Protocol

A Phase 1, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Avacopan in Subjects with Normal Renal Function and Subjects with End-Stage Renal Disease (ESRD) Requiring Hemodialysis

Protocol Amendment 1 Status: Final
Original Protocol Date: 26 April 2024
Protocol Amendment 1 Date: 24 June 2024

Investigational Product: Avacopan

Amgen Protocol Reference Number: 20230265
Fortrea Study Number: 8530204

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This protocol was developed, reviewed, and approved in accordance with Fortrea's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

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INVESTIGATOR AGREEMENT

I have read the attached protocol entitled "A Phase 1, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Avacopan in Subjects with Normal Renal Function and Subjects with End-Stage Renal Disease (ESRD) Requiring Hemodialysis" dated 24 June 2024 and agree to abide by all provisions set forth therein.

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_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

_____

Title and Role of Investigator

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Institution Name

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STUDY IDENTIFICATION

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SYNOPSIS

Title of study: A Phase 1, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Avacopan in Subjects with Normal Renal Function and Subjects with End-Stage Renal Disease (ESRD) Requiring Hemodialysis

Objectives:

The primary objective of the study is:

- to evaluate the pharmacokinetics (PK) of avacopan and metabolite (M1) after a single dose of avacopan in subjects with normal renal function and subjects with ESRD requiring hemodialysis (HD).

The secondary objective of the study is:

- to evaluate the safety and tolerability of a single dose of avacopan in subjects with normal renal function and subjects with ESRD requiring HD.

Study design:

This will be a Phase 1, open-label, single-dose, parallel group study to evaluate the PK, safety, and tolerability of avacopan in subjects with normal renal function (Group 1) and subjects with ESRD requiring HD (Group 2). After informed consent is obtained, potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration.

Subjects in Group 1 (normal renal function) will be admitted into the Clinical Research Unit (CRU) on Day -1 and will be confined to the CRU until discharge on Day 8.

Subjects in Group 1 will receive a single CCI dose of avacopan on Day 1 under fed conditions. Following discharge on Day 8, subjects will return to the CRU on Days 12, 15, and 18 (end of study [EOS] visit) for outpatient visits.

Subjects in Group 2 (ESRD requiring HD) will receive a single dose of CCI avacopan under fed conditions on Day 1 in each of the 2 treatment periods (Period 1/on HD and Period 2/off HD). Subjects in Group 2 will be admitted into the CRU on Period 1 Day -1. Subjects in Group 2 Period 1 (on HD) will receive a single CCI dose of avacopan on Period 1 Day 1, 4 hours prior to the start of HD. Subjects will continue to receive HD on Days 3, 5, and 8 (prior to discharge). Following discharge on Day 8, subjects will return to the CRU on Period 1 Days 12, 15, and 18 for outpatient visits. Subjects in Group 2 will be re-admitted into the CRU for Period 2 Day -1 on the day of their HD. Period 1 Day 18 may occur on the same day as Period 2 Day -1. Subjects will receive a single CCI dose of avacopan on Period 2 Day 1 on an off-HD day (one day after the HD session on Period 2 Day -1). Subjects will continue to receive HD on Days 3, 5, and 7. Subjects will be confined to the CRU until discharge on Period 2 Day 8. Following discharge on Period 2 Day 8, subjects in Group 2 will return to the CRU on Period 2 Days 12, 15, and 18 (EOS) for outpatient visits. There will be no washout between Day 18 of Period 1 and Check-in for Period 2 for subjects in Group 2.

Number of subjects:

Approximately 12 subjects will be enrolled in 2 groups (Groups 1 and 2). Approximately 6 subjects will be enrolled in each group.

Diagnosis and main criteria for inclusion:

Male subjects or female subjects, 18 to 75 years of age (inclusive), and body mass index of 18 to <40 kg/m^2 with normal renal function or ESRD requiring HD.

Investigational products, dose, and mode of administration:

Investigational Medicinal Product: CCI avacopan oral dose under fed conditions

Duration of subject participation in the study:
Planned Screening duration: 4 weeks.
Planned study duration (Screening to EOS): Group 1: approximately 7 weeks,
Group 2: approximately 9 weeks.

Primary Endpoints:
The primary endpoints for this study are avacopan and M1 PK parameters: maximum observed plasma concentration (C_{max}); area under the plasma concentration-time curve (AUC) from time zero to time of last quantifiable concentration (AUC_{last}); area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}); area under the plasma concentration time curve from time zero to 48 hours (AUC_{0-48}), or other partial area comparisons, as appropriate; and HD clearance of drug (and metabolite) from plasma (CL_D).

Secondary Endpoints:
Secondary endpoints for this study are: treatment-emergent adverse events and serious adverse events.

Statistical methods:
The primary PK parameters are C_{max} and AUC. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis. To determine the effect of renal impairment on the PK of avacopan and M1, the ratios (test/reference) for the model-estimated C_{max}, AUC_{0-48}, and AUC_{inf} for the ESRD group (test) relative to the group with normal renal function (reference) will be generated, along with 90% confidence intervals. Applicable PK parameters in the ESRD group on-HD days and off-HD days may also be compared.

The final safety analysis for the study will be performed at EOS. Adverse events will be summarized using descriptive methodology. Each adverse event will be coded using the Medical Dictionary for Regulatory Activities. Endpoints for clinical laboratory tests, electrocardiogram, and vital signs will be summarized.

Additional details will be included in the Statistical Analysis Plan.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCA	anti-neutrophil cytoplasmic autoantibody
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC_{last}	area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC_{0-48}	area under the plasma concentration-time curve from time zero to 48 hours postdose
BIL	bilirubin
BP	blood pressure
C5a	complement component C5a
C5aR	complement 5a receptor
CFR	Code of Federal Regulations
CL_D	hemodialysis clearance of drug (and metabolite) from plasma
C_{max}	maximum observed plasma concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
CYP3A4	cytochrome P450 3A4
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EOS	end of study
ESRD	end-stage renal disease
FSH	follicle-stimulating hormone
f_u	fraction of unbound drug; reported as the arithmetic mean where measured at two time points

GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HD	hemodialysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
MDRD	Modification of Diet in Renal Disease
OSF	Other Safety Finding
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's method
SS	Special Situation
TBL	total bilirubin
t_{max}	time of the maximum observed concentration
ULN	upper limit of normal

1. INTRODUCTION

Refer to the Investigator's Brochure (IB)[1], Prescribing Information[2], and Summary of Product Characteristics[3] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational medicinal product (IMP).

1.1. Background

Investigational Medicinal Product

In the United States, TAVNEOS® (formerly CCX168), hereafter referred to as avacopan, is currently approved as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard therapy including glucocorticoids. Avacopan does not eliminate glucocorticoid use. Avacopan is also approved in the European Union for use in combination with a rituximab or cyclophosphamide regimen and is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis or microscopic polyangiitis. Avacopan has also been approved in Canada, Great Britain, Switzerland, Japan, and the United Arab Emirates, and is under review in several other countries for marketing authorization.

Avacopan is a highly potent and selective antagonist of the human complement 5a (C5a) receptor (C5aR), acting through competitive inhibition of the interaction between human C5aR and the anaphylatoxin complement component C5a; the latter is produced through activation of the complement cascade. As a result of its mechanism of action, avacopan reduces neutrophil activation, chemoattraction, and integrin expression. Avacopan inhibits vascular endothelial cell retraction and permeability, ameliorating the necrotizing vasculitis associated with ANCA-associated vasculitis.

A summary of completed clinical studies for avacopan is provided in the IB (Table 6).[1]

1.2. Pharmacokinetics

The pharmacokinetics (PK) of avacopan has been evaluated in nine Phase 1 studies, two Phase 2 studies, and one Phase 3 study in patients with ANCA-associated vasculitis.

Following single oral administration in healthy subjects at doses ranging from 1 to 100 mg, avacopan was absorbed rapidly with maximum observed plasma concentration (C_{max}) occurring approximately 1 to 2.5 hours postdose. Avacopan is primarily eliminated via extensive metabolism mediated through cytochrome P450 3A4 (CYP3A4) oxidation in the liver which results in the formation of and clearance of the major circulating metabolite, M1, a mono-hydroxylated product of avacopan. Following metabolism, the metabolites are primarily excreted into feces via bile. In the Phase 1 food-effect study, following a single oral dose of 30 mg in the presence of a high-fat, high-calorie meal, avacopan exposures, area under the

plasma concentration-time curve (AUC), and C_{max}, increased by approximately 72% and 8%, respectively, and delayed the time of the maximum observed concentration (t_{max}) by approximately 4 hours (from 2.0 hours to 6.0 hours). The elimination half-lives of avacopan and M1 were 97.6 hours and 55.6 hours, respectively, under fed conditions. Following oral administration of avacopan 100 mg/400 μCi, about 77% and 10% of the radioactive dose was recovered in feces and urine, respectively, and 7% and <0.1% of the radioactive dose was recovered as unchanged avacopan in feces and urine, respectively. Avacopan and metabolite M1 are more than 99.9% plasma-protein bound, primarily to albumin and α1-acid glycoprotein. A Phase 1 study in subjects with hepatic impairment evaluated the PK of avacopan and metabolite M1 following a single CCI dose for up to 18 days. Results from this study showed that plasma avacopan levels appeared to decline with a triphasic profile with a rapid early phase, followed by a longer phase, and finally a terminal phase with a half-life of about 200 to 400 hours in most subjects. Metabolite M1 appeared to decline in a biphasic manner with an elimination half-life of about 68 to 73 hours.[2]

Previously, the impact of moderate renal impairment (estimated glomerular filtration rate [eGFR] between 30 and less than 60 mL/min/1.73 m^2) and severe renal impairment (less than 30 mL/min/1.73 m^2) from patients with ANCA-associated vasculitis from Phase 2 and Phase 3 studies relative to subjects with normal renal function (eGFR >90 mL/min/1.73 m^2) from Phase 1 studies were evaluated using population PK analysis. Results from population PK analyses demonstrated that avacopan and M1 exposures as assessed by C_{max} and AUC were similar (<20%) across the different categories. Therefore, no dose adjustment for avacopan is needed based on renal function.[1]

1.3. Study Rationale

This study will be conducted to evaluate the PK of a single dose of avacopan in subjects with normal renal function and in subjects with end-stage renal disease (ESRD) requiring hemodialysis (HD).

Results from this study will provide information on the safety, tolerability, and PK of avacopan and potentially guide dosing in patients with ESRD requiring HD.

1.4. Benefit-risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study. Refer to the IB[1] for more information.

1.4.1. Therapeutic Context

1.4.1.1. Key Benefits

Healthy and ESRD subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study.

1.4.1.2. Risks

Serious cases of hepatic injury have been observed in subjects taking avacopan. During controlled trials, the avacopan treatment group had a higher incidence of transaminase elevations and hepatobiliary events, including serious and life-threatening events. Avacopan is not recommended for subjects with active, untreated, and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Hepatitis B virus (HBV) reactivation, including life threatening hepatitis B, was observed in the clinical program. Hepatitis B virus reactivation is defined as an abrupt increase in HBV replication, manifesting as a rapid increase in serum HBV DNA levels or detection of hepatitis B surface antigen (HBsAg), in a person who was previously HBsAg negative and anti-hepatitis B core positive. Reactivation of HBV replication is often followed by hepatitis; i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Avacopan may cause hypersensitivity reactions including angioedema. Serious and sometimes fatal infections have been reported in subjects receiving avacopan. The most common serious infections reported in the avacopan group were pneumonia and urinary tract infections. Avacopan use should be avoided in subjects with an active, serious infection, including localized infections and in subjects with a history of chronic or recurrent infection, who have prior infection or have been exposed to tuberculosis, with a history of a serious or an opportunistic infection, who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, or with underlying conditions that may predispose them to infection.

To limit the risk of excessive exposure to healthy subjects in the current study, subjects with normal renal function will be administered a single dose of CCI avacopan and subjects with ESRD requiring HD will be administered a single dose of CCI avacopan in each of 2 study periods (details provided in Section 3.3).

Safety monitoring: During the study, subjects will receive all investigational product doses by site staff. Safety assessments throughout the study include adverse event monitoring, electrocardiograms (ECGs), clinical examination, vital signs, and clinical laboratory evaluations.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to evaluate the PK of avacopan and metabolite (M1) after a single dose of avacopan in subjects with normal renal function and subjects with ESRD requiring HD.

The secondary objective of the study is:

- to evaluate the safety and tolerability of a single dose of avacopan in subjects with normal renal function and subjects with ESRD requiring HD.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints of the study are:

- C_{max}
- area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_{last})
- area under the plasma concentration-time curve from time zero to infinity (AUC_{inf})
- area under the plasma concentration-time curve from time zero to 48 hours (AUC_{0-48}), or other partial area comparisons, as appropriate
- HD clearance of drug (and metabolite) from plasma (CL_D).

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- treatment-emergent adverse events
- serious adverse events.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase 1, open-label, single-dose, parallel group study to evaluate the PK, safety, and tolerability of avacopan in subjects with normal renal function (Group 1) and subjects with ESRD requiring HD (Group 2). After informed consent is obtained, potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration.

Subjects in Group 1 (normal renal function) will be admitted into the Clinical Research Unit (CRU) on Day -1 and will be confined to the CRU until discharge on Day 8. Subjects in Group 1 will receive a single CCI dose of avacopan on Day 1 under fed conditions. Following discharge on Day 8, subjects will return to the CRU on Days 12, 15, and 18 (end of study [EOS] visit) for outpatient visits. An overview of the study schema for Group 1 is shown in Figure 1.

Subjects in Group 2 (ESRD requiring HD) will receive a single dose of CCI avacopan under fed conditions on Day 1 in each of the 2 treatment periods (Period 1/on HD and Period 2/off HD). An overview of the study schema for Group 2 is shown in Figure 2.

Subjects in Group 2 will be admitted into the CRU on Period 1 Day -1 and will be confined to the CRU until discharge on Period 1 Day 8. Subjects in Group 2 Period 1 (on HD) will receive a single CCI dose of avacopan on Period 1 Day 1, 4 hours prior to the start of HD. Subjects will continue to receive HD on Days 3, 5, and 8 (prior to discharge). Following discharge on Day 8, subjects will return to the CRU on Period 1 Days 12, 15, and 18 for outpatient visits. The Group 2 Period 1 (on HD) schema is shown in Figure 3.

Subjects in Group 2 will be re-admitted into the CRU for Period 2 Day -1 on the day of their HD. Period 1 Day 18 may occur on the same day as Period 2 Day -1. Subjects will receive a single CCI dose of avacopan on Period 2 Day 1 on an off-HD day (one day after the HD session on Period 2 Day -1). Subjects will continue to receive HD on Days 3, 5, and 7. Subjects will be confined to the CRU until discharge on Period 2 Day 8. Following discharge on Period 2 Day 8, subjects in Group 2 will return to the CRU on Period 2 Days 12, 15, and 18 (EOS) for outpatient visits. The Group 2 Period 2 (off-HD) schema is shown in Figure 4. There will be no washout between Day 18 of Period 1 and Check-in for Period 2 for subjects in Group 2.

Additional plasma samples will be collected for estimation of plasma protein binding.

The eGFR will be determined by the Modification of Diet in Renal Disease (MDRD) formula[4]:

MDRD formula (mL/min/1.73m^2) = 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

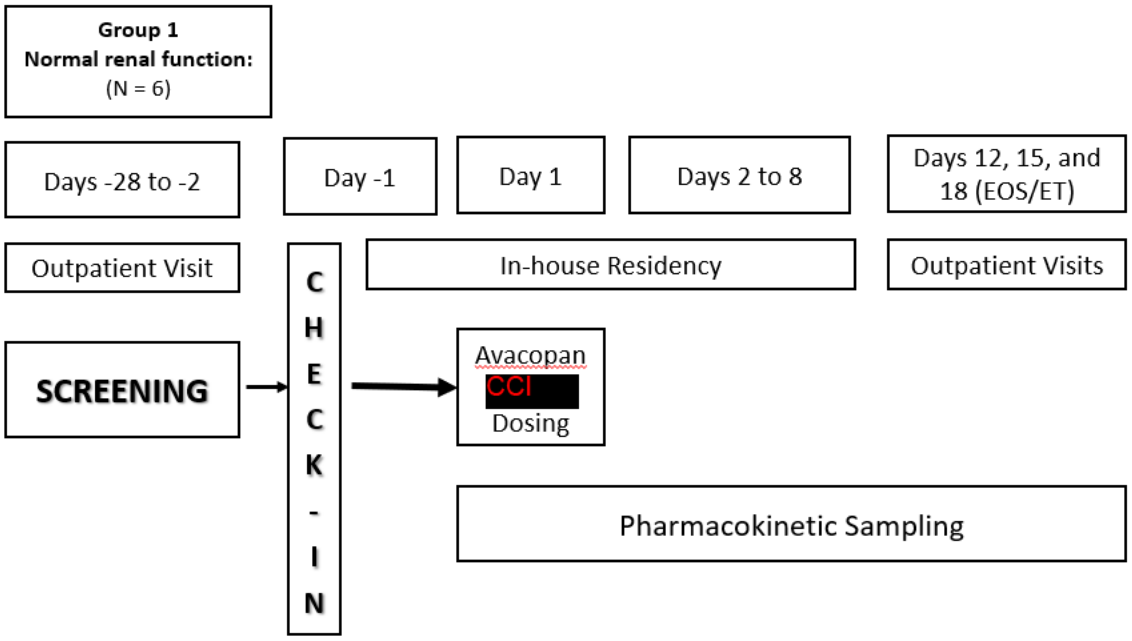
The renal function groups and eGFR values used to assign each subject to a renal function group are shown in Table 1.

Table 1: Classification of Renal Function Study Groups

Population	eGFR (mL/min) [a,b]	Group	Period
Normal renal function	≥90	1	NA
ESRD requiring HD[b]	<15	2	1 2

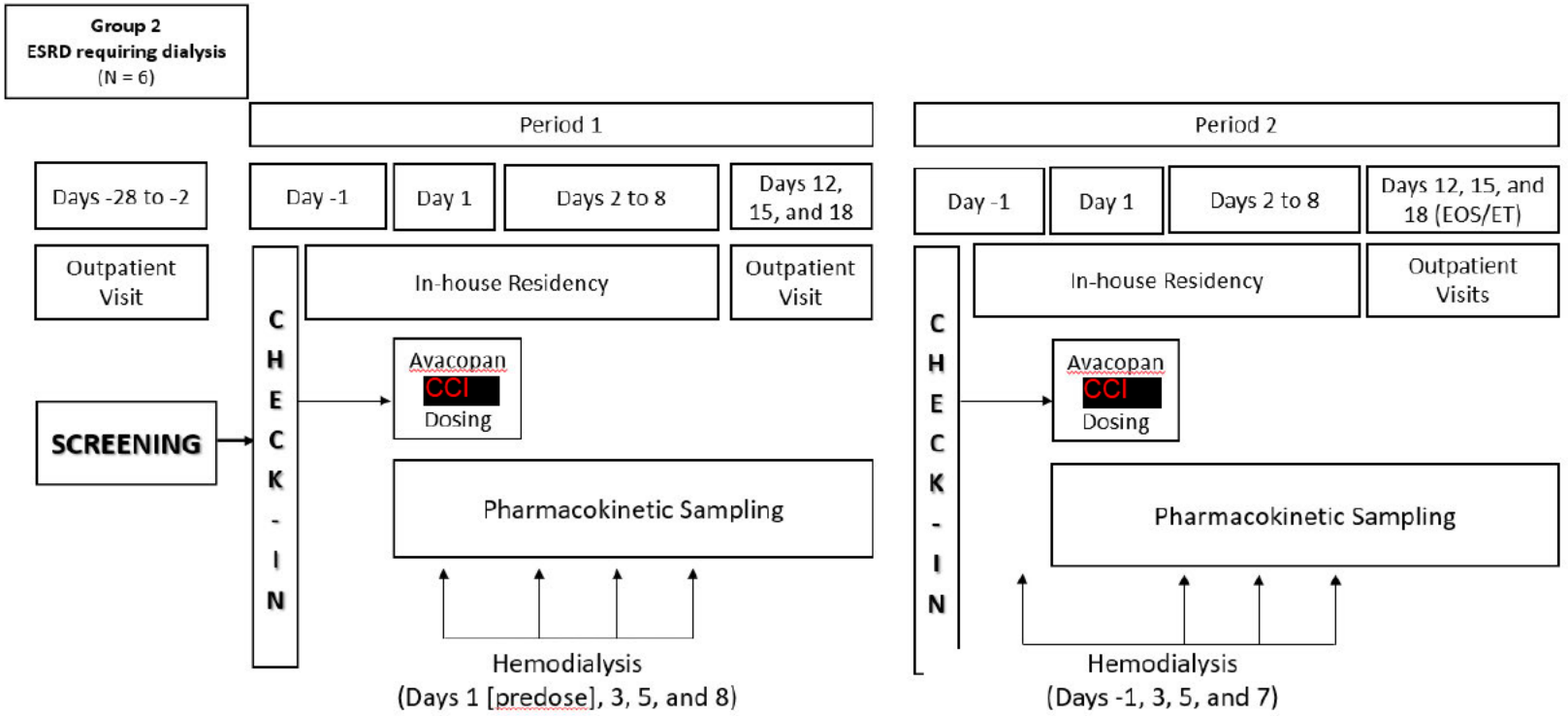
Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HD = hemodialysis; NA = not applicable.
[a] Classification is based on the Food and Drug Administration guidance for renal impairment studies.[4] Estimated glomerular filtration rate based on an estimation equation and expressed in mL/min. To convert mL/min/1.73 m^2 to mL/min, multiply by the individual's body surface area calculated using an appropriate formula and divide by 1.73.
[b] Group 2 subjects will receive intermittent HD. In Period 1, subjects will receive avacopan 4 hours prior to HD. In Period 2, subjects will receive avacopan the day after a HD session.

Figure 1: Study Schema – Group 1 (Normal Renal Function)



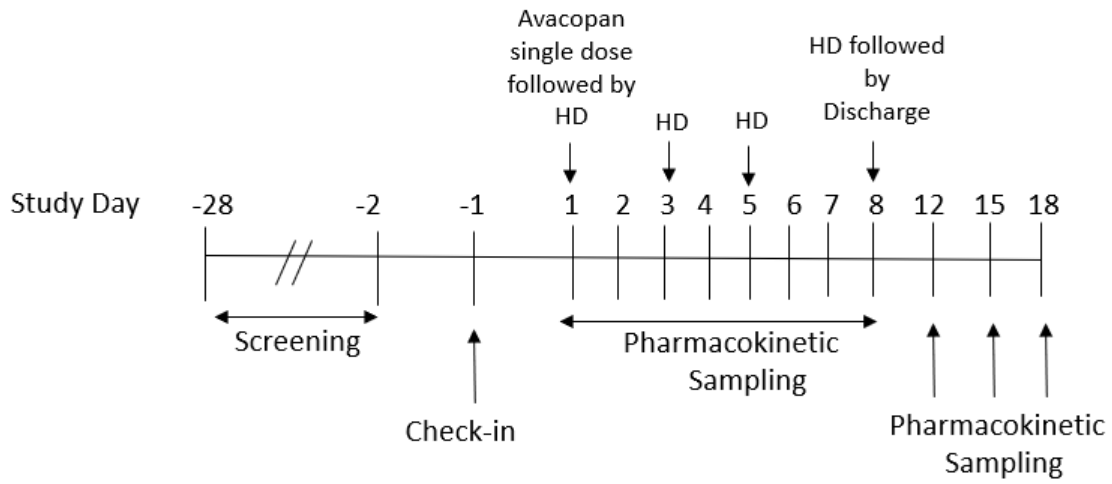
Abbreviations: EOS = end of study visit; ET = early termination.
Notes: Single dose of avacopan will be administered on Day 1 in the morning. See Appendix 9 (Schedule of Assessments) for details on plasma pharmacokinetics and plasma protein binding sampling.

Figure 2: Study Schema – Group 2 (ESRD Requiring Hemodialysis)



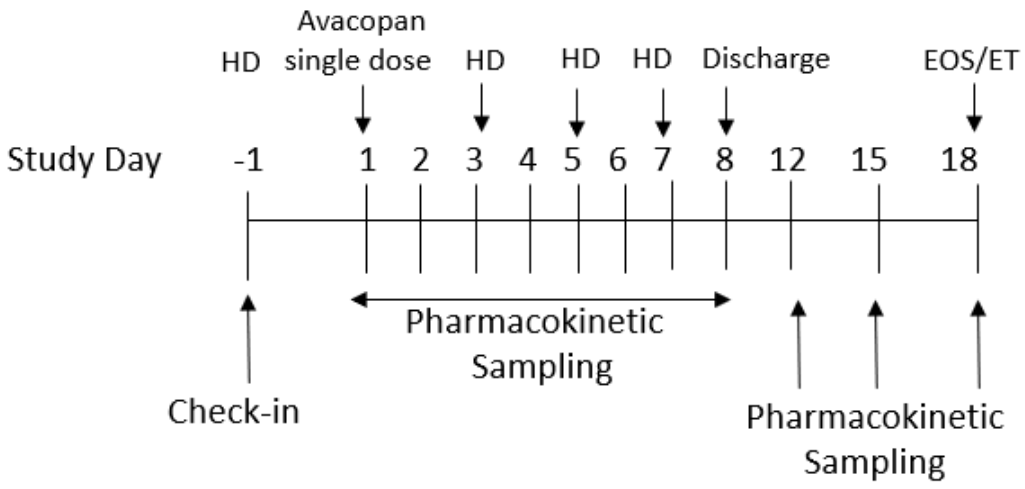
Abbreviations: EOS = end of study visit; ESRD = end-stage renal disease; ET = early termination; HD = hemodialysis.
Group 2 subjects will receive intermittent HD. In Period 1, subjects will receive avacopan 4 hours prior to HD under fed conditions. In Period 2, subjects will receive avacopan the day after a HD session. There will be no washout between Period 1 Day 18 and Period 2 Day -1. Period 1 Day 18 and Period 2 Day -1 may occur on the same day.
The timing of pharmacokinetics sampling relative to HD is provided in Figure 3 for Group 2, Period 1 (on-HD) and in Figure 4 for Group 2, Period 2 (off-HD).

Figure 3: Group 2 (ESRD Requiring Hemodialysis) Schema, Period 1 – On Hemodialysis



Abbreviations: HD = hemodialysis.
Notes: Subjects will receive a single oral dose of avacopan 4 hours prior to start of HD session, under fed conditions. See Appendix 9 (Schedule of Assessments) for details on plasma pharmacokinetics, plasma protein binding sampling, and dialysate pharmacokinetics sampling.

Figure 4: Group 2 (ESRD Requiring Hemodialysis) Schema, Period 2 – Off Hemodialysis



Abbreviations: EOS = end of study; ET = early termination; HD = hemodialysis.
Notes: Subjects will receive a single oral dose of avacopan 1 day after the HD session. See Appendix 9 (Schedule of Assessments) for details on plasma pharmacokinetics and plasma protein binding sampling.

The total duration of study participation for each subject (from Screening through EOS visit) is anticipated to be approximately 7 weeks for Group 1 (normal renal function) and approximately 9 weeks for Group 2 (ESRD requiring HD).

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 9.

3.2. Discussion of Study Design

This study will be open label because the study endpoints are not considered subjective.

The PK results from prior Phase 1 studies demonstrated relatively linear and dose-proportional PK, suggesting that a single-dose study in subjects with renal impairment should adequately describe the PK of the drug. The safety and PK assessments are standard parameters for clinical studies in drug development.

Plasma sampling is timed to sufficiently estimate PK parameters of avacopan exposure, based on characteristics of the concentration-time profile.

This study will be conducted in subjects with normal renal function and in subjects with stable end-stage renal function who require HD. These subjects may have acceptable comorbid conditions in terms of safety and stability that are not anticipated to confound the study results.

The subjects will be selected such that the mean and distribution of Group 1 is similar to the mean and distribution of subjects enrolled in Group 2 for age, sex, and body mass index, as far as possible.

3.3. Selection of Doses in the Study

Avacopan has been approved as an adjunctive treatment of adult subjects with severe active ANCA-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard therapy including glucocorticoids. The recommended dosage is CCI) twice daily, with food.

For this study, a single dose of CCI is considered adequate to evaluate the pharmacokinetics and safety in subjects with normal renal function and in subjects with ESRD requiring HD.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria prior to enrollment unless otherwise stated. Check-in with regards to inclusion criteria applies to Check-in on Period 1 Day -1 only.

1. Subject has provided informed consent before initiation of any study-specific activities or procedures.
2. Male or female subjects, between 18 and 75 years of age (inclusive) at the time of Screening.
3. Body mass index between 18 and <40 kg/m^2 at the time of Screening.
4. Subjects eligible for Group 1 (normal renal function) should be in good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [e.g., suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).
5. For subjects in Group 1 (normal renal function), systolic blood pressure (BP) ≥90 and ≤150 mmHg and diastolic BP ≥50 and ≤100 mmHg, and pulse rate ≥40 and ≤110 bpm at Screening. One repeat BP measurement will be allowed at Screening and Check-in.
6. For subjects in Group 2 (ESRD requiring HD), vital signs, physical examinations, and 12-lead ECGs (reporting heart rate, PR, QRS, QT, and QT interval corrected for heart rate using Fridericia's method [QTcF]), including waveform, are normal or clinically acceptable to the Investigator, if outside the normal range.
7. For subjects in Group 2 (ESRD requiring HD), laboratory test values (clinical chemistry and hematology) are consistent with the level of renal impairment and clinically acceptable to the Investigator.
8. For subjects in Group 2 (ESRD requiring HD), nonhypertensive subjects or subjects with treated, stable hypertension, as defined by systolic BP not exceeding 170 mmHg and diastolic BP not exceeding 100 mmHg at Screening and Check-in.
9. Eligible subjects will be classified based on established need for renal replacement therapy and eGFR, calculated using the MDRD formula. Assignment will be based on eGFR at Screening.
    a. Group 1 (normal renal function): eGFR ≥90 mL/min and no history of renal disease.
    b. Group 2 (ESRD requiring HD): eGFR <15 mL/min and receiving HD.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria prior to enrollment unless otherwise stated. Check-in with regards to exclusion criteria applies to Check-in on Period 1 Day -1 only.

All Subjects:

10. History of uncontrolled or unstable cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematopoietic, psychiatric, or neurological disease, defined as having been hospitalized within 28 days before Check-in, major surgery within 6 months before Check-in, or otherwise unstable in the judgment of the Investigator and/or Medical Monitor (e.g., risk of complications or adverse events unrelated to study participation), or evidence of rapidly deteriorating renal function.
11. History or evidence, at Screening or Check-in, of clinically significant disorder, condition, or disease not otherwise excluded that, in the opinion of the Investigator (or designee), would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
12. Total white blood cell count is below the lower limit of normal at Screening or Check-in.
13. Significant infection (in the judgment of the Investigator and/or Medical Monitor) within 28 days before Check-in.
14. Prior infection with or exposure to tuberculosis, or travel to areas of endemic tuberculosis or endemic mycoses within the past 6 months.
15. Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase or alanine aminotransferase > the upper limit of normal for Group 1 (normal renal function) and >2 times the upper limit of normal for Group 2 (ESRD requiring HD).
16. History or evidence, at Screening or Check-in, of poorly controlled diabetes (regardless of type), based on hemoglobin A1C of >10%.
17. Second-degree atrioventricular block or third-degree atrioventricular block at Screening or Check-in.
18. Clinically significant hyperkalemia (defined by serum potassium concentration as >5.5 mEq/L for Group 1 [normal renal function], >6 mEq/L for Group 2 [ESRD requiring HD]) at Screening or Check-in. Repeat testing and rescreening for screen failures will be permitted.
19. Subjects who have a current, functioning organ transplant and/or are on immunosuppressants.
20. Subjects on the national transplant list (United Network for Organ Sharing) at Screening who anticipate receiving an organ transplant within 4 months.
21. Positive human immunodeficiency virus test.
22. Positive hepatitis B or hepatitis C panel (including positive HBsAg and/or positive hepatitis C antibody) at Screening. Subjects whose results are compatible with prior hepatitis B infection (positive hepatitis B surface antibody, positive hepatitis B core antibody, or negative HBsAg) will be excluded. Subjects whose results are

compatible with prior hepatitis B vaccination (positive hepatitis B surface antibody, negative hepatitis B core antibody, negative HBsAg) may be included.

23. History or evidence of clinically significant arrhythmia at Screening, including any clinically significant findings on the ECG taken at Check-in.
24. History suggestive of esophageal (including esophageal spasm, esophagitis), gastric, or duodenal ulceration, or bowel disease (including but not limited to peptic ulceration, gastrointestinal bleeding, ulcerative colitis, Crohn's disease, or irritable bowel syndrome); or a history of gastrointestinal surgery, other than uncomplicated appendectomy.
25. History of hypersensitivity, intolerance, or allergy to avacopan or any of the excipients.
26. Poor peripheral venous access.
27. Currently taking a moderate or strong inducer of the CYP3A4 enzyme (e.g., carbamazepine, phenobarbital, phenytoin, or rifampin), or use of a strong CYP3A4 inducer, within 5 half-lives or 14 days prior to Check-in (whichever is longer) and through EOS, unless deemed acceptable by the Investigator, Medical Monitor, and/or the Sponsor.
28. Currently taking a moderate or strong inhibitor of the CYP3A4 enzyme (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole), or use of a strong CYP3A4 inhibitor, within 5 half-lives or 14 days prior to Check-in (whichever is longer) and through EOS, unless deemed acceptable by the Investigator, Medical Monitor, and/or the Sponsor.
29. Use of any over-the-counter or prescription medications within 30 days or 5 half-lives (whichever is longer) before enrollment, with the below exceptions:
    a. Acetaminophen (paracetamol; up to 2 g/day) for analgesia will be allowed.
    b. Hormone replacement therapy (e.g., estrogen, thyroid treatments including levothyroxine [Synthroid, Levothroid, Levoxyl, and Unithroid], liothyronine [Cytomel], liotrix [Thyrolar], and natural thyroid [Armour Thyroid, Nature-throid, Westhroid]) will be allowed.
    c. Hormonal contraception will be allowed.
    d. Aside from strong inducers or inhibitors of CYP3A4, therapies for renal disease and treatments of comorbidities, such as hypertension, that have been stable for at least 3 months prior to study drug administration and deemed acceptable by the Investigator (or designee) and Medical Monitor to be given concurrently with avacopan during the study period are permitted. Minor adjustments in dose or formulation of medications used to treat renal disease and associated disorders

without significant change in clinical condition within the past 3 months are permitted.

30. Consumption of foods and beverages containing poppy seeds, pomelos, or Seville oranges within 7 days prior to Check-in and consumption of foods and beverages containing grapefruit within 14 days prior to Check-in.
31. All herbal medicines (e.g., St. John's wort), vitamins, and supplements consumed by the subject within the 30 days prior to enrollment, unless deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.
32. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
33. Alcohol consumption from 48 hours prior to Check-in.
34. Regular alcohol consumption of >14 units per week for males and >7 units for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
35. Significant use of tobacco- or nicotine-containing products (e.g., >½ pack of cigarettes per day) within 3 months prior to Check-in through EOS.
36. Positive alcohol test at Check-in or positive drug screen (confirmed by repeat) at Screening or Check-in, that is not otherwise explained by permitted concomitant or prescription medications. Group 2 (ESRD requiring HD) subjects will be permitted on study if drug screen is positive for opiates or benzodiazepines. Subjects who screen positive for tetrahydrocannabinol/cannabinoids will be excluded. At Check-in, a positive alcohol test may not be repeated.
37. Consumption of caffeine-containing foods and beverages within 48 hours prior to Check-in.
38. Female subjects with a positive pregnancy test at Screening or Check-in.
39. Female subjects lactating/breastfeeding or who plan to breastfeed during the study through 60 days after administration of investigational product.
40. Unwilling to adhere to contraceptive requirements through 60 days after administration of investigational product.
41. Unwilling to abstain from sperm donation and ovum donation through 60 days after administration of investigational product.
42. Male subjects with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
43. Male subjects with a pregnant partner or partner planning to become pregnant who are unwilling to practice sexual abstinence or use contraception while the subject is participating in the study from Check-in until 60 days after administration of investigational product.

44. Subject has received a dose of an investigational drug within the past 30 days or 5 half-lives, whichever is longer, prior to Check-in.
45. Have previously completed or withdrawn from this study or any other study investigating avacopan, or have previously received the investigational product.
46. Donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, or platelets from 6 weeks prior to Check-in.
47. Unwilling to abide with study restrictions.
48. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

Subjects in Group 1 (normal renal function) are excluded if:

49. History of malignancy of any type, with the exception of the following: in situ cervical cancer or surgically excised non-melanomatous skin cancers more than 5 years before receiving avacopan.
50. A QTcF >450 msec in males or >470 msec in females or history/evidence of long QT syndrome at Screening or Check-in.
51. A history of renal disease or renal injury as indicated by medical history or an abnormal renal function profile at Screening or Check-in.

Subjects in Group 2 (ESRD requiring HD) are excluded if:

52. Child-Pugh Class C, indicating severe hepatic impairment assessed at Screening and Check-in (Appendix 10). Child-Pugh will only be evaluated for subjects deemed to have active liver disease by the Investigator (or designee).
53. Active malignancy of any type. Subjects with a history of malignancy that has been eradicated with supporting medical documentation indicating that there is no residual malignancy detected in the past 2 years will be allowed.
54. A change in disease status within 30 days of Screening, as documented by the subject's medical history, deemed clinically significant by the Investigator.
55. A QTcF ≥470 msec in males or ≥480 msec in females.

4.3. Screen Failures and Rescreening

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study because they do not meet eligibility requirements. A minimal set of screen failure information may be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only once.

4.4. CCI

CCI

[redacted]

4.5. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the Sponsor (or designee) will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all EOS assessments, if possible (Appendix 9). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their Adverse Events, Serious Adverse Events, or until the unresolved Adverse Events, Serious Adverse Events are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of 1 or more Adverse Events/Serious Adverse Events thought to be related to the study drug will generally not be replaced.

4.6. Study Termination

The Sponsor may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). Both the Sponsor and the Investigator reserve the right to

terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The Investigator is to notify the Institutional Review Board (IRB) in writing of the study's completion or early termination and send a copy of the notification to the Sponsor. The Sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply investigational product and by what mechanism, after termination of the study.

In addition, the study may be terminated by the Sponsor at any time and for any reason. If the Sponsor decides to terminate the study, they will inform the Investigator as soon as possible.

4.7. Discontinuation of Study Treatment (Group 2 only)

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or study procedures at any time during the study but continue participation in the study. If this occurs, the Investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Assessments (Appendix 9) including different options of follow-up (e.g., in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, Adverse Events, Serious Adverse Events and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or study procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on study to ensure safety surveillance and/or collection of outcome data.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Noncompliance
- Requirement for alternative therapy
- Pregnancy
- Protocol-specified criteria

5. STUDY TREATMENTS

Study treatment is defined as any investigational product, non-investigational product, placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

5.1. Investigational Product

The IMP will be supplied by the Sponsor. Detailed information regarding the storage, preparation, destruction, and administration of IMP will be provided.

All supplies of investigational product, both bulk and subject-specific, will be stored in accordance with the manufacturer's instructions or pharmacy instructions. Until dispensed to the subjects, the investigational and non-investigational products will be stored at the study site in a location that is locked with restricted access.

The IMP will be stored according to the instructions on the label at the CRU.

Table 2: Investigational Product

	Investigational Medicinal Product: Avacopan
Study Treatment Name	
Unit Strength and Formulation	CCI Immediate Release Hard Gelatin Capsule
Dose	CCI
Route of Administration	Oral
Accountability	The quantity administered, date administered, and lot number of investigational product are to be recorded on the appropriate Case Report Form.
Dosing Instructions	The Investigator/designee will administer the treatment after the completion of all predose procedures, under fed conditions. A standardized hemodialysis-friendly standardized meal will be provided to all subjects on Day 1. The dose should be taken within 30 minutes of the start of the meal. CCI should be taken with approximately 8 ounces (240 mL) of water. Capsules should not be broken or chewed.

Except as part of the dose administration, subjects will restrict their consumption of water for 1 hour prior to dosing and for 1 hour after dosing; at all other times during the study, subjects may consume water as desired. Subjects will fast for at least 4 hours postdose.

Subjects will be dosed while standing and will not be permitted to lie supine for 2 hours after administration of IMP, except as necessitated by the occurrence of an adverse event(s) and/or study procedures.

5.2. Investigational Product Administration

Subjects in Group 1 will have 1 dose administration each of CCI of avacopan and subjects in Group 2 will have two dose administrations each of CCI of avacopan. Subjects will be dosed in the order that they were enrolled. Subjects will receive all doses under supervision of the site staff.

5.3. Treatment of Overdose

For this study, any dose of avacopan greater than CCI will be considered an overdose. The effects of overdose of avacopan are not known. In case of overdose, consultation with the Medical Monitor is recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage, and to discuss further management of the subject.

5.3.1. Medical Devices

No investigational medical devices will be used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care. Non-Amgen non-investigational medical devices (e.g., syringes, sterile needles), that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

5.3.2. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational/non-investigational product(s), provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product(s) supplied by Amgen are to be reported.

5.4. Randomization

This is a nonrandomized study. The study has a fixed treatment sequence.

5.5. Blinding

This is an open-label study.

5.6. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- When subjects are dosed at the site, they will receive avacopan directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the eCRF.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

5.7. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of avacopan capsules received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused avacopan will be returned to the Sponsor, retained at the study site, or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects with normal renal function will refrain from use of any prescription or nonprescription medications/products during the study until the EOS visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

For renal-impaired subjects, treatment with chronic stable medications (for at least 3 months prior to study drug administration with the exceptions of minor changes in dose or formulation without change in clinical condition) necessary for maintaining the clinical status of the subject will be permitted if prescribed by the subject's personal physician and approved by the Medical Monitor and Investigator, in consultation with the Sponsor as needed. Except for concomitant

therapies associated with HD sessions, administration of medications should be withheld for at least 4 hours after study drug administration as clinically appropriate, unless needed for treatment of an adverse event, at the discretion of the Investigator. Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care while avoiding those listed in the exclusion criteria.

Acetaminophen (paracetamol) (2 g/day); hormone replacement therapy (e.g., estrogen and thyroid treatments including levothyroxine [Synthroid, Levothroid, Levoxyl, Unithroid], liothyronine [Cytomel], Liotrix [Thyrolar], and natural thyroid [Armour Thyroid, Nature-throid, Westhroid]); or oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an adverse event/serious adverse event. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations. While confined at the study site, subjects will receive a diet provided by the site at scheduled times that do not conflict with other study-related activities. No outside food or beverage will be permitted during confinement.

On dosing days (Day 1 for Group 1 and Day 1 of Periods 1 and 2 for Group 2), subjects will receive a standardized breakfast prior to study drug administration. The standardized breakfast will include approximately 215 fat calories, approximately 320 carbohydrate calories, approximately 125 protein calories, and approximately 1220 mg of sodium.

Refer to Section 5 and Table 2 for diet requirements/restrictions on applicable days of study treatment and/or PK assessments.

Foods and beverages containing poppy seeds, pomelos, or Seville oranges will not be allowed from 7 days prior to Check-in until EOS visit. Foods and beverages containing grapefruit will not be allowed from 14 days prior to Check-in until EOS visit.

Caffeine-containing foods and beverages will not be allowed from 48 hours before Check-in until EOS visit.

Consumption of alcohol will not be permitted from 48 hours prior to Check-in until EOS visit.

6.3. Smoking

Subjects will not be permitted significant use of tobacco- or nicotine-containing products (e.g., > ½ pack of cigarettes per day) within 3 months prior to Check-in through EOS.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before Check-in until the EOS visit. Subjects will otherwise maintain their normal level of physical activity during this time (i.e., will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, and platelets from 6 weeks prior to Check-in until 3 months after the EOS visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving consideration to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. Unless otherwise specified in the Schedule of Assessments, the order of priority for scheduling procedures around a timepoint is:

- predose safety assessments
- predose/trough PK blood samples
- dosing
- PK blood samples (postdose)
- postdose safety assessments (ECGs will be scheduled before vital signs measurements)
- any other procedures.

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, and safety laboratory assessments.

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 9. Arterial and venous PK samples may be collected from the HD catheter or arteriovenous fistula as appropriate.

Dialysate samples will be collected as specified in Appendix 9. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

For Group 2 Period 1, a sample of dialysate will be collected on Day 1 at 0.5, 1, 2, and 3 hours after the start of HD and after HD is complete for drug concentration analysis. The entire dialysate volume, blood flow, and dialysate flow during HD will be recorded for each timepoint, and the make and model of the dialyzer will be recorded.

Any blood sample collected according to the Schedule of Assessments (Appendix 9) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

7.1.2. Analytical Methodology

Plasma concentrations of avacopan and M1 metabolite will be determined using validated analytical procedures. Dialysate concentrations of avacopan and protein binding assessments will be determined using qualified methods. Specifics of the analytical method will be provided in a separate document.

7.2. Safety and Tolerability Assessments

7.2.1. Adverse Events and Serious Adverse Events: Time period and Frequency for Collecting and Reporting Safety Event Information

Adverse event definitions, assignment of severity and causality, and procedures for reporting Adverse Events and Serious Adverse Events are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to EOS. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report Adverse Events and Serious Adverse Events occurring at any other time during the study.

Adverse Events

The adverse event grading scale to be used in this study is described in Appendix 1.

The Investigator is responsible for ensuring that all adverse events observed by the Investigator or reported by the subject that occur after first dose of investigational product through the 30 days after the last day of the dosing interval of investigational product, whichever is later are reported using the Events Case Report Form (CRF).

Serious Adverse Events

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of the informed consent through 30 days after dosing of investigational product or EOS visit, whichever is later, are reported using the appropriate eCRF and reported on the paper-based Serious Adverse Event Report Form (described in Appendix 1).

All serious adverse events will be collected, recorded, and reported to the Sponsor within 24 hours of the Investigator's knowledge of the event. The Investigator will submit any updated Serious Adverse Event data to the Sponsor within 24 hours of it being available.

Since the criteria of the Common Terminology Criteria for Adverse Events (CTCAE) grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to Grade 4 CTCAE toxicity grading scale criteria (e.g., laboratory abnormality reported as Grade 4 without manifestation of life-threatening status), it will be left to the Investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

Serious Adverse Events After the Protocol-Required Reporting Period

After EOS, there is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the Investigator. However, if the Investigator becomes aware of serious adverse events (regardless of causality), then these serious adverse events will be reported to Amgen within 24 hours following the Investigator's awareness of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the Sponsor's safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious

adverse events will be followed, where possible, until resolution, stabilization, until the event is otherwise explained, or the subject is Lost to Follow-up. This will be completed at the Investigator's (or designee's) discretion.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the eCRF.

Regulatory Reporting Requirements for Serious Adverse Events

If the subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.

Prompt notification by the Investigator to the Sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment 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 treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/Independent Ethics Committees, and Investigators.

Individual 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.

Amgen will prepare a single Development Safety Update Report (also referred to as Annual Safety Report in the European Union) for the Amgen Investigational Product. To ensure that consolidated safety information for the study is provided, this single Development Safety Update Report will also include appropriate information on any other investigational products used in the clinical study, if applicable.

An Investigator who receives an individual safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will file it along with the IB and will notify the IRB, if appropriate according to local requirements.

Safety Monitoring Plan

Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.

Other Safety Findings/Special Situations

Medication errors, misuse or abuse of the investigational product is subject to the same reporting obligation as adverse events. Therefore, the following procedures must be followed:

- All medication errors, misuse, or abuse of the investigational product, whether or not the Other Safety Finding (OSF)/Special Situation (SS) is accompanied by a non-serious adverse event or a serious adverse event, as determined by the Investigator, the OSF/SS must be collected and recorded on the OSF/SS CRF.
- If there are any resulting clinical signs, symptoms, or sequelae, the corresponding non-serious adverse event or serious adverse event must also be collected and recorded on the Events CRF.
- All medication errors, misuse, or abuse when associated with a serious adverse event must also be reported to Amgen or designee immediately and no later than 24 hours of the Investigator's awareness of the OSF/SS - medication error, misuse, or abuse by submitting Serious Adverse Event Report Form.

Further details and definitions regarding OSF/ SS - medication errors, misuse, and abuse, can be found in Appendix 1.

Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 60 days after dosing of investigational product.

If a pregnancy is reported, the Investigator is to inform Amgen immediately and no later than 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 4. Amgen Global Patient Safety will follow-up with the Investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 4.

Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes

pregnant it must be reported on the Pregnancy Notification Form, see Figure 6). Refer to Appendix 3 for contraceptive requirements.

A pregnancy test will be performed at the end of the study.

Additional on-treatment pregnancy testing may be performed at the Investigator's discretion or as required per local laws and regulations.

7.2.2. Clinical Laboratory Evaluations

Blood samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, and serology) at the times indicated in the Schedule of Assessments in Appendix 9. Urine samples will be collected for Group 1 only for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 9. Clinical laboratory evaluations are listed in Appendix 2.

The Investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in CRF/eCRF. The Investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

Subjects in Group 1 will provide urine samples for drugs of abuse screen and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 9. Subjects in Group 2 will provide a blood or saliva sample for drugs of abuse screen and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 9. For all female subjects, a pregnancy test and follicle-stimulating hormone (FSH) screen for postmenopausal women will be performed at the times indicated in the Schedule of Assessments in Appendix 9.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.2.3. Vital Signs

Seated or supine BP, seated or supine pulse rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 9. Vital signs may also be performed at other times if judged to be clinically appropriate.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be seated or supine for at least 5 minutes before BP and pulse rate measurements. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as possible, but prior to the blood draw.

Vital signs for subjects will be taken consistently for each subject in either the seated or supine position. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

7.2.4. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 9. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria apply:

- QTcF is >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG and initiate further work-up or intervention as necessary.

7.2.5. Physical Examination

Physical examination will be performed and will include a neurological examination (breast, rectal, and genital examination are not required). Neurologic examination will include evaluation of mental status/cognition/mood/affect, gross and fine motor, sensory, cranial nerves, coordination, and deep tendon reflexes. Physical examination findings should be recorded on the appropriate CRF (e.g., medical history, treatment-emergent adverse event). Physical examinations will be performed at the timepoints specified in the Schedule of Assessments in Appendix 9.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

The sample size for this study is based on studies of similar design and is considered adequate for evaluation of the study objectives.

Approximately 12 subjects are planned to be enrolled in this study. Approximately 6 subjects will be enrolled in each group.

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of avacopan and have evaluable PK data. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an adverse event of vomiting that occurs at or before 2 times median time to maximum concentration or diarrhea within 24 hours of dosing.

8.2.2. Safety Population

The safety population will include all subjects who received at least 1 dose of avacopan and have at least 1 postdose safety assessment.

If a subject has a serious adverse event prior to dosing, reporting of the serious adverse event will be included with the safety population.

8.3. Pharmacokinetic Analyses

Arithmetic mean, coefficient of variation (CV%), standard deviation, median, minimum, maximum, and number of observations will be calculated for the PK parameters for each renal function group. Geometric mean and geometric CV% will be provided for all PK parameters except t_{max}. Median, minimum, maximum, and number of observations will be calculated for t_{max}.

The primary statistical analysis will estimate the relationship between the PK of avacopan and eGFR estimated by the MDRD equation. In addition, a relationship between the PK of M1 and the eGFR may also be evaluated.

The PK parameters C_{max}, t_{max}, apparent plasma terminal elimination half-life, AUC_{inf}, AUC_{0-48}, AUC_{last}, apparent clearance (CL/F), fraction of unbound drug (f_u), apparent volume of distribution (V_z/F), extraction ratio for HD (ERD), and CL_D will be determined, as appropriate, by using noncompartmental methods. Additional PK parameters may be determined as appropriate.

Ratios (test/reference) for the model-estimated C_{max}, AUC_{0-48} (calculated for Group 2 Period 2), and AUC_{inf} (test) relative to the group with normal renal function (reference) will be generated, along with 90% confidence intervals.

For subjects in Group 2, the PK parameters C_{max}, t_{max}, AUC_{0-48}, and AUC_{0-last} will be determined by using noncompartmental methods for doses administered. For subjects in Group 2 Period 1, a sample of dialysate will be collected on Day 1 at 0.5, 1, 2, and 3 hours. In addition, to support determination of avacopan clearance by HD, AUC_{last} will be determined from the arterial and venous plasma samples during HD (for Group 2 Period 1). The ratios (test/reference) of central

values and 90% CIs will be calculated for log-transformed C_{max} and AUC values on HD day (Group 2 Period 1, test) compared to non-HD day (Group 2 Period 2, reference).

Specific details will be presented in the Statistical Analysis Plan for this study.

8.4. Safety Analysis

The number and percentage of subjects reporting any adverse events will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product, and treatment-emergent adverse events will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

Clinical laboratory tests, ECG, and vital signs will be summarized.

8.5. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

1. Amgen. Avacopan – Current Investigator's Brochure.

2. TAVNEOS® (avacopan) capsules, for oral use. Highlights of Prescribing Information.

3. Tavneos (Avacopan). Summary of Product Characteristics. Vifor Fresenius Medical Care Renal Pharma UK Ltd. 30 Aug 2023.

4. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 2024. Guidance for industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing.

10. APPENDICES

Appendix 1: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events and Serious Adverse Events

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event 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 a treatment, combination product, medical device, or procedure. • Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration 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 intentional overdose of either study treatment or a concomitant medication. Intentional overdose will be reported as an adverse event/serious adverse event when it is taken with possible suicidal/self-harming intent. Such intentional overdoses are to be reported regardless of sequelae. Accidental/unintentional overdose will be captured as a medication error.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • 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.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject 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.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) 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 an adverse event. 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 adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to 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 or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Other Safety Findings/Special Situations: Medication Errors, Misuse or Abuse

All medication errors, misuse or abuse of the investigational product are subject to the same reporting obligation as adverse events and must be collected and recorded on the Other Safety Findings (OSF)/Special Situations (SS) case report form (CRF). If there are any resulting clinical signs, symptoms or sequelae, the corresponding non-serious adverse event and serious adverse event must also be collected and recorded on the Events CRF.

All medication errors, misuse, or abuse when associated with a serious adverse event must also be reported to Amgen or designee immediately and no later than 24 hours of Investigator's awareness of the OSF/SS - medication error, misuse, or abuse by submitting the paper-based Serious Adverse Event Report Form.

Other Safety Finding/Special Situation	Collected and Recorded on the Other Safety Findings (OSF)/Special Situations (SS) Case Report Form (CRF)	Primary Reporting Method: Reported/submitted on the paper-based Serious Adverse Event Report Form to Amgen or designee immediately and no later than 24 hours of Investigator's awareness
Medication Error	All (regardless of whether associated with an adverse event/serious adverse event)	Only if associated with a serious adverse event
Misuse	All (regardless of whether associated with an adverse event/serious adverse event)	Only if associated with a serious adverse event
Abuse	All (regardless of whether associated with an adverse event/serious adverse event)	Only if associated with a serious adverse event

	Medication Error: A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the subject (e.g., mistake in the process of

Definitions	prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice.
	Misuse: A misuse refers to situations where the medicinal product, combination product, or medical device is intentionally and inappropriately used not in accordance or outside what is foreseen in the protocol.
	Abuse: An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, combination product, or medical device, which is accompanied by harmful physical or psychological effects.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant adverse event/serious adverse event information in the Event electronic Case Report Form (eCRF).
- The Investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product, other protocol-required therapies;
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to the investigational product(s) and/or study-mandated procedures;
  - Action taken; and
  - Outcome of event.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the appropriate eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor in lieu of completion of the appropriate eCRF page.
- If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the

medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The Investigator will assess severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events (CTCAE), version 5 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
Assessment of Causality
• The Investigator is obligated to assess the relationship between investigational product(s) (investigational product[s], noninvestigational product[s]/auxiliary medicinal product[s], device[s], study-required activity and/or procedure[s]) and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in their assessment. • For each adverse event/serious adverse event, the Investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The Investigator may change their opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
Follow-up of Adverse Event and Serious Adverse Event
• 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 to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or

investigations, histopathological examinations, or consultation with other health care professionals.

- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.
  - If a subject dies during participation in the study, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology if available.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper Serious Adverse Event Report Form

- Facsimile transmission of the Serious Adverse Event Report Form (see Figure 5) is the preferred method to transmit this information.
- If the event is a serious adverse event associated with the Other Safety Finding/Special Situation (medication error, misuse, or abuse) then the site must complete/submit the Serious Adverse Event Report Form for the associated Other Safety Finding/Special Situation (medication error, misuse, or abuse).
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Once the study has ended, serious event(s) should be reported to Amgen (regardless of causality) if the Investigator becomes aware of a serious adverse event. The Investigator should use the paper-based Serious Adverse Event Report Form to report the event.

Figure 5: Sample Serious Adverse Event Report Form

AMGEN®
20230265
Fortrea Study #
8530204
AMG 569

Clinical Trial Serious Adverse Event Report Form– Phase 1–4
Notify Amgen Immediately and no later than 24 Hours of awareness of the serious adverse event/other safety finding/special situation

❑New
❑Follow-up

<<Amgen Safety fax number to be populated by Study Manager/ProtocolAuthor/Designee prior to providing to sites SELECT OR TYPE IN A FAX#.>> If an email address or eFax is used, the Primary Study Team (e.g., Clinical Manager or Delegate) will need to ensure secure email exchange is established between the Provider/Study Sites, Vendor/Supplier, Sites and Amgen

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex ❑F ❑M	Race	If applicable, provide End of Study date

3. SERIOUS ADVERSE EVENT OR Other Safety Finding/Special Situation associated with a Serious Adverse Event

Information in this section must also be entered on the Serious Adverse Event Summary Case Report Form and if applicable, Other Safety Finding/Special Situation, must be entered on the Other Safety Findings(OSF)/Special Situations (SS) Case Report Form

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day Month Year

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event and (if applicable) Other Safety Finding/Special Situation associated with a Serious Adverse Event *List one event per line*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the event may have been caused by IP or an investigational device? If yes see section 10 — AMG 569 (Yes/No, Year)	<Device> (Yes/No, Year)	<Device> (Yes/No, Year)	<Device> (Yes/No, Year)	<Device> (Yes/No, Year)	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: 01 Fatal; 02 Immediately life- threatening; 03 Required hospitalization or prolonged hospitalizaion; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ❑No ❑Yes, If yes, please complete date(s):		

AMGEN 20230265 Fortrea Study # 8530204 AMG 569	**Clinical Trial Serious Adverse Event Report Form– Phase 1–4** *Notify Amgen Immediately and no later than 24 Hours of awareness of the serious adverse event/other safety finding/special situation*	☐New ☐Follow-up

	Site Number	Subject ID Number	

5. INVESTIGATIONAL PRODUCT (IP) / DEVICE

	Initial Start Date	Prior to, or at time of Event				Action Taken with Product	Lot # and Serial #
		Date of Dose	Dose	Route	Frequency		
	Day Month Year	Day Month Year				01 Still being Administered 02 Permanently discontinued 03 Withheld	
AMG 569 ☐Blinded X Open Label							Lot # _____ ☒ Unknown Serial # _____ ☒ Unknown
<<IP/Device>> ☐Blinded ☐Open Label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown
<<IP/Device>> ☐Blinded ☐Open Label							Lot # _____ ☐ Unknown Serial _____ ☐ Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date Day Month Year	Test / Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

AMGEN 20230265 Fortrea Study # 8530204 AMG 569	**Clinical Trial Serious Adverse Event Report Form– Phase 1–4** *Notify Amgen Immediately and no later than 24 Hours of awareness of the serious adverse event/other safety finding/special situation*	❑New ❑Follow-up

	Site Number	Subject ID Number	

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*		

FOR INTERNAL USE ONLY **– *Note for Case Management/LSOs:*** DO NOT send queries to the clinical site. Please direct all follow-up queries related to this SAE to [Medical.Safety@fortrea.com]

Appendix 2: Clinical Laboratory Evaluations

<table>
<tr><th>Clinical chemistry:</th><th>Hematology:</th><th>Urinalysis – Group 1 only:</th></tr>
<tr><td>Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatinine
Direct bilirubin[a]
Gamma-glutamyl transferase
Glucose
Indirect bilirubin[a]
Inorganic phosphate
Potassium
Sodium
Total bilirubin[a]
Total CO_2 (may be measured as bicarbonate)
Total protein
Uric acid</td><td>Hematocrit
Hemoglobin
Hemoglobin A1C[b]
Mean cell hemoglobin
Mean cell hemoglobin concentration
Mean cell volume
Platelet count
Red blood cell (RBC) count
RBC distribution width
White blood cell (WBC) count
WBC differential:
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils</td><td>Bilirubin
Blood
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
pH
Protein
Specific gravity
Urobilinogen
Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)</td></tr>
<tr><th>Serology[c]:</th><th>Drug screen[b]:</th><th>Hormone panel - females only:</th></tr>
<tr><td>Anti-hepatitis B surface antibody
Anti-hepatitis B core antibody
Hepatitis B surface antigen
Hepatitis C antibody
Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen</td><td rowspan="3">Including but not limited to:
Amphetamines/ methamphetamines
Barbiturates
Benzodiazepines
Cocaine (metabolite)
Methadone
Phencyclidine
Opiates
Tetrahydrocannabinol/ cannabinoids
Alcohol breath test[d]</td><td>Follicle-stimulating hormone (postmenopausal females only)[c]
Serum pregnancy test (human chorionic gonadotropin)[e]
Urine pregnancy test[e]</td></tr>
<tr><td rowspan="2">Coagulation panel[b]:
International normalized ratio (INR)
Prothrombin time (PT)
Activated partial thromboplastin time (aPTT)</td><td>Other Tests:</td></tr>
<tr><td>Hepatotoxicity only:
International normalized ratio (INR)[f]</td><td>Estimated glomerular filtration rate (eGFR)[g]</td></tr>
</table>

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Only analyzed at Screening and Check-in.
[c] Only analyzed at Screening.
[d] Alcohol breath test performed at Check-in only. Matrix for drug screen will be flexible, depending on the renal impairment status of the subject.
[e] Performed in serum at Screening and in urine at all other times for females in Group 1. A positive urine pregnancy test will be confirmed with a serum pregnancy test. Serum pregnancy test will be done at all timepoints for subjects in Group 2 (end-stage renal disease [ESRD]).
[f] International normalized ratio will be retested if hepatotoxicity is suspected.
[g] Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease (MDRD) equation.
MDRD formula (mL/min/1.73 m^2) = 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African-American)

Appendix 3: Contraception Requirements

All subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they conceive a child during treatment and for 60 days after administration of the investigational product.

Additional medications given during the study may alter the contraceptive requirements. The Investigator must discuss these contraceptive changes with the subject.

Definitions Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Non-Child-Bearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: males are considered fertile after puberty.

Contraception Requirements

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the Informed Consent Form (ICF) until 60 days after administration of the investigational product.

Primary methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill associated with inhibition of ovulation (as prescribed) without supplementary iron (i.e. Loestrin Fe, Junel Fe, and Lo Loestrin Fe are prohibited)
- combined hormonal patch (as prescribed)

- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
    - Bilateral tubal ligation with confirmation of surgical success
    - Regulatory approved method of hysteroscopic bilateral tubal occlusion with confirmation of occlusion of the fallopian tubes
- hormonal implant
- hormonal or non-hormonal intrauterine device
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects should refrain from donation of ova from Check-in (Day -1) until 60 days after administration of the investigational product.

Male Subjects:

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (i.e., male condom with spermicide) in addition to a second method of acceptable contraception by female partner from Check-in until 60 days after administration of investigational product. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or regulatory approved method of hysteroscopic bilateral tubal occlusion)
- hormonal implant
- hormonal or non-hormonal intrauterine device

- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide.

Male subjects are required to refrain from donation of sperm from Check-in until 60 days after administration of the investigational product.

Sexual Abstinence

Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) is an acceptable method of contraception. The reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 60 days after the EOS visit.

If a subject who practices true abstinence at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously from the time of signing the ICF until 60 days after the EOS visit.

Same-sex Relationships

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously from the time of signing the ICF until 60 days after EOS.

Appendix 4: Collection of Pregnancy and Lactation Information

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking investigational product through 60 days after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Form (see Figure 6). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws.)
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 60 days after dosing of investigational product. This information will be forwarded to Amgen Global Patient Safety. Generally, infant Follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (e.g., spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator will be reported to Amgen Global Patient Safety as described in Appendix 1. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 4.7 for details).

Male Subjects with Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 60 days after dosing of investigational product. The information will be recorded on the Pregnancy Notification Form. The form (see Figure 6) must be submitted to Amgen

Global Patient Safety immediately and no later than 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws.)

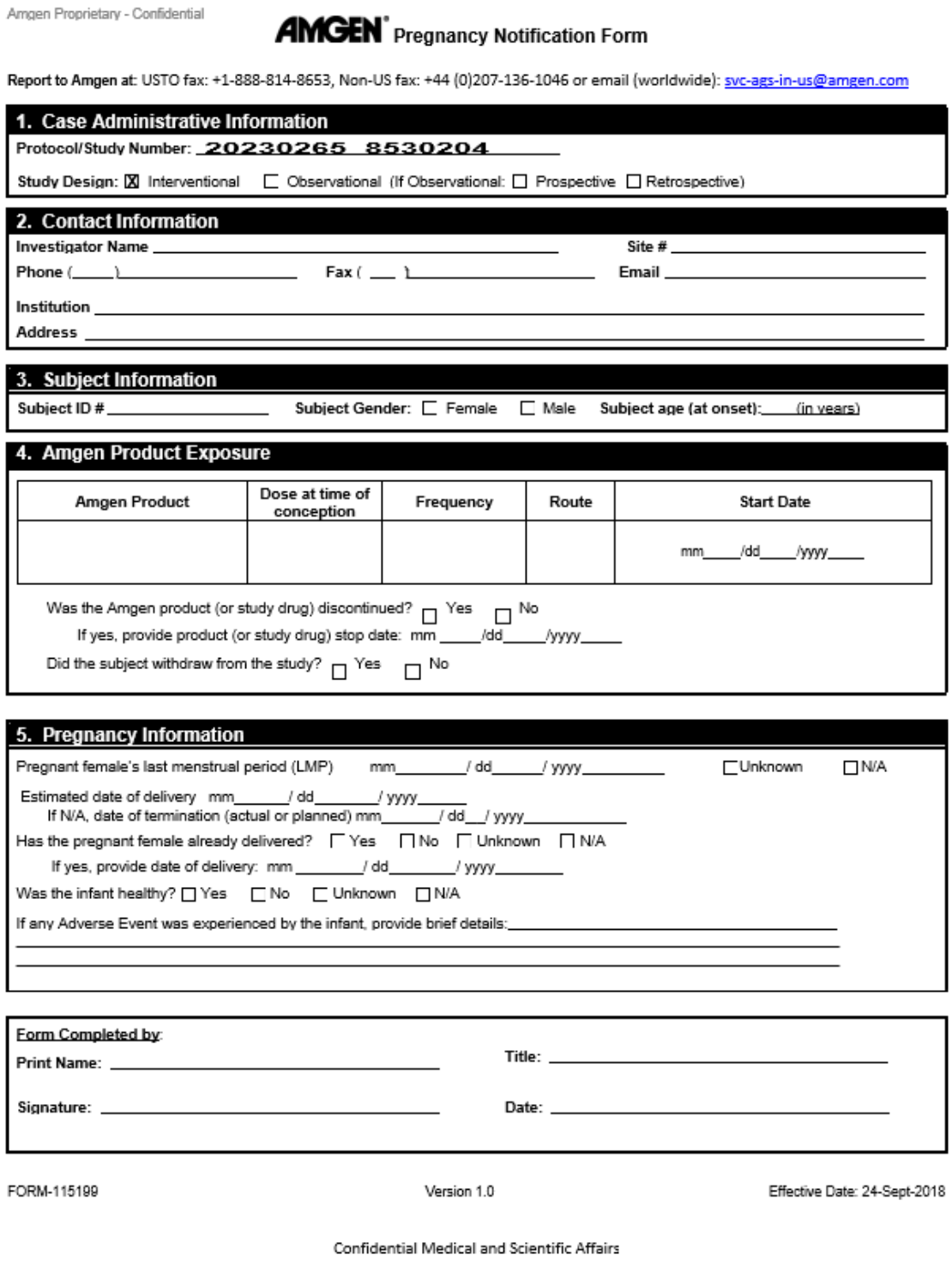
- Males whose partners become pregnant during treatment and for an additional 60 days after dosing of investigational product must practice sexual abstinence or use a condom through 60 days after dosing of investigational product and will be followed for safety until the end of study visit.
- The Investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking investigational product through 60 days after dosing of investigational product.
- Information will be recorded on the Lactation Notification Form (Figure 7) and submitted to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event.
- Study treatment will be discontinued if the female subject breastfeeds during the study.
- With the female subject's signed consent for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking investigational product through 60 days after the last dose of investigational product.

With the female subject's signed consent for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 60 days after discontinuing protocol-required therapies.

Figure 6: Pregnancy Notification Form



Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20230265 8530204

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

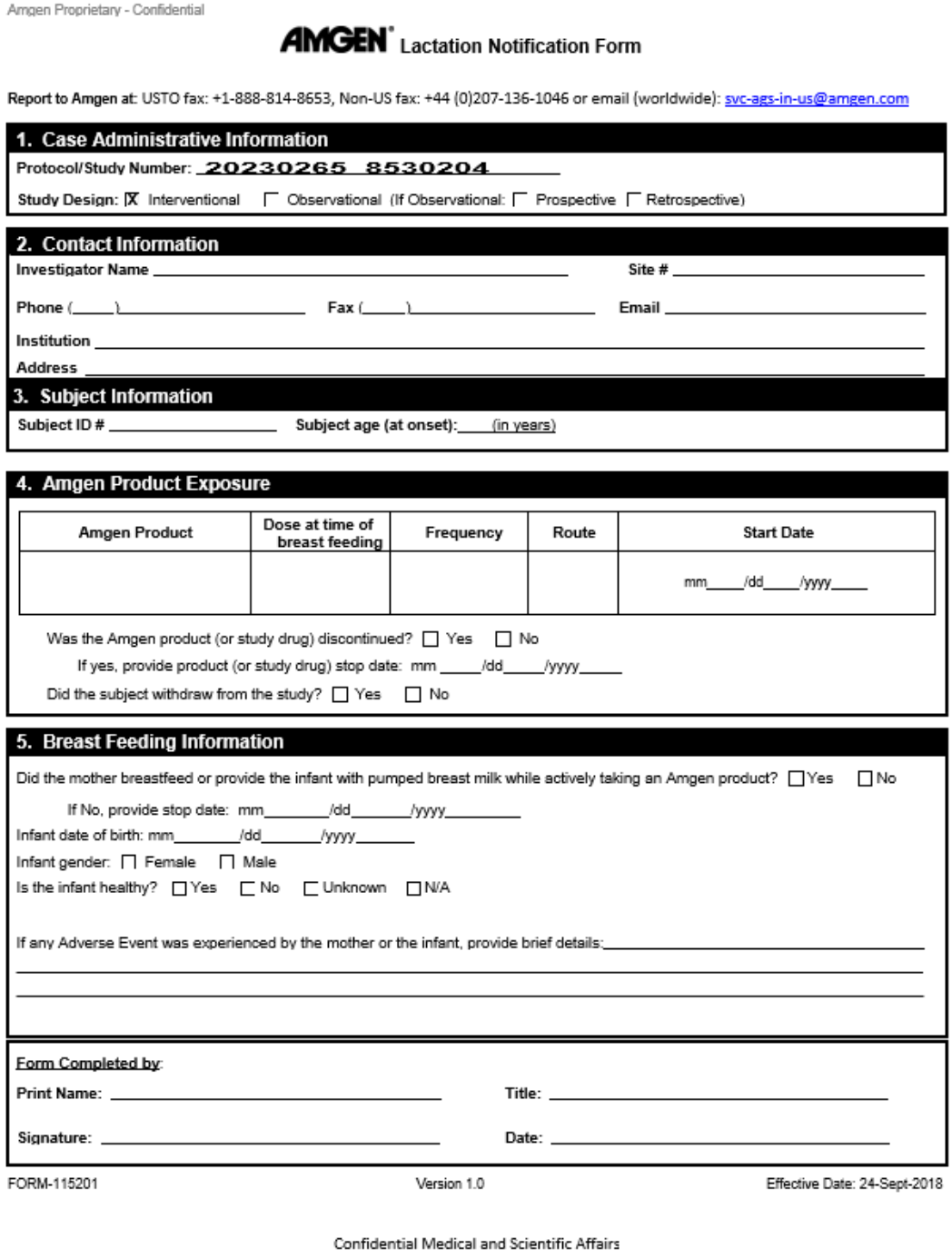
Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Confidential Medical and Scientific Affairs

Figure 7: Lactation Notification Form



Amgen Proprietary - Confidential

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20230265 8530204

Study Design: [X] Interventional [ ] Observational (If Observational: [ ] Prospective [ ] Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? [ ] Yes [ ] No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? [ ] Yes [ ] No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? [ ] Yes [ ] No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: [ ] Female [ ] Male

Is the infant healthy? [ ] Yes [ ] No [ ] Unknown [ ] N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Confidential Medical and Scientific Affairs

Appendix 5: Sample Storage and Destruction

When permitted by local regulations, any blood sample collected according to the Schedule of Assessments (Appendix 9) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded before being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

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 (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

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

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

An initial sample ICF will be provided for the Investigator (or designee) to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Study Manager to the Investigator. The written ICF is to be prepared in the language(s) of the potential study participant population.

The Investigator or their delegated representative will explain to the subject, or their legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and the IRB or study site.

The medical record must include a statement that written informed consent was obtained before the subject 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.

The acquisition of informed consent and the subject's agreement or refusal of their notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 21 days from the previous ICF signature date and the same version of the ICF is in use at the time of rescreening.

Subject Data Protection

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to the Sponsor.

Subjects will be assigned a unique identifier by the Sponsor (or designee). Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic Case Report Form (eCRF) demographics page, in addition to the unique subject identification number (Section 4.4), include the age at time of enrollment.

For serious adverse events reported to the Sponsor (or designee), subjects are to be identified by their unique subject identification number (Section 4.4), (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to the Sponsor (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to their study-related records, including personal information.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential information of the Sponsor, Amgen Inc. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written permission from the Sponsor.

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subjects will be assigned a unique identifier by the Sponsor (or designee). Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the Case Report Form demographics page, in addition to the unique subject identification number (Section 4.4), include the age at the time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number (Section 4.4), initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification 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 subjects 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) 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.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture system on an eCRF in a timely fashion.

All data generated from external sources (e.g., laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or Contract Research Organization (Fortrea), will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the electronic data capture system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

The policy for publication of data obtained during this study will be documented in the Clinical Study Agreement.

Appendix 7: Hepatotoxicity: Suggested Actions and Follow-up Assessments (Group 1 only)

Subjects with normal hepatic function at Screening who experience aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3 x upper limit of normal (ULN) or subjects with elevated values before drug exposure who have a 2-fold increase above baseline values (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009) are to undergo clinical assessments and a period of "close observation" until abnormalities return to normal or to the subject's baseline level as described below.

Clinical Assessments and Observation

Assessments that are to be performed during this period include:

- Repeat AST, ALT, alkaline phosphatase, bilirubin (total and direct), and international normalized ratio (INR) within 24 hours as possible.
- In cases of total bilirubin (TBL) > 2 x ULN or INR > 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours as possible until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
    - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
    - Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Appropriate liver imaging if clinically indicated

- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or are considered stable by the Investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential drug-induced liver injury (DILI) event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding electronic Case Report Form (eCRF).

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (e.g., hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right-sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
- Heritable disorders causing impaired glucuronidation (e.g., Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (e.g., rhabdomylosis, hemolysis).

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, i.e., cases of AST or ALT > 3 x ULN and concurrent TBL > 2 x ULN or INR > 1.5 (for subjects not on anticoagulation therapy) without evidence of alternative cause of the elevations, require the following:

- The event is to be reported to the Sponsor as a serious adverse event within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded)
- The appropriate eCRF captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Sponsor.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 1.

Appendix 8: Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments (Group 2 only)

Subjects with abnormal hepatic laboratory values (i.e., alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (e.g., hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right-sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
- Heritable disorders causing impaired glucuronidation (e.g., Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (e.g., rhabdomylosis, hemolysis).

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 3: Conditions for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding
TBL	>3x ULN at any time
INR	--
	OR
AST/ALT	>8x ULN at any time
	>5x ULN but <8x ULN for ≥2 weeks
	>5x ULN but <8x ULN and unable to adhere to enhanced monitoring schedule
	>3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)
	OR
ALP	>8x ULN at any time

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Table 4: Conditions for Withholding Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Permanent Discontinuation
TBL	>2x ULN
	OR
INR	>1.5 (for subjects not on anticoagulation therapy)
	AND
AST/ALT	>3x ULN (when baseline was < ULN), in the presence of no important alternative causes for elevated AST/ALT and/or TBL values
ALP	--

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, Investigator, and Amgen.

If signs or symptoms recur with rechallenge, then avacopan is to be permanently discontinued.

Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 3) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded).
- The appropriate electronic Case Report Form (eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 1.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 3 and Table 4 or who experience AST or ALT elevations >3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours as possible
- In cases of TBL >2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct) and INR is to be performed every 24 hours as possible until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL.

The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
    - Prior and/or concurrent disease or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
    - Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies

- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis, if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the Investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding eCRFs.

Appendix 9: Schedule of Assessments

Schedule of Assessments for Group 1

Activity per Period	Screening	Check-in	Treatment Period																						
Study Day	D-28 to D-2	D-1	D1												D2		D3	D4	D5	D6	D7	D8	D12	D15	D18 EOS/ET
Time (in hours)	--	--	Pre	0	0.25	0.5	1	2	3	4	6	9	12	16	24	36	48	72	96	120	144	168	264	336	408
In-house Residency		←																				→			
Outpatient Visit	X																						X	X	X
GENERAL AND SAFETY ASSESSMENTS																									
Informed Consent	X																								
Inclusion/Exclusion Criteria	X	X																							
Demographics	X																								
Serology	X																								
Medical History	X	X[a]																							
Height and BMI	X																								
Weight	X	X																							X
Drug Screen	X	X																							
Alcohol Test		X																							
Adverse Events[b]				→																					
Serious Adverse Events[b]	←																					→			
Prior/Concomitant Medications[c]	←																					→			
LABORATORY ASSESSMENTS AND OTHER PROCEDURES																									
Pregnancy Test (females only)[d]	X	X																							X
Serum FSH Test (postmenopausal females only)	X																								
Physical Examination[e]	X	X															X					X			X
12-lead ECG[f]	X	X																				X			X
Vital Signs[g]	X	X	X							X					X		X	X	X	X	X	X			X
Clinical Laboratory Evaluations[h]	X	X																				X			X
Coagulation Panel	X	X																							
eGFR[i]	X	X																							
Plasma Protein Binding												X													

Activity per Period	Screening	Check-in	Treatment Period																						
Study Day	D-28 to D-2	D-1	D1												D2		D3	D4	D5	D6	D7	D8	D12	D15	D18 EOS/ET
Time (in hours)	--	--	Pre	0	0.25	0.5	1	2	3	4	6	9	12	16	24	36	48	72	96	120	144	168	264	336	408
PHARMACOKINETIC ASSESSMENTS																									
Avacopan and M1 Plasma PK[j]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INVESTIGATIONAL PRODUCT																									
Avacopan Dose Administration[k]				X																					

Abbreviations: BMI = body mass index; D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study visit; ET = early termination; FSH = follicle-stimulating hormone; M1 = metabolite; PK = pharmacokinetic; Pre = predose.

[a] Interim medical history only.

[b] Adverse events will be recorded from initiation of study treatment on Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the Informed Consent Form until 30 days after the dose of study treatment or through the EOS, whichever is later.

[c] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to enrollment for over-the-counter or prescription medications, and 30 days prior to enrollment for herbal medicines (e.g., St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic case report form.

[d] Performed in serum at Screening and in urine at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

[e] A full physical examination at Screening, Check-in, Day 3, Day 8, and Day 18 (EOS/ET).

[f] Twelve-lead ECGs will be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws at: Screening; Check-in; Day 8; and Day 18 (EOS/ET). Electrocardiograms should be collected prior to any PK corresponding timepoints. Single trace ECGs will be collected at all timepoints.

[g] Vital signs measurements (seated/supine blood pressure, seated/supine pulse rate, respiratory rate, and oral body temperature) should be carried out prior to having blood drawn. Vital signs will be obtained at: Screening; Check-in; prior to avacopan administration and 4 hours following avacopan administration on Day 1, 24 hours postdose on Day 2, and on Days 3, 4, 5, 6, 7, 8, and 18 (EOS or ET). Pulse rate and blood pressure will be measured using the same arm for each reading after the subject has been resting in the seated/supine position for at least 5 minutes.

[h] Clinical chemistry, hematology, and urinalysis (fasted at least 8 hours).

[i] The eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation.
MDRD formula (mL/min/1.73m^2) = 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African-American)

[j] The PK samples collected on Day 1 will have a sampling window of ±10 minutes. Postdose samples on Day 2 will have a sampling window of ±1 hour. Postdose samples Days 3 to 8 will have a sampling window of ±2 hours. Postdose samples on Days 12, 15, and 18 will have a sampling window of ±4 hours. Times of all PK samples will be recorded to the nearest minute.

[k] Dose administration of avacopan will be given in the morning on Day 1 under fed conditions.

Schedule of Assessments for Group 2 (Period 1 – On Hemodialysis)

Activity per Period	Screening	Check-in	Treatment Period 1																						
Study Day	D-28 to D-2	D-1	D1												D2		D3	D4	D5	D6	D7	D8	D12	D15	D18
Time (in hours)	--	--	Pre	0	0.25	0.5	1	2	3	4	6	9	12	16	24	36	48	72	96	120	144	168	264	336	408
In-house Residency		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→			
Outpatient Visit	X																						X	X	X
GENERAL AND SAFETY ASSESSMENTS																									
Informed Consent	X																								
Inclusion/Exclusion Criteria	X	X																							
Demographics	X																								
Serology	X																								
Medical History	X	X[a]																							
Height and BMI	X																								
Weight	X	X																							
Serum or Saliva Drug Screen	X	X																							
Alcohol Test		X																							
Child-Pugh Assessment	X	X																							
Adverse Events[b]				→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious Adverse Events[b]	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→			
Prior/Concomitant Medications[c]	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→			
LABORATORY ASSESSMENTS AND OTHER PROCEDURES																									
Pregnancy Test (females only)[d]	X	X																							
Serum FSH Test (postmenopausal females only)	X																								
Physical Examination[e]	X	X															X					X			X
12-lead ECG[f]	X	X																				X			
Vital Signs[g]	X	X	X							X					X		X	X	X	X	X	X	X	X	X
Clinical Laboratory Evaluations[h]	X	X																				X			
Coagulation Panel	X	X																							
eGFR[i]	X	X																							
Plasma Protein Binding									X			X													
Hemodialysis[j, k]										X							X		X			X			

Activity per Period	Screening	Check-in	Treatment Period 1																						
Study Day	D-28 to D-2	D-1	D1												D2		D3	D4	D5	D6	D7	D8	D12	D15	D18
Time (in hours)	--	--	Pre	0	0.25	0.5	1	2	3	4	6	9	12	16	24	36	48	72	96	120	144	168	264	336	408
PHARMACOKINETIC ASSESSMENTS																									
Avacopan and M1 Plasma PK[k]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INVESTIGATIONAL PRODUCT																									
Avacopan Dose Administration[l]				X																					

Abbreviations: BMI = body mass index; D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HD = hemodialysis; M1 = metabolite; PK = pharmacokinetic; Pre = predose; SOA = Schedule of Assessments.

[a] Interim medical history only.

[b] Adverse events will be recorded from initiation of study treatment on Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the Informed Consent Form until 30 days after the last dose of study treatment or through the EOS, whichever is later.

[c] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to enrollment for over-the-counter or prescription medications, and 30 days prior to enrollment for herbal medicines (e.g., St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic case report form.

[d] Performed in serum at all timepoints.

[e] A full physical examination at Screening, Check-in, Day 3, Day 8, and Day 18.

[f] Twelve-lead ECGs will be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws at: Screening, Check-in, and Day 8. Electrocardiograms should be collected prior to any PK corresponding timepoints. Single trace ECGs will be collected at all timepoints.

[g] Vital signs measurements (seated/supine blood pressure, seated/supine pulse rate, respiratory rate, and oral body temperature) should be carried out prior to having blood drawn. Vital signs will be obtained at: Screening; Check-in; prior to avacopan administration and prior to HD 4 hours following avacopan administration on Day 1, 24 hours postdose on Day 2, and on Days 3, 4, 5, 6, 7, 8, and Days 12, 15, and 18. Pulse rate and blood pressure will be measured using the same arm for each reading after the subject has been resting in the seated/supine position for at least 5 minutes.

[h] Clinical chemistry and hematology (fasted at least 8 hours). Urinalysis will not be performed for subjects in Group 2.

[i] The eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation.
MDRD formula (mL/min/1.73m^2) = 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

[j] Day 1 assessments will include recording of the date and time of the last HD treatment before avacopan administration. On Day 1, subjects will receive avacopan dose and begin HD at 4 hours postdose. Hemodialysis will occur on Days 3, 5, and 8. Hemodialysis will continue as needed beyond the timepoints specified in the SOA. The study day, and the start and end times will be collected for all HD sessions.

[k] The PK samples collected on Day 1 will have a sampling window of ±10 minutes. Postdose samples on Day 2 will have a sampling window of ±1 hour. Postdose samples Days 3 to 8 will have a sampling window of ±2 hours. Postdose samples on Days 12, 15, and 18 will have a sampling window of ±4 hours. Times of all PK samples will be recorded to the nearest minute. Day 3, Day 5, and Day 8 PK samples will be obtained prior to start of HD. Additional plasma PK samples collected during HD on Day 1: Arterial and venous plasma blood samples will be collected pre-HD and at 0.5, 1, 2, and 3 hours after the start of HD and immediately following the end of HD. Venous plasma PK samples will also be collected at the next HD session on Day 3 (approximately 48 hours after previous one) at pre-HD, at 0.5, 1, 2, and 3 hours post the start of HD, and immediately following the end of HD. A sample of dialysate will be collected on Day 1 at 0.5, 1, 2, and 3 hours after the start of HD and after HD is complete for drug concentration analysis. The dialysate volume at 0.5, 1, 2 and 3 hours after start of dialysis (each dialysate collection time), the entire dialysate volume at the completion of the dialysis session, blood flow, and dialysate flow during HD will be recorded for each timepoint. The make and model of the dialyzer will be recorded.

[l] Dose administration of avacopan will be given in the morning on Day 1, 4 hours prior to HD, under fed conditions.

Schedule of Assessments for Group 2 (Period 2 – Off Hemodialysis)

Activity per Period	Check-in	Treatment Period 2																				
Study Day	D-1	D1											D2		D3	D4	D5	D6	D7	D8	D12	D15	D18 EOS/ET
Time (in hours)	--	Pre	0	0.25	0.5	1	2	3	4	6	9	12	16	24	36	48	72	96	120	144	168	264	336	408
In-house Residency	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►			
Outpatient Visit																						X	X	X
GENERAL AND SAFETY ASSESSMENTS																								
Medical History	X[a]																							
Weight	X																							X
Serum or Saliva Drug Screen	X																							
Alcohol Test	X																							
Adverse Events[b]	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Serious Adverse Events[b]	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Prior/Concomitant Medications[c]	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
LABORATORY ASSESSMENTS AND OTHER PROCEDURES																								
Pregnancy Test (females only)[d]	X																							X
Physical Examination[e]	X														X					X				X
12-lead ECG[f]	X																			X				X
Vital Signs[g]	X	X							X					X		X	X	X	X	X	X			X
Clinical Laboratory Evaluations[h]	X																			X				X
eGFR[i]	X																							
Plasma Protein Binding											X													
Hemodialysis[j]	X															X		X		X				
PHARMACOKINETIC ASSESSMENTS																								
Avacopan and M1 Plasma PK[k]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INVESTIGATIONAL PRODUCT																								
Avacopan Dose Administration[l]			X																					

Abbreviations: D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study visit; ET = early termination; HD = hemodialysis; M1 = metabolite; PK = pharmacokinetic; Pre = predose; SOA = Schedule of Assessments.

[a] Interim medical history only.

[b] Adverse events will be recorded from initiation of study treatment on Period 1 Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the Informed Consent Form until 30 days after the last dose of study treatment or through the EOS, whichever is later.

[c] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to enrollment for over-the-counter or prescription medications, and 30 days prior to enrollment for herbal medicines (e.g., St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic case report form.

[d] Performed in serum at all timepoints.

[e] A full physical examination at Check-in, Day 3, Day 8, and Day 18 (EOS/ET).

[f] 12-lead ECGs will be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws at: Check-in; Day 8; and Day 18 (EOS or ET). Electrocardiograms should be collected prior to any PK corresponding timepoints. Single trace ECGs will be collected at all timepoints.

[g] Vital signs measurements (seated/supine blood pressure, seated/supine pulse rate, respiratory rate, and oral body temperature) should be carried out prior to having blood drawn. Vital signs will be obtained at: Check-in; prior to avacopan administration and 4 hours following avacopan administration on Day 1, 24 hours postdose on Day 2, and on Days 3, 4, 5, 6, 7, 8, and 18 (EOS or ET). Pulse rate and blood pressure will be measured using the same arm for each reading after the subject has been resting in the seated/supine position for at least 5 minutes.

[h] Clinical chemistry and hematology (fasted at least 8 hours). Urinalysis will not be performed for subjects in Group 2.

[i] The eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation.
MDRD formula (mL/min/1.73m^2) = 175 x(serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

[j] Hemodialysis will be completed on Day -1 before the administration of avacopan. Hemodialysis will occur on Days 3, 5, and 7. Hemodialysis will continue as needed beyond the timepoints specified in the SOA. The study day, and the start and end times will be collected for all HD sessions.

[k] The PK samples collected on Day 1 will have a sampling window of ±10 minutes. Postdose samples on Day 2 will have a sampling window of ±1 hour. Postdose samples Days 3 to 8 will have a sampling window of ±2 hours. Postdose samples on Days 12, 15, and 18 will have a sampling window of ±4 hours. Times of all PK samples will be recorded to the nearest minute. Day 3, Day 5, and Day 7 PK samples will be obtained prior to start of HD.

[l] Dose administration of avacopan will be given in the morning on Day 1 under fed conditions following HD session on Day -1.

Appendix 10: Child-Pugh Classification of Severity of Cirrhosis

Parameter	Points Assigned		
	1	**2**	**3**
Ascites[1]	Absent	Slight or Subject on 1 medication to control ascites	Moderate or Severe or Subject on 2 medications to control ascites
Total bilirubin	< 2 mg/dL (< 34.2 µmol/L)	2 – 3 mg/dL (34.2 – 51.3 µmol/L)	> 3 mg/dL (> 51.3 µmol/L)
Albumin	> 3.5 g/dL (35 g/L)	2.8 – 3.5 g/dL (28 – 35 g/L)	< 2.8 g/dL (< 28 g/L)
Prothrombin time			
Seconds over control	< 4	4 – 6	> 6
International normalized ratio	< 1.7	1.7 – 2.3	> 2.3
Hepatic encephalopathy[2]	None	Grade 1 – 2 (or suppressed with medication)	Grade 3 – 4 (refractory)

1 Ascites is graded according to the following criteria:
Absent: No ascites detectable by manual investigation
Slight: Ascites palpitation doubtful
Moderate: Ascites detectable by palpation
Severe: Necessity of paracentesis, does not respond to medication treatment.

2 Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 to 3 cycles per second delta activity

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of total bilirubin and albumin, the prothrombin time (or international normalized ratio), and the degree of hepatic encephalopathy. A total score of 5 to 6 is considered Class A (well compensated disease); 7 to 9 is Class B (significant functional compromise); and 10 to 15 is Class C (decompensated disease).

Subjects in Group 1 will not be assessed for Child-Pugh Scores. Subjects in Group 2 with a Class C Child-Pugh classification will be excluded from the study. Child-Pugh will only be evaluated for subjects deemed to have active liver disease by the Investigator (or designee).

Approval Signatures

Document Name:	Protocol Amendment avacopan 20230265 1
Document Description:	A Phase 1, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Avacopan in Subjects with Normal Renal Function and Subjects with End-Stage Renal Disease (ESRD) Requiring Hemodialysis
Document Number:	CLIN-000345231
Approval Date:	25 Jun 2024
Type of Study Protocol:	Amendment
Protocol Amendment No.:	1

Document Approvals	
Reason for Signing: Management	PPD Date of Signature: 25-Jun-2024 18:53:10 GMT+0000

Protocol

A Phase 1, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Avacopan in Subjects with Normal Renal Function and Subjects with End-Stage Renal Disease (ESRD) Requiring Hemodialysis

Protocol Status: Final
Protocol Date: 26 April 2024
Original Protocol

Investigational Product: Avacopan

Amgen Protocol Reference Number: 20230265
Fortrea Study Number: 8530204

Sponsor:
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320

This protocol was developed, reviewed, and approved in accordance with Fortrea's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

Confidentiality Notice

This document contains confidential information of Amgen Inc.

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INVESTIGATOR AGREEMENT

I have read the attached protocol entitled "A Phase 1, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Avacopan in Subjects with Normal Renal Function and Subjects with End-Stage Renal Disease (ESRD) Requiring Hemodialysis" dated 26 April 2024 and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

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

I agree not to share the confidential information contained in this document without the prior written consent of Amgen Inc.

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

_____

Title and Role of Investigator

_____

Institution Name

_____

Address and Telephone Number of Institution

_____

STUDY IDENTIFICATION

Sponsor	Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320 USA
Sponsor's Study Contact	PPD
Medical Monitor	PPD
Sponsor's Study Manager	PPD
Fortrea Project Manager	PPD

SYNOPSIS

Title of study: A Phase 1, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Avacopan in Subjects with Normal Renal Function and Subjects with End-Stage Renal Disease (ESRD) Requiring Hemodialysis

Objectives:

The primary objective of the study is:

- to evaluate the pharmacokinetics (PK) of avacopan and metabolite (M1) after a single dose of avacopan in subjects with normal renal function and subjects with ESRD requiring hemodialysis (HD).

The secondary objective of the study is:

- to evaluate the safety and tolerability of a single dose of avacopan in subjects with normal renal function and subjects with ESRD requiring HD.

Study design:

This will be a Phase 1, open label, single-dose, parallel group study to evaluate the PK, safety, and tolerability of avacopan in subjects with normal renal function (Group 1) and subjects with ESRD requiring HD (Group 2). After informed consent is obtained, potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration.

Subjects in Group 1 (normal renal function) will be admitted into the Clinical Research Unit (CRU) on Day -1 and will be confined to the CRU until discharge on Day 8.

Subjects in Group 1 will receive a single CCI dose of avacopan on Day 1 under fed conditions. Following discharge on Day 8, subjects will return to the CRU on Days 12, 15, and 18 (end of study [EOS] visit) for outpatient visits.

Subjects in Group 2 (ESRD requiring HD) will receive a single dose of CCI avacopan under fed conditions on Day 1 in each of the 2 treatment periods (Period 1/on HD and Period 2/off HD). Subjects in Group 2 will be admitted into the CRU on Period 1 Day -1. Subjects in Group 2 Period 1 (on HD) will receive a single CCI dose of avacopan on Period 1 Day 1, 4 hours prior to the start of HD. Subjects will continue to receive HD on Days 3, 5, and 8 (prior to discharge). Following discharge on Day 8, subjects will return to the CRU on Period 1 Days 12, 15, and 18 for outpatient visits. Subjects in Group 2 will be re-admitted into the CRU for Period 2 Day -1 on the day of their HD. Period 1 Day 18 may occur on the same day as Period 2 Day -1. Subjects will receive a single CCI dose of avacopan on Period 2 Day 1 on an off-HD day (one day after the HD session on Period 2 Day -1). Subjects will continue to receive HD on Days 3, 5, and 7. Subjects will be confined to the CRU until discharge on Period 2 Day 8. Following discharge on Period 2 Day 8, subjects in Group 2 will return to the CRU on Period 2 Days 12, 15, and 18 (EOS) for outpatient visits. There will be no washout between Day 18 of Period 1 and Check-in for Period 2 for subjects in Group 2.

Number of subjects:

Approximately 12 subjects will be enrolled in 2 groups (Groups 1 and 2). Approximately 6 subjects will be enrolled in each group.

Diagnosis and main criteria for inclusion:

Male subjects or female subjects, 18 to 75 years of age (inclusive), and body mass index of 18 to <40 kg/m^2 with normal renal function or ESRD requiring HD.

Investigational products, dose, and mode of administration:

Investigational Medicinal Product: CCI avacopan oral dose under fed conditions

Duration of subject participation in the study: Planned Screening duration: 4 weeks. Planned study duration (Screening to EOS): Group 1: approximately 7 weeks, Group 2: approximately 9 weeks.
Primary Endpoints: The primary endpoints for this study are avacopan and M1 PK parameters: maximum observed plasma concentration (C_{max}); area under the plasma concentration-time curve (AUC) from time zero to time of last quantifiable concentration (AUC_{last}); area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}); area under the plasma concentration time curve from time zero to 48 hours (AUC_{0-48}), or other partial area comparisons, as appropriate; and HD clearance of drug (and metabolite) from plasma (CL_D). **Secondary Endpoints:** Secondary endpoints for this study are: treatment-emergent adverse events and serious adverse events.
Statistical methods: The primary PK parameters are C_{max} and AUC. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis. To determine the effect of renal impairment on the PK of avacopan and M1, the ratios (test/reference) for the model-estimated C_{max}, AUC_{last}, and AUC_{inf} for the ESRD group (test) relative to the group with normal renal function (reference) will be generated, along with 90% confidence intervals. Applicable PK parameters in the ESRD group on-HD days and off-HD days may also be compared. The final safety analysis for the study will be performed at EOS. Adverse events will be summarized using descriptive methodology. Each adverse event will be coded using the Medical Dictionary for Regulatory Activities. Endpoints for clinical laboratory tests, electrocardiogram, and vital signs will be summarized. Additional details will be included in the Statistical Analysis Plan.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCA	anti-neutrophil cytoplasmic autoantibody
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC_{last}	area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC_{0-48}	area under the plasma concentration-time curve from time zero to 48 hours postdose
BIL	bilirubin
BP	blood pressure
C5a	complement component C5a
C5aR	complement 5a receptor
CFR	Code of Federal Regulations
CL_D	hemodialysis clearance of drug (and metabolite) from plasma
C_{max}	maximum observed plasma concentration
CRF	Case Report Form
CRF	Case Report Form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
CYP3A4	cytochrome P450 3A4
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EOS	end of study
ESRD	end-stage renal disease
FSH	follicle-stimulating hormone

f_u	fraction of unbound drug; reported as the arithmetic mean where measured at two time points
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HD	hemodialysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
MDRD	Modification of Diet in Renal Disease
OSF	Other Safety Finding
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's method
SS	Special Situation
TBL	total bilirubin
t_{max}	time of the maximum observed concentration
ULN	upper limit of normal

1. INTRODUCTION

Refer to the Investigator's Brochure (IB)[1], Prescribing Information[2], and Summary of Product Characteristics[3] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational medicinal product (IMP).

1.1. Background

Investigational Medicinal Product

In the United States, TAVNEOS® (formerly CCX168), hereafter referred to as avacopan, is currently approved as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard therapy including glucocorticoids. Avacopan does not eliminate glucocorticoid use. Avacopan is also approved in the European Union for use in combination with a rituximab or cyclophosphamide regimen and is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis or microscopic polyangiitis. Avacopan has also been approved in Canada, Great Britain, Switzerland, Japan, and the United Arab Emirates, and is under review in several other countries for marketing authorization.

Avacopan is a highly potent and selective antagonist of the human complement 5a (C5a) receptor (C5aR), acting through competitive inhibition of the interaction between human C5aR and the anaphylatoxin complement component C5a; the latter is produced through activation of the complement cascade. As a result of its mechanism of action, avacopan reduces neutrophil activation, chemoattraction, and integrin expression. Avacopan inhibits vascular endothelial cell retraction and permeability, ameliorating the necrotizing vasculitis associated with ANCA-associated vasculitis.

A summary of completed clinical studies for avacopan is provided in the IB (Table 6).[1]

1.2. Pharmacokinetics

The pharmacokinetics (PK) of avacopan has been evaluated in nine Phase 1 studies, two Phase 2 studies, and one Phase 3 study in patients with ANCA-associated vasculitis.

Following single oral administration in healthy subjects at doses ranging from 1 to 100 mg, avacopan was absorbed rapidly with maximum observed plasma concentration (C_{max}) occurring approximately 1 to 2.5 hours postdose. Avacopan is primarily eliminated via extensive metabolism mediated through cytochrome P450 3A4 (CYP3A4) oxidation in the liver which results in the formation of and clearance of the major circulating metabolite, M1, a mono-hydroxylated product of avacopan. Following metabolism, the metabolites are primarily excreted into feces via bile. In the Phase 1 food-effect study, following a single oral dose of 30 mg in the presence of a high-fat, high-calorie meal, avacopan exposures, area under the

plasma concentration-time curve (AUC), and C_{max}, increased by approximately 72% and 8%, respectively, and delayed the time of the maximum observed concentration (t_{max}) by approximately 4 hours (from 2.0 hours to 6.0 hours). The elimination half-lives of avacopan and M1 were 97.6 hours and 55.6 hours, respectively, under fed conditions. Following oral administration of avacopan 100 mg/400 μCi, about 77% and 10% of the radioactive dose was recovered in feces and urine, respectively, and 7% and <0.1% of the radioactive dose was recovered as unchanged avacopan in feces and urine, respectively. Avacopan and metabolite M1 are more than 99.9% plasma-protein bound, primarily to albumin and α1-acid glycoprotein. A Phase 1 study in subjects with hepatic impairment evaluated the PK of avacopan and metabolite M1 following a single CCI dose for up to 18 days. Results from this study showed that plasma avacopan levels appeared to decline with a triphasic profile with a rapid early phase, followed by a longer phase, and finally a terminal phase with a half-life of about 200 to 400 hours in most subjects. Metabolite M1 appeared to decline in a biphasic manner with an elimination half-life of about 68 to 73 hours.[2]

Previously, the impact of moderate renal impairment (estimated glomerular filtration rate [eGFR] between 30 and less than 60 mL/min/1.73 m^2) and severe renal impairment (less than 30 mL/min/1.73 m^2) from patients with ANCA-associated vasculitis from Phase 2 and Phase 3 studies relative to subjects with normal renal function (eGFR >90 mL/min/1.73 m^2) from Phase 1 studies were evaluated using population PK analysis. Results from population PK analyses demonstrated that avacopan and M1 exposures as assessed by C_{max} and AUC were similar (<20%) across the different categories. Therefore, no dose adjustment for avacopan is needed based on renal function.[1]

1.3. Study Rationale

This study will be conducted to evaluate the PK of a single dose of avacopan in subjects with normal renal function and in subjects with end-stage renal disease (ESRD) requiring hemodialysis (HD).

Results from this study will provide information on the safety, tolerability, and PK of avacopan and potentially guide dosing in patients with ESRD requiring HD.

1.4. Benefit-risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study. Refer to the IB[1] for more information.

1.4.1. Therapeutic Context

1.4.1.1. Key Benefits

Healthy and ESRD subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study.

1.4.1.2. Risks

Serious cases of hepatic injury have been observed in subjects taking avacopan. During controlled trials, the avacopan treatment group had a higher incidence of transaminase elevations and hepatobiliary events, including serious and life-threatening events. Avacopan is not recommended for subjects with active, untreated, and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Hepatitis B virus (HBV) reactivation, including life threatening hepatitis B, was observed in the clinical program. Hepatitis B virus reactivation is defined as an abrupt increase in HBV replication, manifesting as a rapid increase in serum HBV DNA levels or detection of hepatitis B surface antigen (HBsAg), in a person who was previously HBsAg negative and anti-hepatitis B core positive. Reactivation of HBV replication is often followed by hepatitis; i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Avacopan may cause hypersensitivity reactions including angioedema. Serious and sometimes fatal infections have been reported in subjects receiving avacopan. The most common serious infections reported in the avacopan group were pneumonia and urinary tract infections. Avacopan use should be avoided in subjects with an active, serious infection, including localized infections and in subjects with a history of chronic or recurrent infection, who have prior infection or have been exposed to tuberculosis, with a history of a serious or an opportunistic infection, who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, or with underlying conditions that may predispose them to infection.

To limit the risk of excessive exposure to healthy subjects in the current study, subjects with normal renal function will be administered a single dose of CCI avacopan and subjects with ESRD requiring HD will be administered a single dose of CCI avacopan in each of 2 study periods (details provided in Section 3.3).

Safety monitoring: During the study, subjects will receive all investigational product doses by site staff. Safety assessments throughout the study include adverse event monitoring, electrocardiograms (ECGs), clinical examination, vital signs, and clinical laboratory evaluations.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to evaluate the PK of avacopan and metabolite (M1) after a single dose of avacopan in subjects with normal renal function and subjects with ESRD requiring HD.

The secondary objective of the study is:

- to evaluate the safety and tolerability of a single dose of avacopan in subjects with normal renal function and subjects with ESRD requiring HD.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints of the study are:

- C_{max}
- area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_{last})
- area under the plasma concentration-time curve from time zero to infinity (AUC_{inf})
- area under the plasma concentration-time curve from time zero to 48 hours (AUC_{0-48}), or other partial area comparisons, as appropriate
- HD clearance of drug (and metabolite) from plasma (CL_D).

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- treatment-emergent adverse events
- serious adverse events.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase 1, open-label, single-dose, parallel group study to evaluate the PK, safety, and tolerability of avacopan in subjects with normal renal function (Group 1) and subjects with ESRD requiring HD (Group 2). After informed consent is obtained, potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration.

Subjects in Group 1 (normal renal function) will be admitted into the Clinical Research Unit (CRU) on Day -1 and will be confined to the CRU until discharge on Day 8. Subjects in Group 1 will receive a single CCI dose of avacopan on Day 1 under fed conditions. Following discharge on Day 8, subjects will return to the CRU on Days 12, 15, and 18 (end of study [EOS] visit) for outpatient visits. An overview of the study schema for Group 1 is shown in Figure 1.

Subjects in Group 2 (ESRD requiring HD) will receive a single dose of CCI avacopan under fed conditions on Day 1 in each of the 2 treatment periods (Period 1/on HD and Period 2/off HD). An overview of the study schema for Group 2 is shown in Figure 2.

Subjects in Group 2 will be admitted into the CRU on Period 1 Day -1 and will be confined to the CRU until discharge on Period 1 Day 8. Subjects in Group 2 Period 1 (on HD) will receive a single CCI dose of avacopan on Period 1 Day 1, 4 hours prior to the start of HD. Subjects will continue to receive HD on Days 3, 5, and 8 (prior to discharge). Following discharge on Day 8, subjects will return to the CRU on Period 1 Days 12, 15, and 18 for outpatient visits. The Group 2 Period 1 (on HD) schema is shown in Figure 3.

Subjects in Group 2 will be re-admitted into the CRU for Period 2 Day -1 on the day of their HD. Period 1 Day 18 may occur on the same day as Period 2 Day -1. Subjects will receive a single CCI dose of avacopan on Period 2 Day 1 on an off-HD day (one day after the HD session on Period 2 Day -1). Subjects will continue to receive HD on Days 3, 5, and 7. Subjects will be confined to the CRU until discharge on Period 2 Day 8. Following discharge on Period 2 Day 8, subjects in Group 2 will return to the CRU on Period 2 Days 12, 15, and 18 (EOS) for outpatient visits. The Group 2 Period 2 (off-HD) schema is shown in Figure 4. There will be no washout between Day 18 of Period 1 and Check-in for Period 2 for subjects in Group 2.

Additional plasma samples will be collected for estimation of plasma protein binding.

The eGFR will be determined by the Modification of Diet in Renal Disease (MDRD) formula[4]:

MDRD formula (mL/min/1.73m^2) = 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

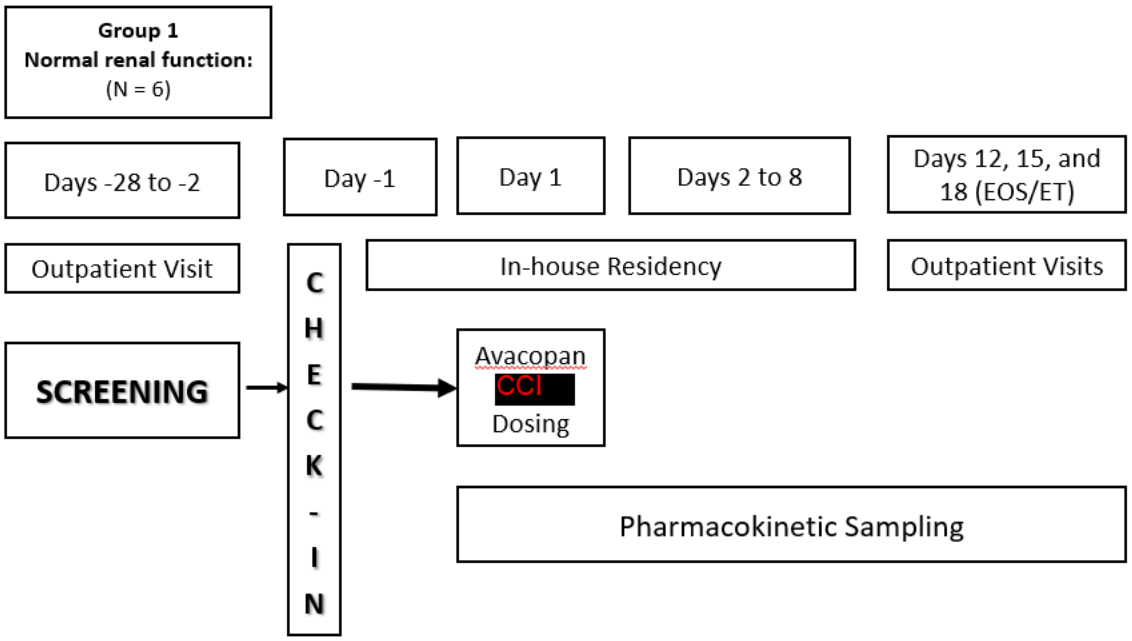
The renal function groups and eGFR values used to assign each subject to a renal function group are shown in Table 1.

Table 1: Classification of Renal Function Study Groups

Population	eGFR (mL/min^2) [a,b]	Group	Period
Normal renal function	≥90	1	NA
ESRD requiring HD[b]	<15	2	1
			2

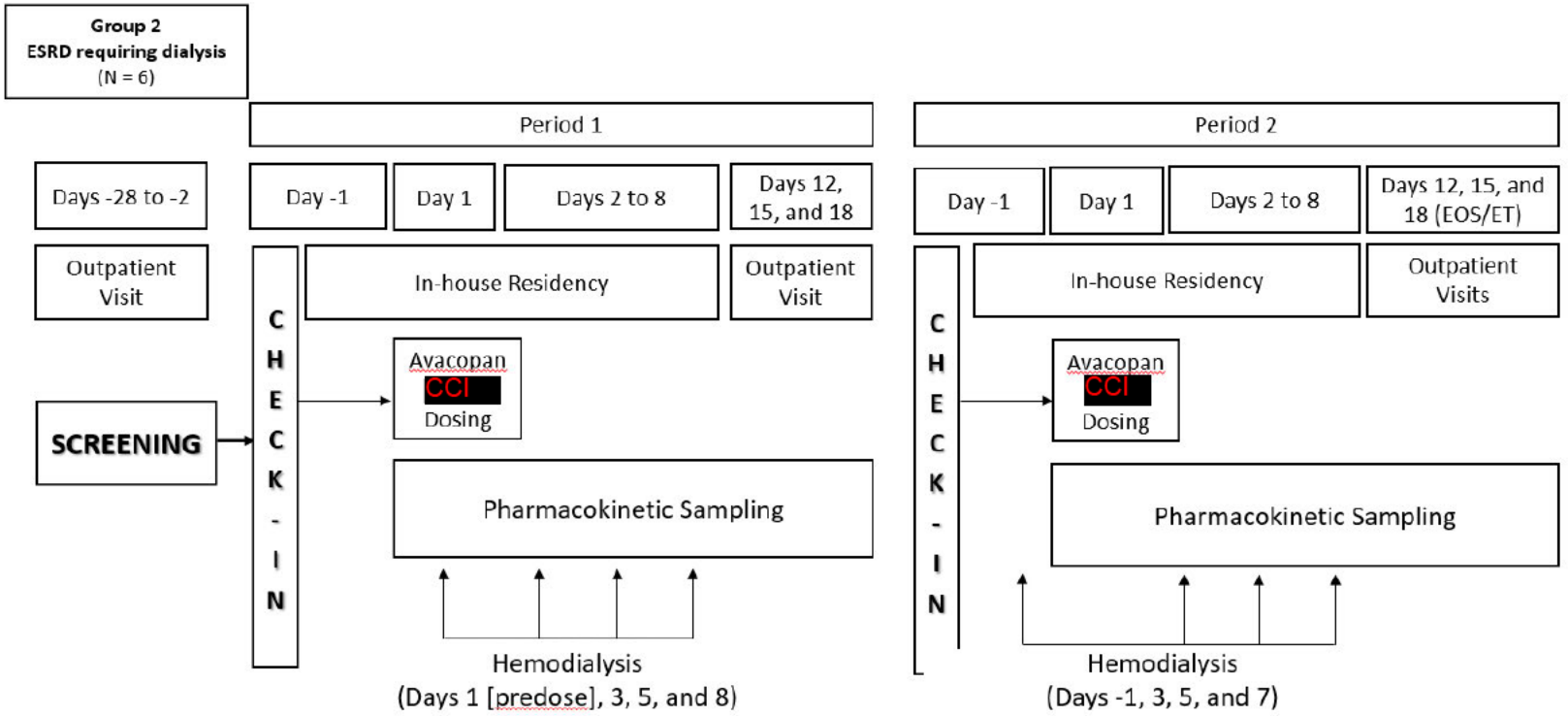
Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HD = hemodialysis; NA = not applicable.
[a] Classification is based on the Food and Drug Administration guidance for renal impairment studies.[4] Estimated glomerular filtration rate based on an estimation equation and expressed in mL/min. To convert mL/min/1.73 m^2 to mL/min, multiply by the individual's body surface area calculated using an appropriate formula and divide by 1.73.
[b] Group 2 subjects will receive intermittent HD. In Period 1, subjects will receive avacopan 4 hours prior to HD. In Period 2, subjects will receive avacopan the day after a HD session.

Figure 1: Study Schema – Group 1 (Normal Renal Function)



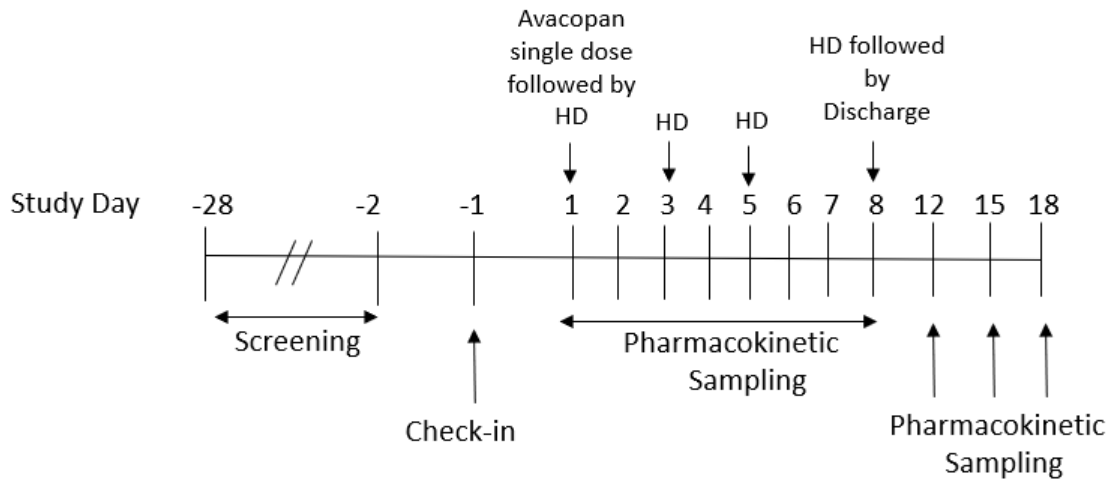
Abbreviations: EOS = end of study visit; ET = early termination.
Notes: Single dose of avacopan will be administered on Day 1 in the morning. See Appendix 9 (Schedule of Assessments) for details on plasma pharmacokinetics and plasma protein binding sampling.

Figure 2: Study Schema – Group 2 (ESRD Requiring Hemodialysis)



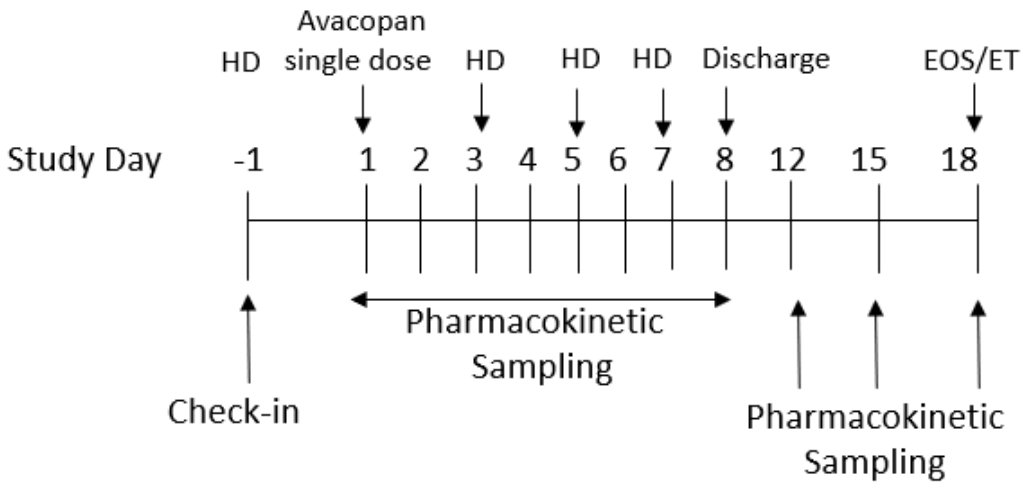
Abbreviations: EOS = end of study visit; ESRD = end-stage renal disease; ET = early termination; HD = hemodialysis.
Group 2 subjects will receive intermittent HD. In Period 1, subjects will receive avacopan 4 hours prior to HD under fed conditions. In Period 2, subjects will receive avacopan the day after a HD session. There will be no washout between Period 1 Day 18 and Period 2 Day -1. Period 1 Day 18 and Period 2 Day -1 may occur on the same day.
The timing of pharmacokinetics sampling relative to HD is provided in Figure 3 for Group 2, Period 1 (on-HD) and in Figure 4 for Group 2, Period 2 (off-HD).

Figure 3: Group 2 (ESRD Requiring Hemodialysis) Schema, Period 1 – On Hemodialysis



Abbreviations: HD = hemodialysis.
Notes: Subjects will receive a single oral dose of avacopan 4 hours prior to start of HD session, under fed conditions. See Appendix 9 (Schedule of Assessments) for details on plasma pharmacokinetics, plasma protein binding sampling, and dialysate pharmacokinetics sampling.

Figure 4: Group 2 (ESRD Requiring Hemodialysis) Schema, Period 2 – Off Hemodialysis



Abbreviations: EOS = end of study; ET = early termination; HD = hemodialysis.
Notes: Subjects will receive a single oral dose of avacopan 1 day after the HD session. See Appendix 9 (Schedule of Assessments) for details on plasma pharmacokinetics and plasma protein binding sampling.

The total duration of study participation for each subject (from Screening through EOS visit) is anticipated to be approximately 7 weeks for Group 1 (normal renal function) and approximately 9 weeks for Group 2 (ESRD requiring HD).

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 9.

3.2. Discussion of Study Design

This study will be open label because the study endpoints are not considered subjective.

The PK results from prior Phase 1 studies demonstrated relatively linear and dose-proportional PK, suggesting that a single-dose study in subjects with renal impairment should adequately describe the PK of the drug. The safety and PK assessments are standard parameters for clinical studies in drug development.

Plasma sampling is timed to sufficiently estimate PK parameters of avacopan exposure, based on characteristics of the concentration-time profile.

This study will be conducted in subjects with normal renal function and in subjects with stable end-stage renal function who require HD. These subjects may have acceptable comorbid conditions in terms of safety and stability that are not anticipated to confound the study results.

The subjects will be selected such that the mean and distribution of Group 1 is similar to the mean and distribution of subjects enrolled in Group 2 for age, sex, and body mass index, as far as possible.

3.3. Selection of Doses in the Study

Avacopan has been approved as an adjunctive treatment of adult subjects with severe active ANCA-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard therapy including glucocorticoids. The recommended dosage is CCI) twice daily, with food.

For this study, a single dose of CCI is considered adequate to evaluate the pharmacokinetics and safety in subjects with normal renal function and in subjects with ESRD requiring HD.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria prior to enrollment unless otherwise stated. Check-in with regards to inclusion criteria applies to Check-in on Period 1 Day -1 only.

1. Subject has provided informed consent before initiation of any study-specific activities or procedures.
2. Male or female subjects, between 18 and 75 years of age (inclusive) at the time of Screening.
3. Body mass index between 18 and <40 kg/m^2 at the time of Screening.
4. Subjects eligible for Group 1 (normal renal function) should be in good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [e.g., suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).
5. For subjects in Group 1 (normal renal function), systolic blood pressure (BP) ≥90 and ≤150 mmHg and diastolic BP ≥50 and ≤100 mmHg, and pulse rate ≥40 and ≤110 bpm at Screening. One repeat BP measurement will be allowed at Screening and Check-in.
6. For subjects in Group 2 (ESRD requiring HD), vital signs, physical examinations, and 12-lead ECGs (reporting heart rate, PR, QRS, QT, and QT interval corrected for heart rate using Fridericia's method [QTcF]), including waveform, are normal or clinically acceptable to the Investigator, if outside the normal range.
7. For subjects in Group 2 (ESRD requiring HD), laboratory test values (clinical chemistry and hematology) are consistent with the level of renal impairment and clinically acceptable to the Investigator.
8. For subjects in Group 2 (ESRD requiring HD), nonhypertensive subjects or subjects with treated, stable hypertension, as defined by systolic BP not exceeding 170 mmHg and diastolic BP not exceeding 100 mmHg at Screening and Check-in.
9. Eligible subjects will be classified based on established need for renal replacement therapy and eGFR, calculated using the MDRD formula. Assignment will be based on eGFR at Screening.
    a. Group 1 (normal renal function): eGFR ≥90 mL/min and no history of renal disease.
    b. Group 2 (ESRD requiring HD): eGFR <15 mL/min and receiving HD.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria prior to enrollment unless otherwise stated. Check-in with regards to exclusion criteria applies to Check-in on Period 1 Day -1 only.

All Subjects:

10. History of uncontrolled or unstable cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematopoietic, psychiatric, or neurological disease, defined as having been hospitalized within 28 days before Check-in, major surgery within 6 months before Check-in, or otherwise unstable in the judgment of the Investigator and/or Medical Monitor (e.g., risk of complications or adverse events unrelated to study participation), or evidence of rapidly deteriorating renal function.
11. History or evidence, at Screening or Check-in, of clinically significant disorder, condition, or disease not otherwise excluded that, in the opinion of the Investigator (or designee), would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
12. Total white blood cell count is below the lower limit of normal at Screening or Check-in.
13. Significant infection (in the judgment of the Investigator and/or Medical Monitor) within 28 days before Check-in.
14. Prior infection with or exposure to tuberculosis, or travel to areas of endemic tuberculosis or endemic mycoses within the past 6 months.
15. Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase or alanine aminotransferase > the upper limit of normal for Group 1 (normal renal function) and >2 times the upper limit of normal for Group 2 (ESRD requiring HD).
16. History or evidence, at Screening or Check-in, of poorly controlled diabetes (regardless of type), based on hemoglobin A1C of >10%.
17. Second-degree atrioventricular block or third degree atrioventricular block at Screening or Check-in.
18. Clinically significant hyperkalemia (defined by serum potassium concentration as >5.5 mEq/L for Group 1 [normal renal function], >6 mEq/L for Group 2 [ESRD requiring HD]) at Screening or Check-in. Repeat testing and rescreening for screen failures will be permitted.
19. Subjects who have a current, functioning organ transplant and/or are on immunosuppressants.
20. Subjects on the national transplant list (United Network for Organ Sharing) at Screening who anticipate receiving an organ transplant within 4 months.
21. Positive human immunodeficiency virus test.
22. Positive hepatitis B or hepatitis C panel (including positive HBsAg and/or positive hepatitis C antibody) at Screening. Subjects whose results are compatible with prior hepatitis B infection (positive hepatitis B surface antibody, positive hepatitis B core antibody, or negative HBsAg) will be excluded. Subjects whose results are

compatible with prior hepatitis B vaccination (positive hepatitis B surface antibody, negative hepatitis B core antibody, negative HBsAg) may be included.

23. History or evidence of clinically significant arrhythmia at Screening, including any clinically significant findings on the ECG taken at Check-in.
24. History suggestive of esophageal (including esophageal spasm, esophagitis), gastric, or duodenal ulceration, or bowel disease (including but not limited to peptic ulceration, gastrointestinal bleeding, ulcerative colitis, Crohn's disease, or irritable bowel syndrome); or a history of gastrointestinal surgery, other than uncomplicated appendectomy.
25. History of hypersensitivity, intolerance, or allergy to avacopan or any of the excipients.
26. Poor peripheral venous access.
27. Currently taking a moderate or strong inducer of the CYP3A4 enzyme (e.g., carbamazepine, phenobarbital, phenytoin, or rifampin), or use of a strong CYP3A4 inducer, within 5 half-lives or 14 days prior to Check-in (whichever is longer) and through EOS, unless deemed acceptable by the Investigator, Medical Monitor, and/or the Sponsor.
28. Currently taking a moderate or strong inhibitor of the CYP3A4 enzyme (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole), or use of a strong CYP3A4 inhibitor, within 5 half-lives or 14 days prior to Check-in (whichever is longer) and through EOS, unless deemed acceptable by the Investigator, Medical Monitor, and/or the Sponsor.
29. Use of any over-the-counter or prescription medications within 30 days or 5 half-lives (whichever is longer) before enrollment, with the below exceptions:
    a. Acetaminophen (paracetamol; up to 2 g/day) for analgesia will be allowed.
    b. Hormone replacement therapy (e.g., estrogen, thyroid treatments including levothyroxine [Synthroid, Levothroid, Levoxyl, and Unithroid], liothyronine [Cytomel], liotrix [Thyrolar], and natural thyroid [Armour Thyroid, Nature-throid, Westhroid]) will be allowed.
    c. Hormonal contraception will be allowed.
    d. Aside from strong inducers or inhibitors of CYP3A4, therapies for renal disease and treatments of comorbidities, such as hypertension, that have been stable for at least 3 months prior to study drug administration and deemed acceptable by the Investigator (or designee) and Medical Monitor to be given concurrently with avacopan during the study period are permitted. Minor adjustments in dose or formulation of medications used to treat renal disease and associated disorders

without significant change in clinical condition within the past 3 months are permitted.

30. Consumption of foods and beverages containing poppy seeds, pomelos, or Seville oranges within 7 days prior to Check-in and consumption of foods and beverages containing grapefruit within 14 days prior to Check-in.
31. All herbal medicines (e.g., St. John's wort), vitamins, and supplements consumed by the subject within the 30 days prior to enrollment, unless deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.
32. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
33. Alcohol consumption from 48 hours prior to Check-in.
34. Regular alcohol consumption of >14 units per week for males and >7 units for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
35. Significant use of tobacco- or nicotine-containing products (e.g., >½ pack of cigarettes per day) within 3 months prior to Check-in through EOS.
36. Positive alcohol test at Check-in or positive drug screen (confirmed by repeat) at Screening or Check-in, that is not otherwise explained by permitted concomitant or prescription medications. Group 2 (ESRD requiring HD) subjects will be permitted on study if drug screen is positive for opiates or benzodiazepines. Subjects who screen positive for tetrahydrocannabinol/ cannabinoids will be excluded. At Check-in, a positive alcohol test may not be repeated.
37. Consumption of caffeine-containing foods and beverages within 48 hours prior to Check-in.
38. Female subjects with a positive pregnancy test at Screening or Check-in.
39. Female subjects lactating/breastfeeding or who plan to breastfeed during the study through 60 days after administration of investigational product.
40. Unwilling to adhere to contraceptive requirements through 60 days after administration of investigational product.
41. Unwilling to abstain from sperm donation and ovum donation through 60 days after administration of investigational product.
42. Male subjects with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
43. Male subjects with a pregnant partner or partner planning to become pregnant who are unwilling to practice sexual abstinence or use contraception while the subject is participating in the study from Check-in until 60 days after administration of investigational product.

44. Subject has received a dose of an investigational drug within the past 90 days or 5 half-lives, whichever is longer, prior to Check-in.
45. Have previously completed or withdrawn from this study or any other study investigating avacopan, or have previously received the investigational product.
46. Donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, or platelets from 6 weeks prior to Check-in.
47. Unwilling to abide with study restrictions.
48. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

Subjects in Group 1 (normal renal function) are excluded if:

49. History of malignancy of any type, with the exception of the following: in situ cervical cancer or surgically excised non-melanomatous skin cancers more than 5 years before receiving avacopan.
50. A QTcF >450 msec in males or >470 msec in females or history/evidence of long QT syndrome at Screening or Check-in.
51. A history of renal disease or renal injury as indicated by medical history or an abnormal renal function profile at Screening or Check-in.

Subjects in Group 2 (ESRD requiring HD) are excluded if:

52. Child-Pugh classification of Class A, B, or C, indicating hepatic impairment assessed at Screening and Check-in (Appendix 10).
53. Active malignancy of any type. Subjects with a history of malignancy that has been eradicated with supporting medical documentation indicating that there is no residual malignancy detected in the past 2 years will be allowed.
54. A change in disease status within 30 days of Screening, as documented by the subject's medical history, deemed clinically significant by the Investigator.
55. A QTcF ≥470 msec in males or ≥480 msec in females.

4.3. Screen Failures and Rescreening

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study because they do not meet eligibility requirements. A minimal set of screen failure information may be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only once.

4.4. CCI

CCI

[redacted]

4.5. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the Sponsor (or designee) will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all EOS assessments, if possible (Appendix 9). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their Adverse Events, Serious Adverse Events, or until the unresolved Adverse Events, Serious Adverse Events are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of 1 or more Adverse Events/Serious Adverse Events thought to be related to the study drug will generally not be replaced.

4.6. Study Termination

The Sponsor may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). Both the Sponsor and the Investigator reserve the right to

terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The Investigator is to notify the Institutional Review Board (IRB) in writing of the study's completion or early termination and send a copy of the notification to the Sponsor. The Sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply investigational product and by what mechanism, after termination of the study.

In addition, the study may be terminated by the Sponsor at any time and for any reason. If the Sponsor decides to terminate the study, they will inform the Investigator as soon as possible.

4.7. Discontinuation of Study Treatment (Group 2 only)

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or study procedures at any time during the study but continue participation in the study. If this occurs, the Investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Assessments (Appendix 9) including different options of follow-up (e.g., in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, Adverse Events, Serious Adverse Events and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or study procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on study to ensure safety surveillance and/or collection of outcome data.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Noncompliance
- Requirement for alternative therapy
- Pregnancy
- Protocol-specified criteria

5. STUDY TREATMENTS

Study treatment is defined as any investigational product, non-investigational product, placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

5.1. Investigational Product

The IMP will be supplied by the Sponsor. Detailed information regarding the storage, preparation, destruction, and administration of IMP will be provided.

All supplies of investigational product, both bulk and subject-specific, will be stored in accordance with the manufacturer's instructions or pharmacy instructions. Until dispensed to the subjects, the investigational and non-investigational products will be stored at the study site in a location that is locked with restricted access.

The IMP will be stored according to the instructions on the label at the CRU.

Table 2: Investigational Product

Study Treatment Name	**Investigational Medicinal Product:** Avacopan
Unit Strength and Formulation	CCI Immediate Release Hard Gelatin Capsule
Dose	CCI)
Route of Administration	Oral
Accountability	The quantity administered, date administered, and lot number of investigational product are to be recorded on the appropriate Case Report Form.
Dosing Instructions	The Investigator/designee will administer the treatment after the completion of all predose procedures, under fed conditions. A standardized hemodialysis-friendly standardized meal will be provided to all subjects on Day 1. The dose should be taken within 30 minutes of the start of the meal. CCI should be taken with approximately 8 ounces (240 mL) of water. Capsules should not be broken or chewed.

Except as part of the dose administration, subjects will restrict their consumption of water for 1 hour prior to dosing and for 1 hour after dosing; at all other times during the study, subjects may consume water as desired. Subjects will fast for at least 4 hours postdose.

Subjects will be dosed while standing and will not be permitted to lie supine for 2 hours after administration of IMP, except as necessitated by the occurrence of an adverse event(s) and/or study procedures.

5.2. Investigational Product Administration

Subjects in Group 1 will have 1 dose administration each of CCI of avacopan and subjects in Group 2 will have two dose administrations each of CCI of avacopan. Subjects will be dosed in the order that they were enrolled. Subjects will receive all doses under supervision of the site staff.

5.3. Treatment of Overdose

For this study, any dose of avacopan greater than CCI will be considered an overdose. The effects of overdose of avacopan are not known. In case of overdose, consultation with the Medical Monitor is recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage, and to discuss further management of the subject.

5.3.1. Medical Devices

No investigational medical devices will be used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care. Non-Amgen non-investigational medical devices (e.g., syringes, sterile needles), that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

5.3.2. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational/non-investigational product(s), provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product(s) supplied by Amgen are to be reported.

5.4. Randomization

This is a nonrandomized study. The study has a fixed treatment sequence.

5.5. Blinding

This is an open-label study.

5.6. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- When subjects are dosed at the site, they will receive avacopan directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the eCRF.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

5.7. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of avacopan capsules received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused avacopan will be returned to the Sponsor, retained at the study site, or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects with normal renal function will refrain from use of any prescription or nonprescription medications/products during the study until the EOS visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

For renal-impaired subjects, treatment with chronic stable medications (for at least 3 months prior to study drug administration with the exceptions of minor changes in dose or formulation without change in clinical condition) necessary for maintaining the clinical status of the subject will be permitted if prescribed by the subject's personal physician and approved by the Medical Monitor and Investigator, in consultation with the Sponsor as needed. Except for concomitant

therapies associated with HD sessions, administration of medications should be withheld for at least 4 hours after study drug administration as clinically appropriate, unless needed for treatment of an adverse event, at the discretion of the Investigator. Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care while avoiding those listed in the exclusion criteria.

Acetaminophen (paracetamol) (2 g/day); hormone replacement therapy (e.g., estrogen and thyroid treatments including levothyroxine [Synthroid, Levothroid, Levoxyl, Unithroid], liothyronine [Cytomel], Liotrix [Thyrolar], and natural thyroid [Armour Thyroid, Nature-throid, Westhroid]); or oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an adverse event/serious adverse event. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations. While confined at the study site, subjects will receive a diet provided by the site at scheduled times that do not conflict with other study-related activities. No outside food or beverage will be permitted during confinement.

On dosing days (Day 1 for Group 1 and Day 1 of Periods 1 and 2 for Group 2), subjects will receive a standardized breakfast prior to study drug administration. The standardized breakfast will include approximately 215 fat calories, approximately 320 carbohydrate calories, approximately 125 protein calories, and approximately 1220 mg of sodium.

Refer to Section 5 and Table 2 for diet requirements/restrictions on applicable days of study treatment and/or PK assessments.

Foods and beverages containing poppy seeds, pomelos, or Seville oranges will not be allowed from 7 days prior to Check-in until EOS visit. Foods and beverages containing grapefruit will not be allowed from 14 days prior to Check-in until EOS visit.

Caffeine-containing foods and beverages will not be allowed from 48 hours before Check-in until EOS visit.

Consumption of alcohol will not be permitted from 48 hours prior to Check-in until EOS visit.

6.3. Smoking

Subjects will not be permitted significant use of tobacco- or nicotine-containing products (e.g., > ½ pack of cigarettes per day) within 3 months prior to Check-in through EOS.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before Check-in until the EOS visit. Subjects will otherwise maintain their normal level of physical activity during this time (i.e., will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, and platelets from 6 weeks prior to Check-in until 3 months after the EOS visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving consideration to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. Unless otherwise specified in the Schedule of Assessments, the order of priority for scheduling procedures around a timepoint is:

- predose safety assessments
- predose/trough PK blood samples
- dosing
- PK blood samples (postdose)
- postdose safety assessments (ECGs will be scheduled before vital signs measurements)
- any other procedures.

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, and safety laboratory assessments.

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 9. Arterial and venous PK samples may be collected from the HD catheter or arteriovenous fistula as appropriate.

Dialysate samples will be collected as specified in Appendix 9. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

For Group 2 Period 1, a sample of dialysate will be collected on Day 1 at 0.5, 1, 2, and 3 hours after the start of HD and after HD is complete for drug concentration analysis. The entire dialysate volume, blood flow, and dialysate flow during HD will be recorded for each timepoint, and the make and model of the dialyzer will be recorded.

Any blood sample collected according to the Schedule of Assessments (Appendix 9) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

7.1.2. Analytical Methodology

Plasma concentrations of avacopan and M1 metabolite will be determined using validated analytical procedures. Dialysate concentrations of avacopan and protein binding assessments will be determined using qualified methods. Specifics of the analytical method will be provided in a separate document.

7.2. Safety and Tolerability Assessments

7.2.1. Adverse Events and Serious Adverse Events: Time period and Frequency for Collecting and Reporting Safety Event Information

Adverse event definitions, assignment of severity and causality, and procedures for reporting Adverse Events and Serious Adverse Events are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to EOS. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report Adverse Events and Serious Adverse Events occurring at any other time during the study.

Adverse Events

The adverse event grading scale to be used in this study is described in Appendix 1.

The Investigator is responsible for ensuring that all adverse events observed by the Investigator or reported by the subject that occur after first dose of investigational product through the 30 days after the last day of the dosing interval of investigational product, whichever is later are reported using the Events Case Report Form (CRF).

Serious Adverse Events

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of the informed consent through 30 days after dosing of investigational product orEOS visit, whichever is later, are reported using the appropriate eCRF and reported on the paper-based Serious Adverse Event Report Form (described in Appendix 1).

All serious adverse events will be collected, recorded, and reported to the Sponsor within 24 hours of the Investigator's knowledge of the event. The Investigator will submit any updated Serious Adverse Event data to the Sponsor within 24 hours of it being available.

Since the criteria of the Common Terminology Criteria for Adverse Events (CTCAE) grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to Grade 4 CTCAE toxicity grading scale criteria (e.g., laboratory abnormality reported as Grade 4 without manifestation of life-threatening status), it will be left to the Investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

Serious Adverse Events After the Protocol-Required Reporting Period

After EOS, there is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the Investigator. However, if the Investigator becomes aware of serious adverse events (regardless of causality), then these serious adverse events will be reported to Amgen within 24 hours following the Investigator's awareness of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the Sponsor's safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious

adverse events will be followed, where possible, until resolution, stabilization, until the event is otherwise explained, or the subject is Lost to Follow-up. This will be completed at the Investigator's (or designee's) discretion.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the eCRF.

Regulatory Reporting Requirements for Serious Adverse Events

If the subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.

Prompt notification by the Investigator to the Sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment 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 treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/Independent Ethics Committees, and Investigators.

Individual 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.

Amgen will prepare a single Development Safety Update Report (also referred to as Annual Safety Report in the European Union) for the Amgen Investigational Product. To ensure that consolidated safety information for the study is provided, this single Development Safety Update Report will also include appropriate information on any other investigational products used in the clinical study, if applicable.

An Investigator who receives an individual safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will file it along with the IB and will notify the IRB, if appropriate according to local requirements.

Safety Monitoring Plan

Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.

Other Safety Findings/Special Situations

Medication errors, misuse or abuse of the investigational product is subject to the same reporting obligation as adverse events. Therefore, the following procedures must be followed:

- All medication errors, misuse, or abuse of the investigational product, whether or not the Other Safety Finding (OSF)/Special Situation (SS) is accompanied by a non-serious adverse event or a serious adverse event, as determined by the Investigator, the OSF/SS must be collected and recorded on the OSF/SS CRF.
- If there are any resulting clinical signs, symptoms, or sequelae, the corresponding non-serious adverse event or serious adverse event must also be collected and recorded on the Events CRF.
- All medication errors, misuse, or abuse when associated with a serious adverse event must also be reported to Amgen or designee immediately and no later than 24 hours of the Investigator's awareness of the OSF/SS - medication error, misuse, or abuse by submitting Serious Adverse Event Report Form.

Further details and definitions regarding OSF/ SS - medication errors, misuse, and abuse, can be found in Appendix 1.

Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 60 days after dosing of investigational product.

If a pregnancy is reported, the Investigator is to inform Amgen immediately and no later than 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 4. Amgen Global Patient Safety will follow-up with the Investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 4.

Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes

pregnant it must be reported on the Pregnancy Notification Form, see Figure 6). Refer to Appendix 3 for contraceptive requirements.

A pregnancy test will be performed at the end of the study.

Additional on-treatment pregnancy testing may be performed at the Investigator's discretion or as required per local laws and regulations.

7.2.2. Clinical Laboratory Evaluations

Blood samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, and serology) at the times indicated in the Schedule of Assessments in Appendix 9. Urine samples will be collected for Group 1 only for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 9. Clinical laboratory evaluations are listed in Appendix 2.

The Investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in CRF/eCRF. The Investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

Subjects in Group 1 will provide urine samples for drugs of abuse screen and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 9. Subjects in Group 2 will provide a blood or saliva sample for drugs of abuse screen and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 9. For all female subjects, a pregnancy test and follicle-stimulating hormone (FSH) screen for postmenopausal women will be performed at the times indicated in the Schedule of Assessments in Appendix 9.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.2.3. Vital Signs

Seated or supine BP, seated or supine pulse rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 9. Vital signs may also be performed at other times if judged to be clinically appropriate.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be seated or supine for at least 5 minutes before BP and pulse rate measurements. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as possible, but prior to the blood draw.

Vital signs for subjects will be taken consistently for each subject in either the seated or supine position. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

7.2.4. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 9. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria apply:

- QTcF is >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG and initiate further work-up or intervention as necessary.

7.2.5. Physical Examination

Physical examination will be performed and will include a neurological examination (breast, rectal, and genital examination are not required). Neurologic examination will include evaluation of mental status/cognition/mood/affect, gross and fine motor, sensory, cranial nerves, coordination, and deep tendon reflexes. Physical examination findings should be recorded on the appropriate CRF (e.g., medical history, treatment-emergent adverse event). Physical examinations will be performed at the timepoints specified in the Schedule of Assessments in Appendix 9.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

The sample size for this study is based on studies of similar design and is considered adequate for evaluation of the study objectives.

Approximately 12 subjects are planned to be enrolled in this study. Approximately 6 subjects will be enrolled in each group.

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of avacopan and have evaluable PK data. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an adverse event of vomiting that occurs at or before 2 times median time to maximum concentration or diarrhea within 24 hours of dosing.

8.2.2. Safety Population

The safety population will include all subjects who received at least 1 dose of avacopan and have at least 1 postdose safety assessment.

If a subject has a serious adverse event prior to dosing, reporting of the serious adverse event will be included with the safety population.

8.3. Pharmacokinetic Analyses

Arithmetic mean, coefficient of variation (CV%), standard deviation, median, minimum, maximum, and number of observations will be calculated for the PK parameters for each renal function group. Geometric mean and geometric CV% will be provided for all PK parameters except t_{max}. Median, minimum, maximum, and number of observations will be calculated for t_{max}.

The primary statistical analysis will estimate the relationship between the PK of avacopan and eGFR estimated by the MDRD equation. In addition, a relationship between the PK of M1 and the eGFR may also be evaluated.

The PK parameters C_{max}, t_{max}, apparent plasma terminal elimination half-life, AUC_{inf}, AUC_{0-48}, AUC_{last}, apparent clearance (CL/F), fraction of unbound drug (f_u), apparent volume of distribution (V_z/F), extraction ratio for HD (ERD), and CL_D will be determined, as appropriate, by using noncompartmental methods. Additional PK parameters may be determined as appropriate.

Ratios (test/reference) for the model-estimated C_{max}, AUC_{0-48} (calculated for Group 2 Period 2), and AUC_{inf} (test) relative to the group with normal renal function (reference) will be generated, along with 90% confidence intervals.

For subjects in Group 2, the PK parameters C_{max}, t_{max}, AUC_{0-48}, and AUC_{0-last} will be determined by using noncompartmental methods for doses administered. For subjects in Group 2 Period 1, a sample of dialysate will be collected on Day 1 at 0.5, 1, 2, and 3 hours. In addition, to support determination of avacopan clearance by HD, AUC_{last} will be determined from the arterial and venous plasma samples during HD (for Group 2 Period 1). The ratios (test/reference) of central

values and 90% CIs will be calculated for log-transformed C_{max} and AUC values on HD day (Group 2 Period 1, test) compared to non-HD day (Group 2 Period 2, reference).

Specific details will be presented in the Statistical Analysis Plan for this study.

8.4. Safety Analysis

The number and percentage of subjects reporting any adverse events will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product, and treatment-emergent adverse events will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

Clinical laboratory tests, ECG, and vital signs will be summarized.

8.5. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

1. Amgen. Avacopan – Current Investigator's Brochure.

2. TAVNEOS® (avacopan) capsules, for oral use. Highlights of Prescribing Information.

3. Tavneous (Avacopan). Summary of Product Characteristics. Vifor Fresenius Medical Care Renal Pharma UK Ltd. 30 Aug 2023.

4. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 2024. Guidance for industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing.

10. APPENDICES

Appendix 1: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events and Serious Adverse Events

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event 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 a treatment, combination product, medical device, or procedure. • Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration 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 intentional overdose of either study treatment or a concomitant medication. Intentional overdose will be reported as an adverse event/serious adverse event when it is taken with possible suicidal/self-harming intent. Such intentional overdoses are to be reported regardless of sequelae. Accidental/unintentional overdose will be captured as a medication error.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • 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.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject 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.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) 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 an adverse event. 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 adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to 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 or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Other Safety Findings/Special Situations: Medication Errors, Misuse or Abuse

All medication errors, misuse or abuse of the investigational product are subject to the same reporting obligation as adverse events and must be collected and recorded on the Other Safety Findings (OSF)/Special Situations (SS) case report form (CRF). If there are any resulting clinical signs, symptoms or sequelae, the corresponding non-serious adverse event and serious adverse event must also be collected and recorded on the Events CRF.

All medication errors, misuse, or abuse when associated with a serious adverse event must also be reported to Amgen or designee immediately and no later than 24 hours of Investigator's awareness of the OSF/SS - medication error, misuse or abuse by submitting the paper-based Serious Adverse Event Report Form.

Other Safety Finding/Special Situation	Collected and Recorded on the Other Safety Findings (OSF)/Special Situations (SS) Case Report Form (CRF)	Primary Reporting Method: Reported/submitted on the paper-based Serious Adverse Event Report Form to Amgen or designee immediately and no later than 24 hours of Investigator's awareness
Medication Error	All (regardless of whether associated with an adverse event/serious adverse event)	Only if associated with a serious adverse event
Misuse	All (regardless of whether associated with an adverse event/serious adverse event)	Only if associated with a serious adverse event
Abuse	All (regardless of whether associated with an adverse event/serious adverse event)	Only if associated with a serious adverse event

	Medication Error: A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the subject (e.g., mistake in the process of

Definitions	prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice.
	Misuse: A misuse refers to situations where the medicinal product, combination product, or medical device is intentionally and inappropriately used not in accordance or outside what is foreseen in the protocol.
	Abuse: An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, combination product, or medical device, which is accompanied by harmful physical or psychological effects.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant adverse event/serious adverse event information in the Event electronic Case Report Form (eCRF).
- The Investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product, other protocol-required therapies;
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to the investigational product(s) and/or study-mandated procedures;
  - Action taken; and
  - Outcome of event.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the appropriate eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor in lieu of completion of the appropriate eCRF page.
- If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the

medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The Investigator will assess severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events (CTCAE), version 5 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
Assessment of Causality
• The Investigator is obligated to assess the relationship between investigational product(s) (investigational product[s], noninvestigational product[s]/auxiliary medicinal product[s], device[s], study-required activity and/or procedure[s]) and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in their assessment. • For each adverse event/serious adverse event, the Investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The Investigator may change their opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
Follow-up of Adverse Event and Serious Adverse Event
• 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 to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or

investigations, histopathological examinations, or consultation with other health care professionals.

- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.
  - If a subject dies during participation in the study, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology if available.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper Serious Adverse Event Report Form

- Facsimile transmission of the Serious Adverse Event Report Form (see Figure 5) is the preferred method to transmit this information.
- If the event is a serious adverse event associated with the Other Safety Finding/Special Situation (medication error, misuse, or abuse) then the site must complete/submit the Serious Adverse Event Report Form for the associated Other Safety Finding/Special Situation (medication error, misuse, or abuse).
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Once the study has ended, serious event(s) should be reported to Amgen (regardless of causality) if the Investigator becomes aware of a serious adverse event. The Investigator should use the paper-based Serious Adverse Event Report Form to report the event.

Figure 5: Sample Serious Adverse Event Report Form

AMGEN®
20230265
Fortrea Study #
8530204
AMG 569

Clinical Trial Serious Adverse Event Report Form– Phase 1–4
Notify Amgen Immediately and no later than 24 Hours of awareness of the serious adverse event/other safety finding/special situation

❑New
❑Follow-up

<<Amgen Safety fax number to be populated by Study Manager/ProtocolAuthor/Designee prior to providing to sites SELECT OR TYPE IN A FAX#.>> If an email address or eFax is used, the Primary Study Team (e.g., Clinical Manager or Delegate) will need to ensure secure email exchange is established between the Provider/Study Sites, Vendor/Supplier, Sites and Amgen

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		❑F ❑M		

3. SERIOUS ADVERSE EVENT OR Other Safety Finding/Special Situation associated with a Serious Adverse Event

Information in this section must also be entered on the Serious Adverse Event Summary Case Report Form and if applicable, Other Safety Finding/Special Situation, must be entered on the Other Safety Findings(OSF)/Special Situations (SS) Case Report Form

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day Month Year

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event and (if applicable) Other Safety Finding/Special Situation associated with a Serious Adverse Event *List one event per line*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the event may have been caused by IP or an investigational device? If yes see section 10 — AMG 569 Yes/No	AMG 569 Yes/No	<Device> Yes/No	<Device> Yes/No	<Device> Yes/No	<Device> Yes/No	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: 01 Fatal; 02 Immediately life- threatening; 03 Required hospitalization or prolonged hospitalizaion; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ❑No ❑Yes, If yes, please complete date(s):		

AMGEN
20230265
Fortrea Study #
8530204
AMG 569

Clinical Trial Serious Adverse Event Report Form– Phase 1–4

Notify Amgen Immediately and no later than 24 Hours of awareness of the serious adverse event/other safety finding/special situation

☐New
☐Follow-up

Site Number | Subject ID Number

5. INVESTIGATIONAL PRODUCT (IP) / DEVICE

	Initial Start Date (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product (01 Still being Administered; 02 Permanently discontinued; 03 Withheld)	Lot # and Serial #
AMG 569 ☐Blinded X Open Label							Lot # _____ ☒ Unknown Serial # _____ ☒ Unknown
<<IP/Device>> ☐Blinded ☐Open Label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown
<<IP/Device>> ☐Blinded ☐Open Label							Lot # _____ ☐ Unknown Serial _____ ☐ Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy)

Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)*

Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

	Test											
Date (Day Month Year)	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)*

Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN 20230265 Fortrea Study # 8530204 AMG 569	**Clinical Trial Serious Adverse Event Report Form– Phase 1–4** *Notify Amgen Immediately and no later than 24 Hours of awareness of the serious adverse event/other safety finding/special situation*	☐New ☐Follow-up

	Site Number	Subject ID Number	

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*		

FOR INTERNAL USE ONLY **– *Note for Case Management/LSOs:*** DO NOT send queries to the clinical site. Please direct all follow-up queries related to this SAE to [Medical.Safety@fortrea.com]

Appendix 2: Clinical Laboratory Evaluations

<table>
<tr><th>Clinical chemistry:</th><th>Hematology:</th><th>Urinalysis – Group 1 only:</th></tr>
<tr><td>Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatinine
Direct bilirubin[a]
Gamma-glutamyl transferase
Glucose
Indirect bilirubin[a]
Inorganic phosphate
Potassium
Sodium
Total bilirubin[a]
Total CO_2 (may be measured as bicarbonate)
Total protein
Uric acid</td><td>Hematocrit
Hemoglobin
Hemoglobin A1C[b]
Mean cell hemoglobin
Mean cell hemoglobin concentration
Mean cell volume
Platelet count
Red blood cell (RBC) count
RBC distribution width
White blood cell (WBC) count
WBC differential:
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils</td><td>Bilirubin
Blood
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
pH
Protein
Specific gravity
Urobilinogen
Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)</td></tr>
<tr><th>Serology[c]:</th><th>Drug screen[b]:</th><th>Hormone panel - females only:</th></tr>
<tr><td>Anti-hepatitis B surface antibody
Anti-hepatitis B core antibody
Hepatitis B surface antigen
Hepatitis C antibody
Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen</td><td rowspan="3">Including but not limited to:
Amphetamines/ methamphetamines
Barbiturates
Benzodiazepines
Cocaine (metabolite)
Methadone
Phencyclidine
Opiates
Tetrahydrocannabinol/ cannabinoids
Alcohol breath test[d]</td><td>Follicle-stimulating hormone (postmenopausal females only)[c]
Serum pregnancy test (human chorionic gonadotropin)[e]
Urine pregnancy test[e]</td></tr>
<tr><th>Coagulation panel[b]:</th><th colspan="2">Other Tests:</th></tr>
<tr><td>International normalized ratio (INR)
Prothrombin time (PT)
Partial thromboplastin time (PTT)</td><td>Hepatotoxicity only:
International normalized ratio (INR)[f]</td><td>Estimated glomerular filtration rate (eGFR)[g]</td></tr>
</table>

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Only analyzed at Screening and Check-in.
[c] Only analyzed at Screening.
[d] Alcohol breath test performed at Check-in only. Matrix for drug screen will be flexible, depending on the renal impairment status of the subject.
[e] Performed in serum at Screening and in urine at all other times for females in Group 1. A positive urine pregnancy test will be confirmed with a serum pregnancy test. Serum pregnancy test will be done at all timepoints for subjects in Group 2 (end-stage renal disease [ESRD]).
[f] International normalized ratio will be retested if hepatotoxicity is suspected.
[g] Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease (MDRD) equation.
MDRD formula (mL/min/1.73 m^2) = 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African-American)

Appendix 3: Contraception Requirements

All subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they conceive a child during treatment and for 60 days after administration of the investigational product.

Additional medications given during the study may alter the contraceptive requirements. The Investigator must discuss these contraceptive changes with the subject.

Definitions Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Non-Child-Bearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: males are considered fertile after puberty.

Contraception Requirements

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the Informed Consent Form (ICF) until 60 days after administration of the investigational product.

Primary methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill associated with inhibition of ovulation (as prescribed) without supplementary iron (i.e. Loestrin Fe, Junel Fe, and Lo Loestrin Fe are prohibited)
- combined hormonal patch (as prescribed)

- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
    - Bilateral tubal ligation with confirmation of surgical success
    - Regulatory approved method of hysteroscopic bilateral tubal occlusion with confirmation of occlusion of the fallopian tubes
- hormonal implant
- hormonal or non-hormonal intrauterine device
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects should refrain from donation of ova from Check-in (Day -1) until 60 days after administration of the investigational product.

Male Subjects:

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (i.e., male condom with spermicide) in addition to a second method of acceptable contraception by female partner from Check-in until 60 days after administration of investigational product. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or regulatory approved method of hysteroscopic bilateral tubal occlusion)
- hormonal implant
- hormonal or non-hormonal intrauterine device

- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide.

Male subjects are required to refrain from donation of sperm from Check-in until 60 days after administration of the investigational product.

Sexual Abstinence

Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) is an acceptable method of contraception. The reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 60 days after the EOS visit.

If a subject who practices true abstinence at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously from the time of signing the ICF until 60 days after the EOS visit.

Same-sex Relationships

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously from the time of signing the ICF until 60 days after EOS.

Appendix 4: Collection of Pregnancy and Lactation Information

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking investigational product through 60 days after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Form (see Figure 6). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws.)
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 60 days after dosing of investigational product. This information will be forwarded to Amgen Global Patient Safety. Generally, infant Follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (e.g., spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator will be reported to Amgen Global Patient Safety as described in Appendix 1. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 4.7 for details).

Male Subjects with Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 60 days after dosing of investigational product. The information will be recorded on the Pregnancy Notification Form. The form (see Figure 6) must be submitted to Amgen

Global Patient Safety immediately and no later than 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws.)

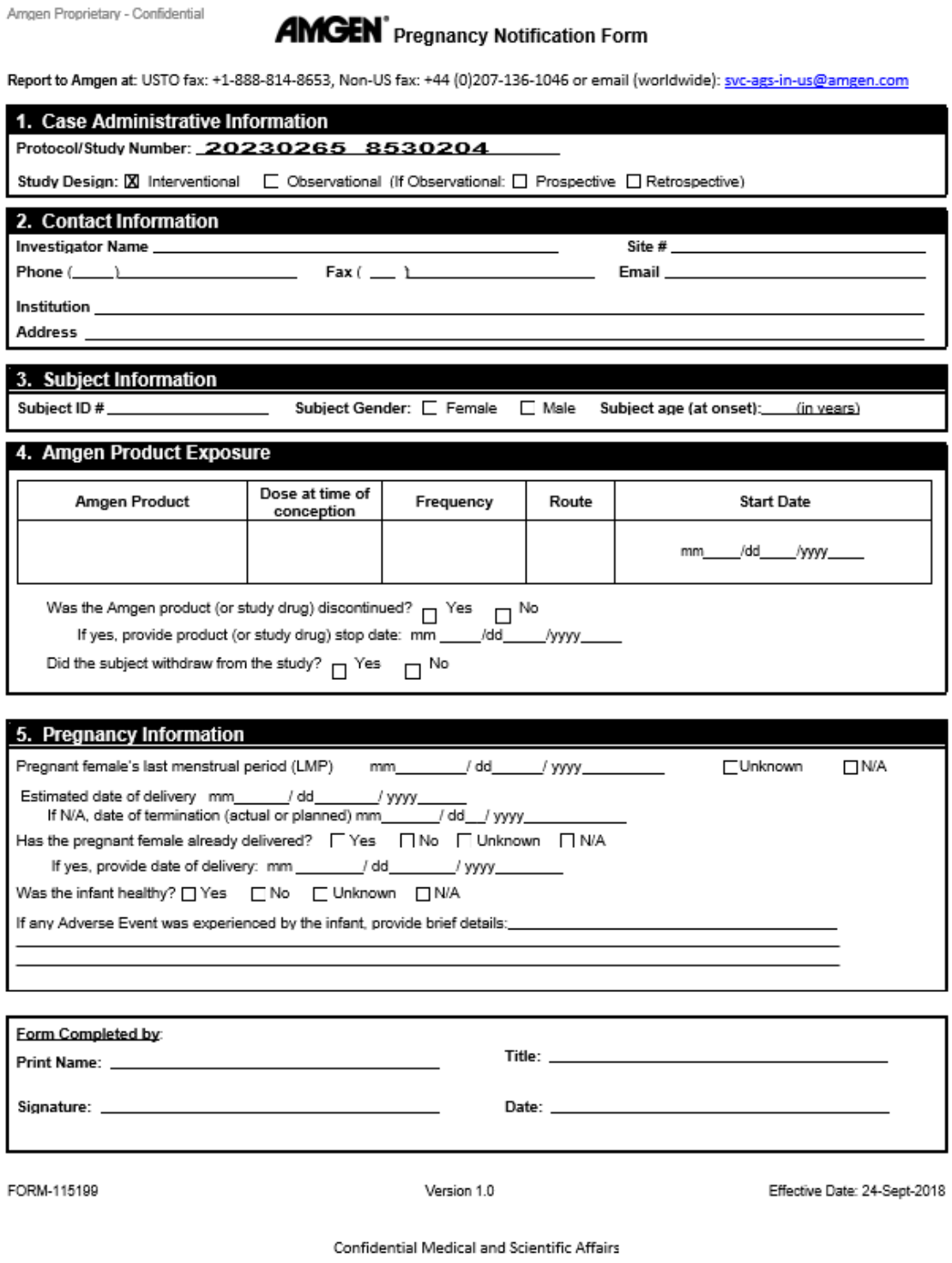
- Males whose partners become pregnant during treatment and for an additional 60 days after dosing of investigational product must practice sexual abstinence or use a condom through 60 days after dosing of investigational product and will be followed for safety until the end of study visit.
- The Investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking investigational product through 60 days after dosing of investigational product.
- Information will be recorded on the Lactation Notification Form (
- Figure 7) and submitted to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event.
- Study treatment will be discontinued if the female subject breastfeeds during the study.
- With the female subject's signed consent for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking investigational product through 60 days after the last dose of investigational product.

With the female subject's signed consent for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 60 days after discontinuing protocol-required therapies.

Figure 6: Pregnancy Notification Form



Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20230265 8530204

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

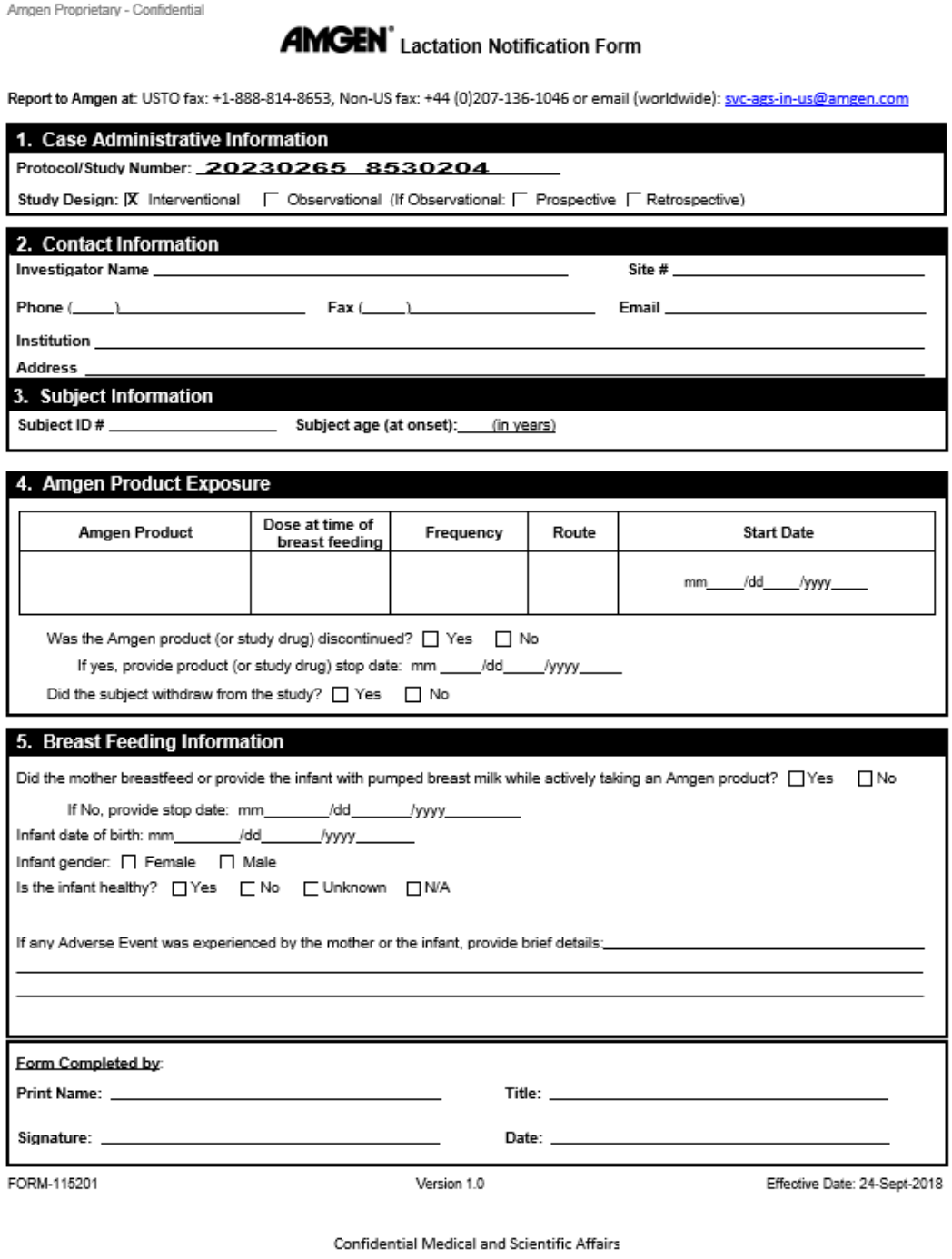
Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Confidential Medical and Scientific Affairs

Figure 7: Lactation Notification Form



Amgen Proprietary - Confidential

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20230265 8530204

Study Design: [X] Interventional [ ] Observational (If Observational: [ ] Prospective [ ] Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? [ ] Yes [ ] No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? [ ] Yes [ ] No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? [ ] Yes [ ] No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: [ ] Female [ ] Male

Is the infant healthy? [ ] Yes [ ] No [ ] Unknown [ ] N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Confidential Medical and Scientific Affairs

Appendix 5: Sample Storage and Destruction

When permitted by local regulations, any blood sample collected according to the Schedule of Assessments (Appendix 9) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded before being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

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 (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

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

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

An initial sample ICF will be provided for the Investigator (or designee) to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Study Manager to the Investigator. The written ICF is to be prepared in the language(s) of the potential study participant population.

The Investigator or their delegated representative will explain to the subject, or their legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and the IRB or study site.

The medical record must include a statement that written informed consent was obtained before the subject 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.

The acquisition of informed consent and the subject's agreement or refusal of their notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 21 days from the previous ICF signature date and the same version of the ICF is in use at the time of rescreening.

Subject Data Protection

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to the Sponsor.

Subjects will be assigned a unique identifier by the Sponsor (or designee). Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic Case Report Form (eCRF) demographics page, in addition to the unique subject identification number (Section 4.4), include the age at time of enrollment.

For serious adverse events reported to the Sponsor (or designee), subjects are to be identified by their unique subject identification number (Section 4.4), (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to the Sponsor (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to their study-related records, including personal information.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential information of the Sponsor, Amgen Inc. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written permission from the Sponsor.

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subjects will be assigned a unique identifier by the Sponsor (or designee). Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the Case Report Form demographics page, in addition to the unique subject identification number (Section 4.4), include the age at the time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number (Section 4.4), initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification 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 subjects 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) 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.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture system on an eCRF in a timely fashion.

All data generated from external sources (e.g., laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or Contract Research Organization (Fortrea), will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the electronic data capture system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

The policy for publication of data obtained during this study will be documented in the Clinical Study Agreement.

Appendix 7: Hepatotoxicity: Suggested Actions and Follow-up Assessments (Group 1 only)

Subjects with normal hepatic function at Screening who experience aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3 x upper limit of normal (ULN) or subjects with elevated values before drug exposure who have a 2-fold increase above baseline values (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009) are to undergo clinical assessments and a period of "close observation" until abnormalities return to normal or to the subject's baseline level as described below.

Clinical Assessments and Observation

Assessments that are to be performed during this period include:

- Repeat AST, ALT, alkaline phosphatase, bilirubin (total and direct), and international normalized ratio (INR) within 24 hours as possible.
- In cases of total bilirubin (TBL) > 2 x ULN or INR > 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours as possible until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
    - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
    - Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Appropriate liver imaging if clinically indicated

- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or are considered stable by the Investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential drug-induced liver injury (DILI) event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding electronic Case Report Form (eCRF).

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (e.g., hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right-sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
- Heritable disorders causing impaired glucuronidation (e.g., Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (e.g., rhabdomylosis, hemolysis).

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, i.e., cases of AST or ALT > 3 x ULN and concurrent TBL > 2 x ULN or INR > 1.5 (for subjects not on anticoagulation therapy) without evidence of alternative cause of the elevations, require the following:

- The event is to be reported to the Sponsor as a serious adverse event within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded)
- The appropriate eCRF captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Sponsor.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 1.

Appendix 8: Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments (Group 2 only)

Subjects with abnormal hepatic laboratory values (i.e., alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (e.g., hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right-sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
- Heritable disorders causing impaired glucuronidation (e.g., Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (e.g., rhabdomylosis, hemolysis).

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 3: Conditions for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding
TBL	>3x ULN at any time
INR	--
	OR
AST/ALT	>8x ULN at any time
	>5x ULN but <8x ULN for ≥2 weeks
	>5x ULN but <8x ULN and unable to adhere to enhanced monitoring schedule
	>3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)
	OR
ALP	>8x ULN at any time

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Table 4: Conditions for Withholding Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Permanent Discontinuation
TBL	>2x ULN OR
INR	>1.5x (for subjects not on anticoagulation therapy) AND
AST/ALT	>3x ULN (when baseline was < ULN), in the presence of no important alternative causes for elevated AST/ALT and/or TBL values
ALP	--

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, Investigator, and Amgen.

If signs or symptoms recur with rechallenge, then avacopan is to be permanently discontinued.

Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 3) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded).
- The appropriate electronic Case Report Form (eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 1.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 3 and Table 4 or who experience AST or ALT elevations >3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours as possible
- In cases of TBL >2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct) and INR is to be performed every 24 hours as possible until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL.

The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
    - Prior and/or concurrent disease or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
    - Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies

- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis, if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the Investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding eCRFs.

Appendix 9: Schedule of Assessments

Schedule of Assessments

Schedule of Assessments for Group 1

Activity per Period	Screening	Check-in	Treatment Period																						
Study Day	D-28 to D-2	D-1	D1												D2		D3	D4	D5	D6	D7	D8	D12	D15	D18 EOS/ET
Time (in hours)	--	--	Pre	0	0.25	0.5	1	2	3	4	6	9	12	16	24	36	48	72	96	120	144	168	264	336	408
In-house Residency		◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄			
Outpatient Visit	X																						X	X	X
GENERAL AND SAFETY ASSESSMENTS																									
Informed Consent	X																								
Inclusion/Exclusion Criteria	X	X																							
Demographics	X																								
Serology	X																								
Medical History	X	X[a]																							
Height and BMI	X																								
Weight	X	X																							X
Drug Screen	X	X																							
Alcohol Test		X																							
Adverse Events[b]				◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄
Serious Adverse Events[b]	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄
Prior/Concomitant Medications[c]	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄	◄
LABORATORY ASSESSMENTS AND OTHER PROCEDURES																									
Pregnancy Test (females only)[d]	X	X																							X
Serum FSH Test (postmenopausal females only)	X																								
Physical Examination[e]	X	X															X					X			X
12-lead ECG[f]	X	X																				X			X
Vital Signs[g]	X	X	X							X					X		X	X	X	X	X	X			X
Clinical Laboratory Evaluations[h]	X	X																				X			X
Coagulation Panel	X	X																							
eGFR[i]	X	X																							
Plasma Protein Binding												X													

Activity per Period	Screening	Check-in	Treatment Period																						
Study Day	D-28 to D-2	D-1	D1												D2		D3	D4	D5	D6	D7	D8	D12	D15	D18 EOS/ET
Time (in hours)	--	--	Pre	0	0.25	0.5	1	2	3	4	6	9	12	16	24	36	48	72	96	120	144	168	264	336	408
PHARMACOKINETIC ASSESSMENTS																									
Avacopan and M1 Plasma PK[j]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INVESTIGATIONAL PRODUCT																									
Avacopan Dose Administration[k]				X																					

Abbreviations: BMI = body mass index; D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study visit; ET = early termination; FSH = follicle-stimulating hormone; M1 = metabolite; PK = pharmacokinetic; Pre = predose.

[a] Interim medical history only.

[b] Adverse events will be recorded from initiation of study treatment on Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the Informed Consent Form until 30 days after the dose of study treatment or through the EOS, whichever is later.

[c] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to enrollment for over-the-counter or prescription medications, and 30 days prior to enrollment for herbal medicines (e.g., St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic case report form.

[d] Performed in serum at Screening and in urine at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

[e] A full physical examination at Screening, Check-in, Day 3, Day 8, and Day 18 (EOS/ET).

[f] Twelve-lead ECGs will be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws at: Screening; Check-in; Day 8; and Day 18 (EOS/ET). Electrocardiograms should be collected prior to any PK corresponding timepoints. Single trace ECGs will be collected at all timepoints.

[g] Vital signs measurements (seated/supine blood pressure, seated/supine pulse rate, respiratory rate, and oral body temperature) should be carried out prior to having blood drawn. Vital signs will be obtained at: Screening; Check-in; prior to avacopan administration and 4 hours following avacopan administration on Day 1, 24 hours postdose on Day 2, and on Days 3, 4, 5, 6, 7, 8, and 18 (EOS or ET). Pulse rate and blood pressure will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes.

[h] Clinical chemistry, hematology, and urinalysis (fasted at least 8 hours).

[i] The eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation.
MDRD formula ($mL/min/1.73m^2$) = 175 x $(serum\ creatinine)^{-1.154}$ x $(age)^{-0.203}$ x (0.742 if female) x (1.212 if African-American)

[j] The PK samples collected on Day 1 will have a sampling window of ±10 minutes. Postdose samples on Day 2 will have a sampling window of ±1 hour. Postdose samples Days 3 to 8 will have a sampling window of ±2 hours. Postdose samples on Days 12, 15, and 18 will have a sampling window of ±4 hours. Times of all PK samples will be recorded to the nearest minute.

[k] Dose administration of avacopan will be given in the morning on Day 1 under fed conditions.

Schedule of Assessments for Group 2 (Period 1 – On Hemodialysis)

Activity per Period	Screening	Check-in	Treatment Period 1																						
Study Day	D-28 to D-2	D-1	D1												D2		D3	D4	D5	D6	D7	D8	D12	D15	D18
Time (in hours)	--	--	Pre	0	0.25	0.5	1	2	3	4	6	9	12	16	24	36	48	72	96	120	144	168	264	336	408
In-house Residency		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→			
Outpatient Visit	X																						X	X	X
GENERAL AND SAFETY ASSESSMENTS																									
Informed Consent	X																								
Inclusion/Exclusion Criteria	X	X																							
Demographics	X																								
Serology	X																								
Medical History	X	X[a]																							
Height and BMI	X																								
Weight	X	X																							
Serum or Saliva Drug Screen	X	X																							
Alcohol Test		X																							
Child-Pugh Assessment	X	X																							
Adverse Events[b]				→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious Adverse Events[b]	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→			
Prior/Concomitant Medications[c]	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→			
LABORATORY ASSESSMENTS AND OTHER PROCEDURES																									
Pregnancy Test (females only)[d]	X	X																							
Serum FSH Test (postmenopausal females only)	X																								
Physical Examination[e]	X	X															X					X			X
12-lead ECG[f]	X	X																				X			
Vital Signs[g]	X	X	X							X					X		X	X	X	X	X	X	X	X	X
Clinical Laboratory Evaluations[h]	X	X																				X			
Coagulation Panel	X	X																							
eGFR[i]	X	X																							
Plasma Protein Binding									X			X													
Hemodialysis[j, k]										X							X		X			X			

Activity per Period	Screening	Check-in	Treatment Period 1																						
Study Day	D-28 to D-2	D-1	D1												D2		D3	D4	D5	D6	D7	D8	D12	D15	D18
Time (in hours)	--	--	Pre	0	0.25	0.5	1	2	3	4	6	9	12	16	24	36	48	72	96	120	144	168	264	336	408
PHARMACOKINETIC ASSESSMENTS																									
Avacopan and M1 Plasma PK[k]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INVESTIGATIONAL PRODUCT																									
Avacopan Dose Administration[l]				X																					

Abbreviations: BMI = body mass index; D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HD = hemodialysis; M1 = metabolite; PK = pharmacokinetic; Pre = predose; SOA = Schedule of Assessments.

[a] Interim medical history only.

[b] Adverse events will be recorded from initiation of study treatment on Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the Informed Consent Form until 30 days after the last dose of study treatment or through the EOS, whichever is later.

[c] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to enrollment for over-the-counter or prescription medications, and 30 days prior to enrollment for herbal medicines (e.g., St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic case report form.

[d] Performed in serum at all timepoints.

[e] A full physical examination at Screening, Check-in, Day 3, Day 8, and Day 18.

[f] Twelve-lead ECGs will be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws at: Screening, Check-in, and Day 8. Electrocardiograms should be collected prior to any PK corresponding timepoints. Single trace ECGs will be collected at all timepoints.

[g] Vital signs measurements (seated/supine blood pressure, seated/supine pulse rate, respiratory rate, and oral body temperature) should be carried out prior to having blood drawn. Vital signs will be obtained at: Screening; Check-in; prior to avacopan administration and prior to HD 4 hours following avacopan administration on Day 1, 24 hours postdose on Day 2, and on Days 3, 4, 5, 6, 7, 8, and Days 12, 15, and 18. Pulse rate and blood pressure will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes.

[h] Clinical chemistry and hematology (fasted at least 8 hours). Urinalysis will not be performed for subjects in Group 2.

[i] The eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation.
MDRD formula (mL/min/1.73m^2) = 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

[j] Day 1 assessments will include recording of the date and time of the last HD treatment before avacopan administration. On Day 1, subjects will receive avacopan dose and begin HD at 4 hours postdose. Hemodialysis will occur on Days 3, 5, and 8. Hemodialysis will continue as needed beyond the timepoints specified in the SOA. The study day, and the start and end times will be collected for all HD sessions.

[k] The PK samples collected on Day 1 will have a sampling window of ±10 minutes. Postdose samples on Day 2 will have a sampling window of ±1 hour. Postdose samples Days 3 to 8 will have a sampling window of ±2 hours. Postdose samples on Days 12, 15, and 18 will have a sampling window of ±4 hours. Times of all PK samples will be recorded to the nearest minute. Day 3, Day 5, and Day 8 PK samples will be obtained prior to start of HD. Additional plasma PK samples collected during HD on Day 1: Arterial and venous plasma blood samples will be collected pre-HD and at 0.5, 1, 2, and 3 hours after the start of HD and immediately following the end of HD. Venous plasma PK samples will also be collected at the next HD session on Day 3 (approximately 48 hours after previous one) at pre-HD, at 0.5, 1, 2, and 3 hours post the start of HD, and immediately following the end of HD. A sample of dialysate will be collected on Day 1 at 0.5, 1, 2, and 3 hours after the start of HD and after HD is complete for drug concentration analysis. The dialysate volume at 0.5, 1, 2 and 3 hours after start of dialysis (each dialysate collection time), the entire dialysate volume at the completion of the dialysis session, blood flow, and dialysate flow during HD will be recorded for each timepoint. The make and model of the dialyzer will be recorded.

[l] Dose administration of avacopan will be given in the morning on Day 1, 4 hours prior to HD, under fed conditions.

Schedule of Assessments for Group 2 (Period 2 – Off Hemodialysis)

Activity per Period	Check-in	Treatment Period 2																				
Study Day	D-1	D1											D2		D3	D4	D5	D6	D7	D8	D12	D15	D18 EOS/ET
Time (in hours)	--	Pre	0	0.25	0.5	1	2	3	4	6	9	12	16	24	36	48	72	96	120	144	168	264	336	408
In-house Residency	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►			
Outpatient Visit																						X	X	X
GENERAL AND SAFETY ASSESSMENTS																								
Medical History	X[a]																							
Weight	X																							X
Serum or Saliva Drug Screen	X																							
Alcohol Test	X																							
Adverse Events[b]	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Serious Adverse Events[b]	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Prior/Concomitant Medications[c]	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
LABORATORY ASSESSMENTS AND OTHER PROCEDURES																								
Pregnancy Test (females only)[d]	X																							X
Physical Examination[e]	X														X					X				X
12-lead ECG[f]	X																			X				X
Vital Signs[g]	X	X							X					X		X	X	X	X	X	X			X
Clinical Laboratory Evaluations[h]	X																			X				X
eGFR[i]	X																							
Plasma Protein Binding											X													
Hemodialysis[j]	X															X		X		X				
PHARMACOKINETIC ASSESSMENTS																								
Avacopan and M1 Plasma PK[k]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INVESTIGATIONAL PRODUCT																								
Avacopan Dose Administration[l]			X																					

Abbreviations: D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study visit; ET = early termination; HD = hemodialysis; M1 = metabolite; PK = pharmacokinetic; Pre = predose; SOA = Schedule of Assessments.

[a] Interim medical history only.

[b] Adverse events will be recorded from initiation of study treatment on Period 1 Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the Informed Consent Form until 30 days after the last dose of study treatment or through the EOS, whichever is later.

[c] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to enrollment for over-the-counter or prescription medications, and 30 days prior to enrollment for herbal medicines (e.g., St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic case report form.

[d] Performed in serum at all timepoints.

[e] A full physical examination at Check-in, Day 3, Day 8, and Day 18 (EOS/ET).

[f] 12-lead ECGs will be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws at: Check-in; Day 8; and Day 18 (EOS or ET). Electrocardiograms should be collected prior to any PK corresponding timepoints. Single trace ECGs will be collected at all timepoints.

[g] Vital signs measurements (seated/supine blood pressure, seated/supine pulse rate, respiratory rate, and oral body temperature) should be carried out prior to having blood drawn. Vital signs will be obtained at: Check-in; prior to avacopan administration and 4 hours following avacopan administration on Day 1, 24 hours postdose on Day 2, and on Days 3, 4, 5, 6, 7, 8, and 18 (EOS or ET). Pulse rate and blood pressure will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes.

[h] Clinical chemistry and hematology (fasted at least 8 hours). Urinalysis will not be performed for subjects in Group 2.

[i] The eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation.
MDRD formula (mL/min/1.73m^2) = 175 x(serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

[j] Hemodialysis will be completed on Day -1 before the administration of avacopan. Hemodialysis will occur on Days 3, 5, and 7. Hemodialysis will continue as needed beyond the timepoints specified in the SOA. The study day, and the start and end times will be collected for all HD sessions.

[k] The PK samples collected on Day 1 will have a sampling window of ±10 minutes. Postdose samples on Day 2 will have a sampling window of ±1 hour. Postdose samples Days 3 to 8 will have a sampling window of ±2 hours. Postdose samples on Days 12, 15, and 18 will have a sampling window of ±4 hours. Times of all PK samples will be recorded to the nearest minute. Day 3, Day 5, and Day 7 PK samples will be obtained prior to start of HD.

[l] Dose administration of avacopan will be given in the morning on Day 1 under fed conditions following HD session on Day -1.

Appendix 10: Child-Pugh Classification of Severity of Cirrhosis

Parameter	Points Assigned		
	1	**2**	**3**
Ascites[1]	Absent	Slight or Subject on 1 medication to control ascites	Moderate or Severe or Subject on 2 medications to control ascites
Total bilirubin	< 2 mg/dL (< 34.2 µmol/L)	2 – 3 mg/dL (34.2 – 51.3 µmol/L)	> 3 mg/dL (> 51.3 µmol/L)
Albumin	> 3.5 g/dL (35 g/L)	2.8 – 3.5 g/dL (28 – 35 g/L)	< 2.8 g/dL (< 28 g/L)
Prothrombin time			
Seconds over control	< 4	4 – 6	> 6
International normalized ratio	< 1.7	1.7 – 2.3	> 2.3
Hepatic encephalopathy[2]	None	Grade 1 – 2 (or suppressed with medication)	Grade 3 – 4 (refractory)

1 Ascites is graded according to the following criteria:
Absent: No ascites detectable by manual investigation
Slight: Ascites palpitation doubtful
Moderate: Ascites detectable by palpation
Severe: Necessity of paracentesis, does not respond to medication treatment.

2 Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 to 3 cycles per second delta activity

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of total bilirubin and albumin, the prothrombin time (or international normalized ratio), and the degree of hepatic encephalopathy. A total score of 5 to 6 is considered Class A (well compensated disease); 7 to 9 is Class B (significant functional compromise); and 10 to 15 is Class C (decompensated disease).

Subjects in Group 1 will not be assessed for Child-Pugh Scores. Subjects in Group 2 with a Class A, B, or C Child-Pugh classification will be excluded from the study.

Approval Signatures

Document Name:	Protocol Original avacopan 20230265
Document Description:	A Phase 1, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Avacopan in Subjects with Normal Renal Function and Subjects with End-Stage Renal Disease (ESRD) Requiring Hemodialysis
Document Number:	CLIN-000345231
Approval Date:	30 Apr 2024
Type of Study Protocol:	Original
Protocol Amendment No.:	

Document Approvals	
Reason for Signing: Management	PPD Date of Signature: 30-Apr-2024 18:48:44 GMT+0000
Reason for Signing: Management	PPD Date of Signature: 30-Apr-2024 22:27:29 GMT+0000