (SAA), PK data (TOUR006 concentrations) and anti-drug antibodies.

8.3 Pharmacodynamic Assessments

Blood samples will be collected for measurement of hs-CRP, CCI [redacted]

Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Each serum sample will be divided into aliquots. Samples collected for analyses of PD may also be used to further characterize safety findings.

Aliquots from the PD samples may be retained as backup for retesting if necessary.

CCI [redacted]

8.5 Pharmacokinetic Assessments

Blood samples will be collected for measurement of serum concentrations of TOUR006 as specified in the SoA (Section 1.3).

Instructions for the collection and handling of biological samples will be provided by the sponsor in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of TOUR006. Each serum sample will be divided into aliquots. Samples collected for analyses of TOUR006 serum concentration may also be used to further evaluate safety or PD findings.

Aliquots from the PK samples may be retained as backup for retesting if necessary.

Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6 Immunogenicity Assessments

Antibodies to TOUR006 (ie, anti-drug antibody [ADA]) will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Each serum sample will be divided into aliquots.

The detection and characterization of antibodies to TOUR006 will be performed using a validated assay method by or under the supervision of the sponsor. If the participant tests positive for ADA after confirmatory and reactive titer testing, the sample will be further characterized and/or evaluated for their ability to neutralize the activity of the study drug(s). Regardless of neutralizing antibodies (NAb) positivity, ADA will continue to be evaluated throughout the study as outlined in the SoA (Section 1.3).

Samples may be retained as backup for retesting, if necessary.

8.7 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.7.1 Physical Examinations

Physical examinations will include assessments of the skin, oropharynx, lungs, heart, abdomen, and extremities. In addition, care should be taken to assess any abnormalities that may be present as indicated by symptoms reported by the participant, the participant's medical history, AEs, or other findings, with particular attention to signs of infection. Physical examinations will be performed by a medically qualified individual such as a licensed physician, physician's assistant, or a registered nurse practitioner.

As needed to further assess any AEs, additional physical examination assessments should be performed in accordance with appropriate clinical care.

Clinically significant abnormalities in the physical examination that emerge after study drug initiation (or worsen from baseline) should be captured as AEs. Clinically significant physical examination abnormalities identified before study drug initiation, unless considered procedure -related (Section 8.8.6), will be recorded as medical history.

Height and weight will also be measured and recorded as per the SoA (Section 1.3). Body mass index will be calculated using the height and weight values.

8.7.2 Vital Signs

The following vital signs will be collected: heart rate (HR), BP, respiratory rate (RR), and oral or tympanic temperature (°Celsius or °Fahrenheit).

At study drug dosing visits, vital signs will be obtained prior to study drug injection and twice after injection. Post-dose vital signs will be obtained 15 minutes (±10 minutes) and 45 minutes (±15 minutes) after study drug administration. When the timing of these measurements coincides

with a blood collection, all vital signs are to be obtained before the nominal time of the blood collection (see SoA, Section 1.3).

To standardize the collection of vital signs:

- Vital signs should be obtained after at least 5 minutes in the sitting position or, when necessary, in a semi-recumbent position.
- BP and HR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. If HR is measured manually, then the pulse rate should be measured in the brachial or radial artery for at least 30 seconds (with appropriate calculation to achieve a per 60 second rate).
- The BP cuff with proper size should be used to measure BP each time. The participant's arm should be supported (eg, resting on a desk).
- The RR should be measured for at least 30 seconds (with appropriate calculation to achieve a per 60 second rate).
- Temperature should be collected using the tympanic or oral methods and the same method should be used consistently for the participant throughout the study. If the same method is not used, then this should be noted in the eCRF.

Vital sign abnormalities may be repeated as needed to rule out the possibility of a procedural error or abnormality.

Clinically significant abnormalities in the vital signs that emerge after study drug initiation (or worsen from baseline) should be captured as AEs. Clinically significant vital sign abnormalities identified before study drug initiation, unless considered procedure-related (Section 8.8.6), will be recorded as medical history.

8.7.3 Electrocardiograms

Single 12-lead ECG(s) will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the HR and measures PR, RR, QRS, and QT intervals.

All scheduled ECGs will be performed after the participant has rested quietly for at least 5 minutes in a supine position. When the timing of the measurements coincides with a blood collection, the ECG should be obtained first. If appropriate, ECGs may be repeated to rule out improper lead placement or other procedural error or abnormality as contributing to an ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

Clinically significant ECG abnormalities that emerge after study drug initiation (or worsen from baseline) should be captured as AEs. Clinically significant ECG abnormalities identified before

study drug initiation, unless considered procedure-related (Section 8.8.6), will be recorded as medical history.

Electrocardiograms will be interpreted by the investigator (or qualified designee) at the site. There is no central reader of ECGs for this study. Copies of all raw ECG data (ie, ECG strips or reports) will be retained with the source documentation.

8.7.4 Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory results and document this review. Abnormal laboratory values must be reviewed by the investigator for potential clinical significance.

Clinically significant or Grade 3 or higher (based on Common Terminology Criteria for Adverse Events [CTCAE] v5.0) laboratory test abnormalities that emerge after study drug initiation (or worsen from baseline) should be captured as AEs (Section 10.3.1). Clinically significant laboratory value abnormalities identified before study drug initiation, unless considered procedure related (Section 8.8.6), will be recorded as medical history.

All laboratory tests with values considered clinically significantly abnormal that worsen compared to baseline during participation in the study drug or follow-up period should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or until at least the values remain stable at a new baseline. Unscheduled visits may be added as needed in order to follow laboratory values considered abnormal and clinically significant.

All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

As needed to further assess any AEs, additional laboratory assessments should be performed in accordance with appropriate clinical care.

8.7.5 Pregnancy Testing

Pregnancy testing will be conducted for WOCBP. Refer to Section 5.2 for the exclusion criterion pertaining to pregnancy and the SoA (Section 1.3) for timing of the pregnancy test(s).

A serum test is required at screening, and a urine test is to be used at all other designated visits per the SoA. A positive urine test must be followed by serum testing for confirmation. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulations, to establish the absence of pregnancy at any time during participation in the study.

Participants who become pregnant during the trial must not receive further study drug and should be followed according to the procedures outlined in Section 8.8.5.

8.7.6 Post-dose Safety Contact

Within 7 days after study drug administration on Baseline and Day 30 visits, the site must inquire (through email, text, or phone call) whether the participant has experienced any AEs or hypersensitivity reaction following dosing. The site should make at least 2 attempts to contact the participant within 7 days post dose administration. If there is any such reaction or AE, the site must collect applicable information as needed as an AE, and the investigator must determine whether further monitoring and/or safety intervention is warranted for the safety of the participant.

8.8 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

The definitions of unsolicited and solicited AEs can be found in Section 10.3.1.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.4.

8.8.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from initial study drug dose at the Baseline visit until the Day 365 follow-up visit at the timepoints specified in the SoA (Section 1.3). However, any event occurring after signing of the optional pre-screening ICF or the full study ICF that meets the definition of a procedure-related AE (Section 8.8.6) should be reported as an AE.

CCI and SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.5. The investigator will submit any updated SAECCI data to the sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor or designee.

8.8.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.8.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs CCI (as defined in Section 10.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.4.

8.8.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.8.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study drug and until 32 weeks after last dose of study drug.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy or female partner pregnancy of male participant (after obtaining the necessary signed informed consent from the female partner).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.

Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study drug.

8.8.6 Procedure-related Adverse Events

Procedure-related AEs are those events considered by the investigator to be related to the conduct of the clinical study, independent of the study drug. That is, the event may be related to the fact that a participant is participating in the trial. Examples of procedure-related AEs include:

- Injection-related symptoms (eg, bruising, pain, bleeding), excluding ISRs
- Pain, bruising, dizziness, syncope due to blood collection
- Vomiting or dizziness due to fasting for an examination or injection
- Skin irritation, redness, or itching during an ECG

If the investigator determines that the AE is associated with study procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements.

8.8.7 Injection Site Reactions

Injection site reactions are a type of AE that can develop following administration of any SC administered therapy. Injection site reactions will be collected as part of the routine surveillance for AEs overall. The most common manifestations of ISRs are itching, redness, swelling, pain, induration, and ulceration.

Injection site reactions need to be differentiated from symptoms associated with the technique of administering SC injections (eg, procedure-related AEs of local trauma due to the injection) rather than the study drug itself. ISRs are generally delayed in onset and/or prolonged in duration compared with symptoms associated with the technique of administering SC injections.

The intensity of ISRs will be graded as follows on the relevant eCRF:

- Grade 1: Mild, transient reaction; no treatment required
- Grade 2: Moderate; may require symptomatic treatment for ≤24 hours (eg, antihistamine, non-steroidal anti-inflammatory drugs [NSAIDS], narcotics, IV fluids)
- Grade 3: Severe; prolonged reaction not responsive to symptomatic treatment for ≤24 hours; recurrence of symptoms following initial improvement; hospitalization may be required for clinical sequelae
- Grade 4: Life-threatening consequences; urgent intervention required
- Grade 5: Death

For each ISR, the relevant manifestation(s) will be recorded (eg, pain, redness, swelling, ulceration, itching).

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9 STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP text will be finalized before the primary analysis is conducted. No changes to the SAP can be made after unblinding for the primary analysis. See Section 9.6 for details on the primary analysis versus final analysis. The SAP will serve as a companion document to the protocol. The SAP will further describe the statistical analyses.

Analyses presented in the SAP will supersede those presented in this protocol.

9.1 General Considerations

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, North Carolina).

Summary statistics will be presented by treatment arm. Continuous and ordinal variables will be summarized by the number of participants (n), mean, standard deviation (SD), median (IQR), minimum, and maximum for actual values and change from baseline. The quartiles (Q1 and Q3) may be presented as well. Binary and categorical variables will be summarized for each treatment arm by presenting the number and percentage of participants in the categories. Statistical tests for comparison between treatments will be performed using a two-sided alpha level of 5%. Point estimates will be presented with the respective 95% two-sided confidence intervals (CIs).

Pharmacodynamic endpoints will be analyzed using modified intent-to-treat (mITT) and per protocol populations. Safety endpoints will be analyzed using the safety population. Inclusion into these analytical populations will require at least one dose of study medication. mITT will additionally require at least one post-baseline hs-CRP assessment. Details will be provided in the SAP.

9.2 Primary Endpoint Analysis

The primary endpoint analysis will analyze time-averaged percent change from baseline in hs-CRP through Day 90 for the per protocol population.

The baseline hs-CRP value is defined as the average of the hs-CRP result at the qualifying visit (the most recent pre-baseline value, ie, the pre-screening, screening, or retest value) and the hs-CRP result at the Baseline visit.

Methodology for the main primary endpoint analyses as well as sensitivity and supportive analyses will be specified in the SAP. The SAP will be finalized prior to these analyses.

Subgroup analyses will be performed by the randomization stratification factor, CKD status to one of two strata:

- stage 3 [eGFR 30-59 mL/min/1.73m^2] *or* Urinary protein-to-creatine ration (UPCR) ≥200 mg/g and eGFR ≥60 mL/min/1.73m^2 vs

- stage 4 [15-29 mL/min/1.73m^2].

Subgroups defined by other demographic and baseline characteristics including baseline hs-CRP values will be described in the SAP.

Strategies to address missing data will be detailed in the SAP.

9.3 Analysis of Other Pharmacodynamic Endpoints

The key secondary endpoint is the percent of participants achieving a time-averaged hs-CRP <2 mg/L through Day 90. Methodology for the key secondary, additional secondary, and exploratory endpoint analyses as well as sensitivity and supportive analyses will be specified in the SAP.

9.4 Safety Analyses

Safety parameters will be analyzed for the safety population, according to the treatment actually received.

9.4.1 Adverse Events

The AE verbatim terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 26.1. Adverse events will be coded to a primary System Organ Class (SOC) and preferred term (PT).

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

An overview of AEs will be provided including counts and percentages of participants in the following categories:

- Any TEAE (overall and by maximum severity)
- Any study drug related TEAE (overall and by maximum severity)
- Any serious TEAE
- Any severe TEAE (CTCAE Grade 3 or higher)
- Any TEAE leading to discontinuation of study drug
- Any TEAE leading to death

If a participant experiences >1 TEAE meeting the criteria of interest, the occurrence with the greatest severity and the closest relationship with study drug will be used in the corresponding summary tables.

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

Treatment-emergent safety events of special interest (Section 8.8.8) will be summarized by category and PT (overall and by maximum severity).

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

9.4.2 Laboratory Tests

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

Laboratory parameters of interest include white blood cell count, ANC, platelet count, ALT, AST, cholesterol (total, LDL), and triglycerides. Grades will be calculated for these applicable laboratory tests of interest, using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. A shift table of baseline to worst on-treatment CTCAE grade for applicable laboratory parameters will be presented. Additionally, a shift table of baseline to worst on-treatment value (low, normal, high, as compared to the normal range) may be presented.

9.4.3 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 participants with exceeding pre-defined threshold values will be summarized:

- systolic blood pressure >160 mmHg
- systolic blood pressure <90 mmHg
- heart rate >110 bpm
- heart rate <50 bpm

9.4.4 Electrocardiograms

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

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

- QTcF >450 msec
- QTcF >480 msec
- QTcF >500 msec
- QTcF increase from baseline >30 msec
- QTcF increase from baseline >60 msec

9.4.5 Physical Exams and Other Safety

Physical examination results and pregnancy data will be listed.

9.5 Pharmacokinetic Analysis

The TOUR006 concentration will be summarized by scheduled assessment times and treatment group.

9.6 Primary and Final Analyses

A primary analysis of PD effect and safety will be performed after all randomized/treated participants have completed at least their Day 90 visit (or discontinued early). After the completion of the safety follow-up period, a subsequent final analysis will be performed, following final database lock. The study database will be monitored, cleaned, and frozen through the data cut time point for each analysis (primary and final). The study team, except the unblinded team members, should remain blinded for the duration of the study until after final database lock. Dissemination of the primary analysis results will be managed according to the sponsor's communication plan and may include public disclosure and sharing summary results with external stakeholders. The sponsor and CRO personnel who are unblinded will be separate from the direct study team. The sponsor and CRO will still maintain the blind for study team members who will be involved in daily study conduct, study management, safety and data monitoring through the completion of the study. There will be no impact on study conduct, analysis, or reporting. Additional details for statistical methods will be provided in the SAP.

9.7 Interim Analysis

No formal interim analysis is planned for the PD evaluation.

9.8 Sample Size Determination

Approximately 30 participants will be randomized per treatment group or placebo for a total of 120 participants. Additional participants may be enrolled (up to 20%, or an additional 24 participants beyond the 120 planned) to account for participants whose Baseline hs-CRP is

<2.0 mg/L, ≥15 mg/L, or decreased by 50% or more from the Screening (or optional Pre-screening) hs-CRP value. No formal power calculation was performed for sample size.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and national regulatory authority (as applicable) before the study is initiated.

Protocols and any amendments to the protocol will require IRB/IEC and national regulatory authority approval (as applicable) before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study as directed by the site's IRB.

A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is required to sign a new ICF.

10.1.4 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

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10.1.6 Dissemination of Clinical Study Data

The sponsor will comply with current regulatory requirements for disclosure and submission or study results. The sponsor's policy on publication of study information and tabular study results is described in Section 10.1.10.

10.1.7 Data Quality Assurance

Investigators and site staff will be trained on protocol procedures and eCRF completion before enrolling participants in the study.

All participant data relating to the study will be recorded on eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of eCRFs will be provided by the sponsor.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator or institution/site as applicable, for the period of time established in the clinical study agreement entered by the investigator's study site unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must be available.

Definition of what constitutes source data and its origin can be found in ICH Guidance for Industry E6 GCP: Consolidated Guidance.

The sponsor or designee study monitors will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the first participant signs the ICF.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study drug development
- Safety data suggesting that further study drug exposure would pose an undue risk to participants

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

The results of this study may be published or presented at scientific meetings. The investigator shall submit all feedback on manuscripts or abstracts to the sponsor before submission in accordance with the terms and conditions as set forth in the applicable clinical trial agreement, for its comment and approval, as applicable. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with all such requirements for publication of study results as set forth in the applicable clinical trial agreement. In accordance with standard editorial and ethical practice,

the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

10.1.11 Confidentiality

All information concerning TOUR006, including but not limited to, sponsor operations, patent applications, formulas, manufacturing processes, scientific data, and formulation information, supplied to the investigator by a sponsor representative and not previously published, is considered confidential and remains the sole property of the sponsor. The investigator must agree to use this information solely for the purposes of carrying out this trial and must not use it for other purposes without the sponsor's advanced written consent.

All terms addressing the confidential treatment of sponsor's information shall be as set forth in the applicable clinical trial agreement.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 5 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study drug administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study drug decision or response evaluation, the results must be recorded.

The clinical laboratory values will be reported to the investigator, who will review them for clinical significance and consideration of abnormal values as potential AEs. Investigators must document their review of each laboratory safety report.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5: Protocol-Required Laboratory Tests

Laboratory Tests	Parameters
Chemistry	• alanine aminotransferase • albumin • alkaline phosphatase • aspartate aminotransferase • bicarbonate • blood urea nitrogen • calcium • chloride • creatinine • direct bilirubin • gamma-glutamyl transferase • glucose • phosphate • potassium • sodium • total bilirubin • total protein • eGFR
Hematology	• hematocrit • hemoglobin • red blood cell indices (mean corpuscular hemoglobin, mean corpuscular volume, red blood cell count, red cell distribution width, reticulocyte count) • platelet count • white blood cell count • white blood cell differential (basophils, eosinophils, immature forms, lymphocytes, monocytes, neutrophils)
Coagulation	• INR (among participants treated with warfarin)
Infection tests (screening)	• SARS-CoV-2 test (local) • QuantiFERON-TB test • hepatitis B surface antigen (HBsAg) • hepatitis C antibody (HCVAb), HCV RNA (reflex testing if HCVAb positive) • human immunodeficiency virus (HIV)-1 and HIV-2 antibody
Additional screening blood tests	• hemoglobin A1c

	• immunoglobulin G (IgG)
Inflammatory biomarkers	• high-sensitivity C-reactive protein CCI [redacted]
Lipids	• total cholesterol • triglycerides • HDL cholesterol • LDL cholesterol [direct]
CCI [redacted]	CCI [redacted]
Pregnancy tests	• serum beta- human chorionic gonadotropin (β-HCG) • urine β-HCG (local)
CCI [redacted]	CCI [redacted]
Pharmacokinetic tests	• TOUR006 drug concentration • anti-drug antibodies
Urine tests[1]	• dipstick (glucose, heme, ketones, leukocyte esterase, nitrite, protein) • microscopy (reflex if abnormal dipstick) • protein and creatinine (UPCR) • albumin

Abbreviations: β-HCG = beta-human chorionic gonadotropin; CHIP=clonal hematopoiesis of indeterminate potential; eGFR=estimated glomerular filtration rate; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCVAb = hepatitis C antibody; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; IgG = immunoglobulin G; CCI [redacted]; INR=international normalized ratio; LDL = low-density lipoprotein; TB = tuberculosis; UPCR = urine protein creatinine ratio

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of Adverse Event

Adverse Event Definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study drug, whether or not considered related to the study drug.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

An AE also includes those events considered by the investigator to be related to study procedures, independent of the study drug.

Treatment-emergent Adverse Event Definition

An AE that starts after first application of study drug or that started before the first application of study drug but increased in severity after the application.

Unsolicited and Solicited Adverse Event Definition

An unsolicited AE is an AE that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.

Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next visit.

Solicited AEs are predefined local (at the injection site [see Section 8.8.7]) and systemic events for which the participant is specifically questioned by the investigator or designee.

Events Meeting the Adverse Event Definition

The following events will be considered AEs:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition

- New condition detected or diagnosed after study drug initiation even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant therapy or intervention. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

It is preferable to record a diagnosis as the AE term rather than a series of signs and symptoms relating to a diagnosis.

In addition, any abnormal laboratory test result (hematology, clinical chemistry, or urinalysis) or other safety assessment (eg, ECG, radiological scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered clinically significant in the judgment of the investigator must be reported as an AE. Grade 3 or higher laboratory abnormalities (see Table 6) should be reported as AEs.

Specifically, such an abnormality is considered clinically significant if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study drug (eg, pausing of dosing)

- Results in a medical intervention

- Is considered clinically significant in the investigator's judgment for a medical reason other than as outlined above

Note: if the laboratory (or other assessment) abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. If a clinically significant laboratory (or other assessment) abnormality is a sign of a disease or syndrome, only the diagnosis should be reported. Observations of the same clinically significant abnormality from visit to visit should only be recorded once as an AE.

Lack of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the PD assessments.

Special Cases

Adverse events that are secondary to other AEs:

- These events are also called "cascade events" or "clinical sequelae."

- In general, these events should be identified by their primary cause, with the exception of severe or serious secondary events.

- If a medically significant secondary AE occurs, the event may be recorded as an independent AE after consultation with the sponsor.

- All AEs should be recorded separately if it is not evident whether the events are associated.

Persistent and recurrent AEs:

- Persistent AE: AE that extends continuously, without resolution, between participant evaluation time points. Record only once. The initial severity of the AE will be recorded at the time the event is first reported. If it becomes more severe, the most extreme severity should be recorded. If it becomes serious, the end date of the AE will be the date the AE became serious, which will be the same as the start date of the SAE. For this SAE, all requirements for SAEs apply.

- Recurrent AE: AE that resolves between participant visits and subsequently recurs. Each recurrence must be recorded as a separate AE.

Events <u>not</u> Meeting the Adverse Event Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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[redacted]

10.3.3 Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, inpatient hospitalization signifies that the participant has been admitted for at least 24 hours at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

- Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE or SAE (eg, for work-up of persistent pretreatment laboratory abnormality).

- Planned/Scheduled Hospitalization: A hospitalization planned and scheduled before ICF is to be considered a therapeutic intervention and not the result of a new SAE. It is not enough to know that in the near future the participant will need said surgery; the surgery needs to be already scheduled before ICF for it not to be considered an AE/SAE. If the planned hospitalization or procedure is executed as planned, it will be recorded in the participant's medical history or procedures. However, if the event/condition worsens during the trial, it must be reported as an AE and/or SAE.

- Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:

    - Social admission (eg, participant has no place to sleep)

    - Administrative admission (eg, for yearly physical exam)

    - Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery).

As a reminder, "hospitalization" should not be reported as the event term, and the same is true for procedures. The cause of the hospitalization and/or procedure should be the reported event term.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, development of intervention dependency or intervention abuse, Grade 4 laboratory abnormalities, and GI perforations and abscesses.

10.3.4 Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information.

It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the SAE/required form.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant

number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Serious adverse event recording: for an AE to be serious, it needs to meet one of the regulatory seriousness criteria defined in Section 10.3.3. Hence, event start and end dates should match the start and end dates of when the criterion/criteria was/were met (eg, if a participant is hospitalized from Friday to Sunday, the start date will be Friday and the end date will be Sunday). If the investigator feels that the event also met another seriousness criterion outside of the hospitalization dates, the event start and end dates may be different than the admission and discharge dates as the extra days are covered by the additional seriousness criterion.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study according to the National Cancer Institute CTCAE Grading Scale, Version 5 or higher (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50). Only AEs not listed in the CTCAE should be graded as summarized in Table 6. For classification of intensity of COVID-19 infection, see Section 10.5.

Table 6: Adverse Event Intensity Criteria

CTCAE Grade	Equivalent To	Definition
Grade 1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4	Life threatening/ disabling	Life threatening consequences; urgent intervention indicated
Grade 5	Death	Death related to AE

Abbreviations: ADL=activities of daily living; AE=adverse event; CTCAE=common technology criteria for adverse events. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship according to Table 7.

Table 7: Adverse Event Causality Assessment Criteria

Assessment	Definition
Unrelated	No evidence of any causal relationship with the study drug.
Related	Some evidence to suggest a causal relationship (eg, occurrence within a reasonable time after administration of the study drug), but other factors may have contributed to the event (eg, another clinical condition or other concomitant treatment).

A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.

The investigator must review and provide an assessment of causality for each AE/SAE and document this in the AE eCRF and SAE CCI report forms. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

New or updated information will be submitted as a follow-up SAE[redacted] report with the investigator's signature and date.

The investigator will submit any updated SAE[redacted] data to the sponsor or designee within 24 hours of receipt of the information.

10.3.5 Reporting of Serious Adverse Events [redacted]

SAE Reporting to Sponsor via an Electronic Data Collection Tool

The site will enter the SAE[redacted] data into the electronic system within 24 hours of awareness.

Should technical issues not allow for transmission of the SAE[redacted] report form via the electronic data capture system, a paper form may be submitted via email [redacted] as a backup method. Once the system is functioning, data should be entered on the eCRF in a timely manner.

10.4 Appendix 4: Contraceptive Guidance

10.4.1 Definitions

For the purposes of this study, WOCBP are defined as postmenarchal women who are not surgically sterile (presence of ovaries, uterus, and either fallopian tube) AND not definitively postmenopausal, defined as absence of menses for 24 consecutive months before the Screening visit.

10.4.2 Contraception Guidance

The effects of TOUR006 on conception, pregnancy, and lactation are unknown.

To date, reproductive and developmental toxicity studies with TOUR006 have not been conducted. No preneoplastic or neoplastic findings were observed in the completed toxicity studies, and reproductive organ/organ systems were not affected in the repeat-dose toxicology studies with cynomolgus monkeys.

Women of childbearing potential must use at least 1 highly effective method of contraception, preferably with low user dependency, during the treatment, until the end of the relevant systemic exposure, and for 32 weeks after the last dose of study drug.

Male participants who are not surgically sterile or, if sexually active with a WOCBP participant, are required to use a condom during treatment and until the end of the relevant systemic exposure and 4 months after completion of study drug administration.

The use of contraceptive methods is not required if the female participant or female partner of a male participant is not considered WOCBP. The acceptable methods of contraception allowed during the trial are listed in Table 8 (Hatcher et al, 2007).

Table 8: Methods of Contraception Allowed During the Trial

Highly Effective Methods[1] That Have Low User Dependency[2]
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[3]
Intrauterine device
Intrauterine hormone-releasing system[3]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[1] That Are User Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant.

Abbreviations: WOCBP=women of childbearing potential.
[1] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[2] These methods of contraception, which are considered to have low user dependency, should preferably be used, in particular when contraception is introduced as a result of participation in the clinical trial.
[3] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
Note: Contraceptive use by males or females should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials.

10.5 Appendix 5: Clinical Spectrum of COVID-19 Infection

From United States National Institutes of Health Covid Treatment Guidelines (06 March 2023)

Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories; however, the criteria for each category may overlap or vary across clinical guidelines and clinical trials, and a patient's clinical status may change over time.

- Asymptomatic or presymptomatic infection: Individuals who test positive for SARS-CoV-2 using a virologic test (ie, a nucleic acid amplification test or an antigen test) but have no symptoms consistent with COVID-19.
- Mild illness: Individuals who have any of the various signs and symptoms of COVID-19 (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.
- Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an SpO2 ≥94% on room air at sea level.
- Severe illness: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a RR >30 breaths/min, or lung infiltrates >50%.
- Critical illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

10.6 Appendix 6: CKD-EPI Equation to Estimate Glomerular Filtration Rate (Inker 2021)

Estimated glomerular filtration rate will be calculated automatically at the central laboratory based on age, sex, and serum creatinine using the CKD-EPI equations below.

CKD-EPI Equation for Estimating GFR on the Natural Scale Expressed for Specified Sex, Standardized Serum Creatinine and Standardized Serum Cystatin C (From New Eng J Med 2021)

Sex	Serum Creatinine (mg/dL)	Equation
Female	≤0.7	$GFR = 142 \times (Scr/0.7)^{-0.241} \times 0.9938^{Age} \times 1.012$
Female	>0.7	$GFR = 142 \times (Scr/0.7)^{-1.200} \times 0.9938^{Age} \times 1.012$
Male	≤0.9	$GFR = 142 \times (Scr/0.9)^{-0.302} \times 0.9938^{Age}$
Male	>0.9	$GFR = 142 \times (Scr/0.9)^{-1.200} \times 0.9938^{Age}$

Reference: https://www.tuftsmedicalcenter.org/research-clinical-trials/institutes-centers-labs/chronic-kidney-disease-epidemiology-collaboration/gfr-estimating-equations/creatinine-based-equations; Inker 2021.

10.7 Appendix 7: Summary of Protocol changes

Summary of Protocol Changes

Protocol (Date Issued)	**Version**
Version 1.0 (20 Dec 2023)	Original Protocol
Version 2.0 (16 May 2024)	Protocol Version 2.0
Version 3.0 (11 Sep 2024)	Protocol Version 3.0
Version 4.0 (07 Apr 2025)	Protocol Version 4.0

Protocol Version 4.0 Summary of Changes

Applicable to all investigational sites? Yes

Revision prompted by safety concern? No

Changes to the protocol are provided in the table below. Changes to formatting and grammar are not included in the table.

Protocol Section	Protocol Language from Version 3.0 (11 Sep 2024)	Updated Protocol Version 4.0 (07 Apr 2025)	Rationale
Section 1.1 Synopsis Objectives and Endpoints Section 3 Objectives and Endpoints	Primary Endpoint Change from baseline in hs-CRP after 90 days of treatment	Primary Endpoint Time-averaged percent change from baseline in hs-CRP through Day 90	Time-averaged reduction is considered a more robust approach to inform dosing in Phase 3 than analysis restricted to a single timepoint. First, averaging hs-CRP values mitigates the variability of the biomarker. Second, cumulative exposure to inflammation, assessed by multiple assessments of hs-CRP, is more closely associated with cardiovascular risk than inflammation at a single timepoint (Wang et al., 2017)
Section 1.1 Synopsis Objectives and Endpoints Section 3 Objectives and Endpoints	N/A	Key Secondary Objective Evaluate the effects of TOUR006 compared with placebo on hs-CRP Key Secondary Endpoint Percent of participants with time-averaged hs-CRP <2 mg/L through Day 90	Percent of participants with time-averaged hs-CRP <2 mg/L has emerged as a key endpoint for targeted anti-inflammatory therapies. This threshold has been used to identify patients at residual systemic inflammatory risk. CANTOS and JUPITER studies showed that patients who achieve hs-CRP <2 mg/L have a significant improvement in MACE.
Section 1.1 Synopsis Objectives and Endpoints Section 3 Objectives and Endpoints	Secondary Objective Evaluate the effects of TOUR006 compared with placebo on hs-CRP Secondary Endpoint Change from baseline in hs-CRP after 180 days of treatment	Additional Secondary Objective Evaluate the effects of TOUR006 compared with placebo on hs-CRP Additional Secondary Endpoint Change from baseline in hs-CRP through Day 180	Distinguish secondary objectives and endpoints from the key secondary objectives and endpoints and clarify the time period in which hs-CRP is measured.
Section 1.1 Synopsis Objectives and Endpoints Section 3 Objectives and Endpoints	Secondary Objective Evaluate the pharmacokinetics of TOUR006	Additional Secondary Objective Evaluate the pharmacokinetics of TOUR006	Distinguish secondary objectives and endpoints from the key secondary objectives and endpoints.

Protocol Section	Protocol Language from Version 3.0 (11 Sep 2024)	Updated Protocol Version 4.0 (07 Apr 2025)	Rationale
	Secondary Endpoint • Serum drug concentrations of TOUR006 at Baseline and after 30, 60, 90, 120, 150, and 180 days of treatment Serum drug concentrations of TOUR006 at 240, 300, and 365 days	Additional Secondary Endpoint • Serum drug concentrations of TOUR006 at Baseline and after 30, 60, 90, 120, 150, and 180 days of treatment Serum drug concentrations of TOUR006 at 240, 300, and 365 days	
Section 1.1 Synopsis Overall Design Section 4.1 Overall Design	The end of the treatment period is Study Day 180, after which participants will be followed for safety until Study Day 365. The primary pharmacodynamic endpoint evaluation will occur at Study Day 90.	The end of the treatment period is Study Day 180, after which participants will be followed for safety until Study Day 365. The primary endpoint is the time-averaged percent change from baseline in hs-CRP through Day 90. The primary evaluation will occur after the last participant has their Day 90 assessments.	Time-averaged reduction is considered a more robust approach to inform dosing in Phase 3 than analysis restricted to a single timepoint. First, averaging hs-CRP values mitigates the variability of the biomarker. Second, cumulative exposure to inflammation, assessed by multiple assessments of hs-CRP, is more closely associated with cardiovascular risk than inflammation at a single timepoint (Wang et al., 2017)
Section 1.1 Synopsis Statistical Methods Section 9.1 General Considerations	Section 9.2 Table 5: Analysis Sets	Section 9.1 Deleted Table 5 Pharmacodynamic endpoints will be analyzed using modified intent-to-treat (mITT) and per protocol populations. Safety endpoints will be analyzed using the safety population. Inclusion into these analytical populations will require at least one dose of study medication. mITT will additionally require at least one post-baseline hs-CRP assessment. Details will be provided in the SAP.	Clarification and refinement of analytical populations for the assessment of hs-CRP and other pharmacodynamic parameters informed by recent trials of IL-6 inhibitors in CKD (Chertow et al., 2024). A brief description of analytical populations is summarized with details to be provided in the SAP.
Schedule of Activities Footnote 10	10. hs-CRP CCI sampling to be acquired prior to dosing. CCI	10. hs-CRP CCI sampling to be acquired prior to dosing	CCI

Protocol Section	Protocol Language from Version 3.0 (11 Sep 2024)	Updated Protocol Version 4.0 (07 Apr 2025)	Rationale
	CCI		
Schedule of Activities Footnote 15	15. INR will be evaluated among participants treated with warfarin.	15. INR will be evaluated among participants treated with warfarin and should be collected in a coagulation tube.	Clarification that INR should be collected in a coagulation tube
		CCI	CCI
CCI			
Section 5.2 Exclusion Criteria	32. Diagnosis of cachexia and/or unintended weight loss of >5% within 3 months prior to the Baseline visit.	32. Diagnosis of cachexia and/or unintended weight loss of ≥5% within 3 months prior to the Baseline visit.	Incorrectly listed as >5% in Section 5.2 but correctly listed as ≥5% in the synopsis in protocol version 3.0. Updated to align in both places.
CCI			
CCI			

Protocol Section	Protocol Language from Version 3.0 (11 Sep 2024)	Updated Protocol Version 4.0 (07 Apr 2025)	Rationale
CCI Appendix 2: Clinical Laboratory Tests Table 5	CCI	[redacted]	[redacted]
Section 8.7.1 Physical Examinations	Clinically significant abnormalities in the physical examination that emerge during the study (or worsen from baseline) should be captured as AEs. Clinically significant physical examination abnormalities identified before study drug administration, unless considered procedure-related, will be recorded as medical history or as an AE if identified after study drug administration.	Clinically significant abnormalities in the physical examination that emerge after study drug initiation (or worsen from baseline) should be captured as AEs. Clinically significant physical examination abnormalities identified before study drug initiation, unless considered procedure related, will be recorded as medical history.	Clarification of timing for physical examination findings to be recorded as AEs or medical history.
Section 8.7.2 Vital Signs	Clinically significant abnormalities in the vital signs that emerge during the study (or worsen from baseline) should be captured as AEs. Clinically significant vital signs abnormalities identified before study drug administration, unless considered procedure-related, will be recorded as medical history or as an AE if identified after study drug administration.	Clinically significant abnormalities in the vital signs that emerge after study drug initiation (or worsen from baseline) should be captured as AEs. Clinically significant vital signs abnormalities identified before study drug initiation, unless considered procedure -related, will be recorded as medical history.	Clarification of timing for vital sign findings to be recorded as AEs or medical history.
Section 8.7.3 Electrocardiograms	Clinically significant ECG abnormalities that emerge during the study (or worsen from baseline) should be captured as AEs. Clinically significant ECG abnormalities identified before study drug administration, unless considered	Clinically significant ECG abnormalities that emerge after study drug initiation (or worsen from baseline) should be captured as AEs. Clinically significant ECG abnormalities identified before study drug initiation, unless considered	Clarification of timing for ECG findings to be recorded as AEs or medical history.

Protocol Section	Protocol Language from Version 3.0 (11 Sep 2024)	Updated Protocol Version 4.0 (07 Apr 2025)	Rationale
	procedure-related, will be recorded as medical history or as an AE if identified after study drug administration.	procedure -related, will be recorded as medical history.	
Section 8.7.4 Clinical Safety Laboratory Tests	Clinically significant or Grade 3 or higher (based on Common Terminology Criteria for Adverse Events [CTCAE] v5.0) laboratory test abnormalities that emerge during the study (or worsen from baseline) should be captured as AEs. All laboratory tests with values considered clinically significantly abnormal that worsen compared to baseline during participation in the study drug or follow-up period should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or until at least the values remain stable at a new baseline. Unscheduled visits may be added as needed in order to follow laboratory values considered abnormal and clinically significant. Clinically significant laboratory value abnormalities identified before study drug administration, unless considered procedure-related, will be recorded as medical history or as an AE if identified after study drug administration.	Clinically significant or Grade 3 or higher (based on Common Terminology Criteria for Adverse Events [CTCAE] v5.0) laboratory test abnormalities that emerge after study drug initiation (or worsen from baseline) should be captured as AEs. Clinically significant laboratory value abnormalities identified before study drug initiation, unless considered procedure related, will be recorded as medical history. All laboratory tests with values considered clinically significantly abnormal that worsen compared to baseline during participation in the study drug or follow-up period should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or until at least the values remain stable at a new baseline. Unscheduled visits may be added as needed in order to follow laboratory values considered abnormal and clinically significant.	Clarification of timing for clinical laboratory test abnormalities to be recorded as AEs or medical history.
Section 9.2 Primary Endpoint Analysis	The primary endpoint analysis will analyze change from baseline in hs-CRP at Day 90 for the Primary Pharmacodynamic Set	The primary endpoint analysis will analyze time-averaged percent change from baseline in hs-CRP through Day 90 for the per protocol population.	Time-averaged reduction is considered a more robust approach to inform dosing in Phase 3 than analysis restricted to a single timepoint. First, averaging

Protocol Section	Protocol Language from Version 3.0 (11 Sep 2024)	Updated Protocol Version 4.0 (07 Apr 2025)	Rationale
	(PDS; see definition of analysis set above). Baseline hs-CRP will be based on the most recent value prior to receiving first dose of study drug. Methodology for the main primary endpoint analyses as well as sensitivity and supportive analyses will be specified in the SAP.	The baseline hs-CRP value is defined as the average of the hs-CRP result at the qualifying visit (the most recent pre-baseline value, ie, the pre-screening, screening, or retest value) and the hs-CRP result at the Baseline visit. Methodology for the main primary endpoint analyses as well as sensitivity and supportive analyses will be specified in the SAP. The SAP will be finalized prior to these analyses.	hs-CRP values mitigates the variability of the biomarker. Second, cumulative exposure to inflammation, assessed by multiple assessments of hs-CRP, is more closely associated with cardiovascular risk than inflammation at a single timepoint (Wang et al., 2017)
Section 9.3 Analysis of Other Pharmacodynamic Endpoints	All secondary and other pharmacodynamic endpoints will be analyzed based on the PDS. The secondary pharmacodynamic endpoint will analyze change from baseline in hs-CRP at Day 180. Methodology for the secondary endpoint analyses as well as sensitivity and supportive analyses will be specified in the SAP. All other continuous exploratory pharmacodynamic endpoints will be summarized by treatment group and by time point. The observed values, changes from baseline, and percent changes from baseline (as applicable) will be calculated using descriptive statistics. The differences between the active treatment groups and placebo may be calculated also at each time point: [redacted]	The key secondary endpoint is the percent of participants achieving a time-averaged hs-CRP <2 mg/L through Day 90. Methodology for the key secondary, additional secondary, and exploratory endpoint analyses as well as sensitivity and supportive analyses will be specified in the SAP.	Percent of participants with time-averaged hs-CRP <2 mg/L has emerged as a key endpoint for targeted anti-inflammatory therapies. This threshold has been used to identify patients at residual systemic inflammatory risk. CANTOS and JUPITER studies showed that patients who achieve hs-CRP <2 mg/L have a significant improvement in MACE.

Protocol Section	Protocol Language from Version 3.0 (11 Sep 2024)	Updated Protocol Version 4.0 (07 Apr 2025)	Rationale
	[redacted]		
Section 9.6 Primary and Final Analysis	The study team, except the unblinded team members, should remain blinded for the duration of the study until after final database lock. Dissemination of the primary analysis results will be limited to the unblinded reporting team of the contract research organization (CRO) and sponsor management.	The study team, except the unblinded team members, should remain blinded for the duration of the study until after final database lock. Dissemination of the primary analysis results will be managed according to the sponsor's communication plan and may include public disclosure and sharing summary results with external stakeholders.	Updated approach to communication of primary results.
[redacted]	CCI [redacted]	[redacted]	[redacted]

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