Statistical Analysis Plan Addendum

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

Statistical Analysis Plan Addendum: 1.0
Statistical Analysis Plan Addendum Date: 24MAR2025

Investigational Product: Avacopan

Protocol Reference: 20230265
Fortrea Study ID: 8530204
Sponsor: Amgen, Inc.

Author:

PPD

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- **INTRODUCTION TO CHANGE DOCUMENTATION**

Post database lock additions (e.g. sub-group analyses, sensitivity analyses, data driven inferential method changes, adding new tables/figures/listings) need to be documented here.

This document should not be used for tracking updates, corrections of typographical errors, modification of spelling, etc.

This document was prepared following final database lock 27NOV2024 and final SAP Version 1.0 dated 20JUN2024.

- **POST-SAP FINALIZATION CHANGES (POST DATABASE LOCK)**

○ Additional Changes in SAP or TFL outputs

SAP Changes from Final SAP Version-1

1) Change from baseline definition

SAP section 9.1.3 Definition of Baseline and Change from Baseline

SAP V1: The baseline was defined as the last value recorded prior to the ***first dose***. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to the ***first dose***.

Addendum V1: The baseline was defined as the last value recorded prior to the ***first dose in each period***. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to the ***first dose in each period***.

2) eGFR units updated to mL/min

SAP Section 9.3 Screening Demographic and Baseline Characteristics

SAP V1: 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) x body surface area (BSA)

Addendum V1: MDRD formula (mL/min) = 175 x (serum creatinine)-1.154 x (age)-0.203 x (0.742 if female) x (1.212 if African American) x body surface area (BSA)***/1.73***

SAP Section 9.5.3 Pharmacokinetic Statistical Methodology

SAP V1: Scatterplot of PK Parameters vs ***Baseline eGFR (mL/min/1.73m^2)***

Addendum V1: Scatterplot of PK Parameters vs ***Screening eGFR (mL/min)***

3) Updates to the Statistical Analysis

SAP Section 9.5.3 Pharmacokinetic Statistical Methodology

AddendumV1:

- In the analysis of the effect of renal impairment on the PK of avacopan, subject as random effect statement was excluded from the model as each subject will contribute to the model only once.
- In the analysis to measure the effect of hemodialysis on the PK of avacopan, period was removed from fixed effect term in the model as the study has fixed sequence.
- Example SAS code changed to reflect the above changes in the SAP
- sensitivity analysis was conducted for AUCinf to get values with >20% extrapolated included in comparisons.

4) Removed the AE listings of safety findings/special situations and updated the rule for TEAE summary statistics

SAP Section 9.6.1 Adverse events

Addendum V1:

Updated the SAP to delete the listings of safety findings and special situation as this is not done for this study and rule for the calculation of the TEAE summary statistics updated as

- For the calculation of TEAE summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as ***1 TEAE for that treatment under the maximum severity recorded; this will be done separately for TEAEs and treatment-related TEAEs***.

5) Minor editorial changes

Addendum V1:

- Other minor editorial and formatting revisions were made to the TFLs but have not been summarized due to being minor.

Statistical Analysis Plan

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

SAP Status: Final
SAP Version: 1
SAP Date: 20JUN2024

Investigational Medicinal Product: Avacopan

Protocol Reference: 20230265
Fortrea Study: 8530204

Sponsor:
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LIST OF IN-TEXT TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

$\%AUC_{extrap}$	percentage of area under the plasma concentration-time curve due to extrapolation from last quantifiable concentration to infinity
ADaM	Analysis Data Model
AE	adverse event
Ae_d	amount of analyte (avacopan or M1) recovered in dialysate
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
$AUC_{post\text{-}dialyzer}$	area under the plasma concentration-time curve from time zero to the end of hemodialysis, as determined from samples collected post-dialyzer
$AUC_{pre\text{-}dialyzer}$	area under the plasma concentration-time curve from time zero to the end of hemodialysis, as determined from samples collected pre-dialyzer
$AUC_{0\text{-}48}$	area under the plasma concentration-time curve from time zero to 48 hours
BLQ	below the limit of quantification
BSA	body surface area
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL_D	hemodialysis clearance of drug (and metabolite) from plasma
CL/F	apparent clearance
C_{max}	maximum observed plasma concentration
CRU	clinical study unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
D1L1	drug-induced liver injury
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	end of study
ERD	extraction ratio

ESRD	End-Stage Renal Disease
fe_d	fraction of dose recovered in dialysate
f_u	fraction of unbound drug; reported as the arithmetic mean where measured at two time points
ET	early termination
GLSM	geometric least squares mean
HD	hemodialysis
ICH	International Council for/Conference on Harmonisation
ln	natural log
LSM	least squares mean
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
M1	metabolite
NA	not applicable
PK	pharmacokinetic(s)
QTcF	QT interval corrected using Fridericia's formula
R^2	coefficient for determination
SAP	statistical analysis plan
SD	standard deviation
SDV	source document verification
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
$t_{1/2}$	apparent plasma terminal elimination half-life
t_{last}	time of last quantifiable concentration
t_{max}	time of the maximum observed concentration
V_z/F	apparent volume of distribution during the terminal phase
WHODrug	World Health Organization Drug Dictionary
λ_z	apparent terminal elimination rate constant
λ_z Lower	start of exponential fit
λ_z N	number of data points included in the log-linear regression
λ_z Span Ratio	time period over which λ_z was determined as a ratio of $t_{1/2}$
λ_z Upper	end of exponential fit

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1.0 dated 26 April 2024) and electronic case report form (eCRF).

This SAP describes the planned analysis of the pharmacokinetic (PK), safety, and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Amgen, Inc. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation.

This SAP must be finalized prior to the lock of the clinical database. Additionally, the SAP and TFL shells should be finalized prior to any programming activities commencing.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Amgen, Inc and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, ICH E9 guideline *Statistical Principles for Clinical Trials*.[1,2,3]

The document history is presented in Appendix 1.

2. STUDY 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 end-stage renal disease (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.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The primary endpoints of the study are:

- maximum observed plasma concentration (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).

3.2. Secondary Endpoints

The secondary endpoints of the study are:

- treatment-emergent adverse events (TEAEs).
- serious adverse events (SAEs).

4. 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. 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 estimated glomerular filtration rate (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

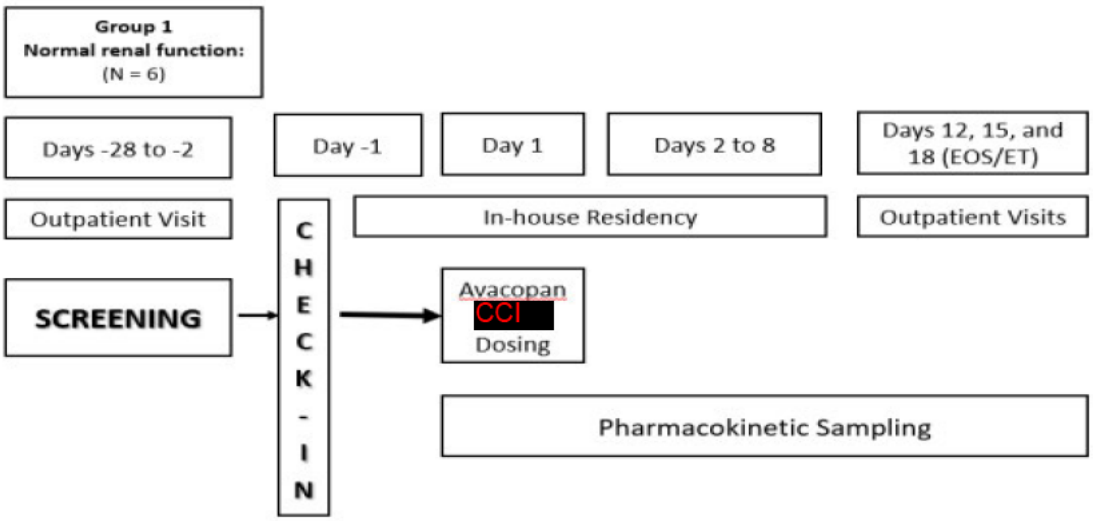
Population	eGFR (mL/min)[a,b]	Group	Period
Normal renal function	≥90	1	NA
ESRD requiring HD[b]	<15	2	1 and 2

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.

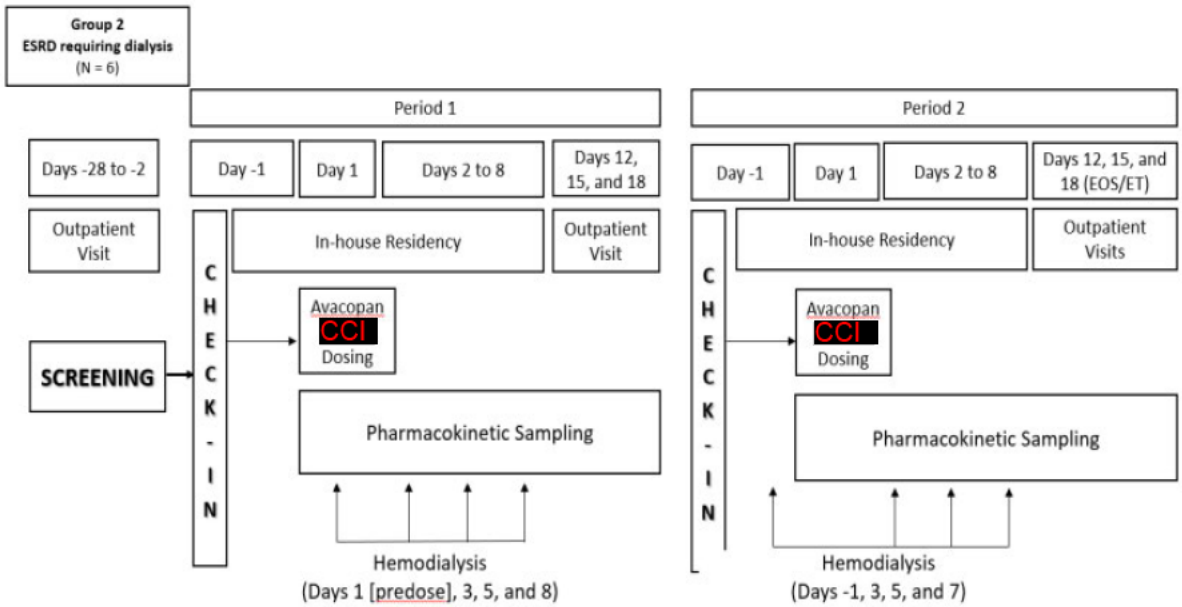
Figure 1: Study Schema – Group 1 (Normal Renal Function)



Abbreviations: EOS = end of study visit; ET = early termination.

Notes: Single dose of avacopan will be administered on Day 1 in the morning.

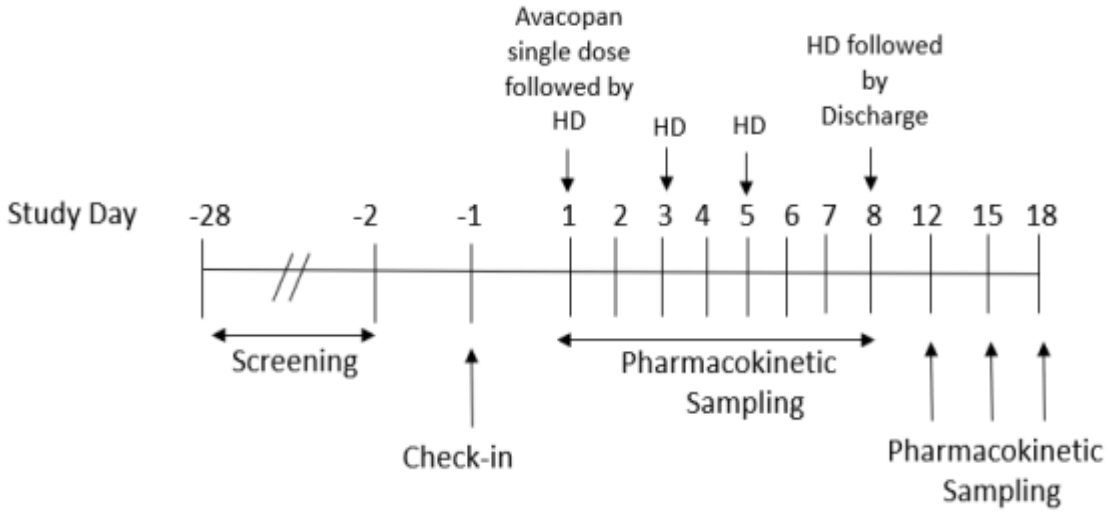
Figure 2: Study Schema – Group 2 (ESRD Requiring Hemodialysis)



Abbreviations: EOS = end of study visit; ESRD = end-stage renal disease; ET = early termination; HD = hemodialysis.

Notes: 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.

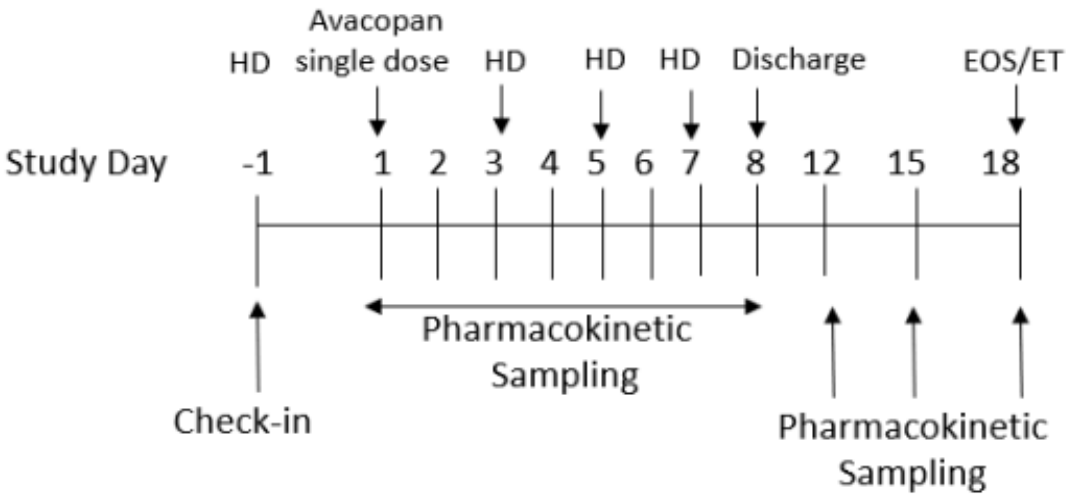
Figure 3: Group 2 (ESRD Requiring Hemodialysis) Schema, Period 1 – On Hemodialysis



Abbreviations: HD = hemodialysis.

Notes: Subjects will receive a single oral dose of avacopan 4 hours prior to start of HD session, under fed conditions.

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.

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).

5. SAMPLE SIZE JUSTIFICATION

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.

6. STUDY TREATMENTS

All subjects will receive a single dose of CCI avacopan orally under fed conditions (subjects in Group 2 will receive a single dose in each period). The treatment label used in the TFLs will be "CCI avacopan".

All TFLs will be based on actual treatments.

7. RENAL FUNCTIONS

The renal function names, abbreviations, and ordering to be used in the TFLs are presented in Table 2.

Table 2: Presentation of Renal Functions in TFLs

Renal Function Group	Abbreviation	Order in TFLs
Normal renal function	Normal	1
End Stage Renal Disease Requiring Dialysis (on-dialysis)	ESRD Requiring HD (on-HD)	2
End Stage Renal Disease Requiring Dialysis (off-dialysis)	ESRD Requiring HD (off-HD)	3

8. DEFINITIONS OF POPULATIONS

Any protocol deviations will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

8.1. All Subjects Population

The all-subjects population will include all subjects who signed the informed consent form and had any study assessment recorded in the database per the protocol.

8.2. Safety Population

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

9. STATISTICAL METHODOLOGY

9.1. General

Listings will be provided for all data captured in the database, with the exception of medical history. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Subjects are considered to have completed the study if they complete the scheduled end of study visit (rather than early termination visit). Any subject who discontinues the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if a new version is issued during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if a new version is issued during the study) and CDISC ADaM Implementation Guide Version 1.3 (or higher if a new version is issued during the study). Pinnacle 21 Community Validator Version 4.0.2 (or higher if a new version is issued during the study) will be utilized to ensure compliance with CDISC standards.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to 'valid' data, this refers to non-missing data which meet the predetermined criteria (eg, are not flagged for exclusion).

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, and changes from baseline.

All figures will be produced on linear-linear or discrete-linear scales, as applicable, unless specifically stated otherwise.

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in by subject listings. Summary statistics and inferential analysis of derived PK parameters will be performed by using the unrounded values and the statistical results will be rounded for reporting purposes.

Derived PK parameters will be reported in 3 significant digits.

9.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- Quantitative variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum values. Geometric mean and geometric CV will be included for plasma PK concentrations and parameters, where applicable.
- If the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- In general, as early termination visit data are not associated with any scheduled timepoint, they will be excluded from all calculations of summary statistics and statistical analyses. Exceptions may be made where justified.

For categorical data the following rules will be applied:

- For ordered categorical data (eg, adverse event [AE] severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category.
- For non-ordered categorical data (eg, race), only those categories for which there is at least 1 subject represented will be included, unless specifically stated otherwise.

- Missing values will not be imputed, unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

9.1.2. Repeat and Unscheduled Readings

For vital signs and 12-lead ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations, with the exception of the 12-lead ECG outlier analysis (see Section 9.6.4).

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see Section 9.1.3) and 12-lead ECG outlier analysis (see Section 9.6.4).

9.1.3. Definitions of Baseline and Change from Baseline

The baseline will be defined as the last value recorded prior the first dose. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to the first dose.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the postdose timepoint.

The summary statistics for change from baseline will be derived from individual subjects' values (eg, mean change from baseline will be the mean of the individual changes from baseline for all subjects, rather than difference between the mean value at the postdose timepoint and mean value at baseline).

See Section 9.1.2 for more detail on handling repeat and unscheduled readings in the calculations.

9.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed, based on the all subjects population.

A summary table by renal function group will be provided, based on the safety population.

9.3. Screening Demographics and Baseline Characteristics

The screening demographics and baseline characteristics including age, sex, race, ethnicity, height, body weight, body mass index, and screening eGFR will be listed.

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) x body surface area (BSA)

Summary tables by renal function and timepoint will be provided for all eGFRs based on the safety population.

9.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to dosing. Concomitant medication will be defined as medication that starts during or after dosing or starts but does not end prior to dosing.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version March 2024 (or later if a new version is issued during the study; see the data management plan [DMP] for more details). Prior and concomitant medications will be listed.

9.5. Pharmacokinetic Assessments

9.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of avacopan and its metabolite M1 using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.3.5 or higher):

Parameter	Units[a]	Definition
AUC_{last}	h*ng/mL	area under the plasma concentration-time curve from time zero to time of last quantifiable concentration[b]
AUC_{0-48}	h*ng/mL	area under the plasma concentration-time curve from time zero to 48 hours postdose[b]
AUC_{inf}	h*ng/mL	area under the plasma concentration-time curve from time zero extrapolated to infinity[b, c]
$\%AUC_{extrap}$	%	percentage of area under the plasma concentration-time curve due to extrapolation from last quantifiable concentration to infinity
C_{max}	ng/mL	maximum observed plasma concentration
t_{max}	h	time of the maximum observed concentration
t_{last}	h	time of last quantifiable concentration

$t_{1/2}$	h	apparent plasma terminal elimination half-life
f_u	NA	fraction of unbound drug; reported as the arithmetic mean where measured at two time points (i.e., for Group 2, Period 1)
CL/F	L/h	apparent clearance (avacopan only)
V_z/F	L	apparent volume of distribution during the terminal phase (avacopan only)

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Area under the concentration-time curves will be calculated using the linear trapezoidal linear interpolation rule.
[c] Based on the last observed quantifiable concentration.
NA = Not applicable.

The following PK parameters will be determined from avacopan and M1 concentrations in plasma samples collected during dialysis; samples are to be collected pre-dialyzer (referred to as arterial) and/or post-dialyzer (referred to as venous) from Group 2 subjects receiving hemodialysis in Period 1, where possible:

Parameter	Units[a]	Definition
$AUC_{pre\text{-}dialyzer}$	h*ng/mL	area under the plasma concentration-time curve from time zero (just prior to the start of hemodialysis on Day 1) to the end of hemodialysis, as determined from samples collected pre-dialyzer[b]
$AUC_{post\text{-}dialyzer}$	h*ng/mL	area under the plasma concentration-time curve from time zero (just prior to the start of hemodialysis on Day 1 and Day 3) to the end of hemodialysis, as determined from samples collected post-dialyzer[b]
ER_D	%	extraction ratio during hemodialysis, calculated as $100*((AUC_{pre\text{-}dialyzer} - AUC_{post\text{-}dialyzer})/AUC_{pre\text{-}dialyzer})$, where samples for pre- and post- dialyzer are sampled before and after the dialyzer at the following times on Day 1: 0, 0.5, 1, 2, 3h, and immediately after the end of dialysis. Negative ERD results to be reported as 0.

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Area under the concentration-time curves will be calculated using the linear trapezoidal linear interpolation rule.

The following PK parameters will be determined where possible from the dialysate concentrations of avacopan and M1 from subjects in Group 2, on Period 1, Day 1:

Parameter	Units	Definition
Ae_d	mg	amount of analyte recovered in dialysate
fe_d	NA	fraction of dose recovered in dialysate
CL_D	L/h	hemodialysis clearance of drug from plasma

Abbreviations: NA = Not applicable.

Additional PK parameters may be determined where appropriate.

PK analysis will be carried out where possible using actual dose administered (mg) and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

9.5.1.1. Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each subject will be defined by visual inspection. Generally, the first point at which there is no systematic deviation from the log-linear decline in concentrations will be selected as the start time to include only the apparent terminal elimination phase in the slope selection.

The apparent terminal elimination rate constant (λ_z) will only be calculated when a reliable estimate can be obtained using at least 3 data points, preferably not including C_{max}, and the coefficient for determination of exponential fit (R^2) of the regression line is ≥0.8. Parameters requiring λ_z for their calculation (eg, AUC_{inf}, $t_{1/2}$, CL/F, and V_z/F) will only be calculated if the R^2 value of the regression line is ≥0.8.

The following regression-related diagnostic PK parameters will be determined, when possible:

Parameter	Units	Definition
λ_z	1/h	apparent terminal elimination rate constant
λ_z Upper	h	end of exponential fit
λ_z Lower	h	start of exponential fit
λ_z N	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2	NA	coefficient for determination of exponential fit

Abbreviations: NA = Not applicable

Where possible, the span of time used in the determination of λ_z (ie, the difference between λ_z Upper and λ_z Lower) should be ≥2 half-lives. If the λ_z Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the CSR.

9.5.1.2. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only

3 consecutive concentrations, at least 1 should follow C_{max}. An exception may be made for metabolites, where C_{max} may be the last timepoint.

If the extrapolated area is >20%, AUC_{inf} (and derived parameters) may be excluded from the summary statistics and statistical analysis at the discretion of the sponsor or PK'ist.

If AUC_{inf} cannot be determined reliably for the majority of subjects, an alternative AUC measure, such as AUC to a fixed timepoint or AUC_{last}, may be used in the statistical analysis.

9.5.1.3. Calculation of Avacopan and M1 Dialysate Parameters

The amount of the analyte recovered (Ae) in dialysate (Ae_d) as avacopan and M1 for each collection interval (t_1-t_2) will be calculated as the product of analyte concentration and dialysate volume. Where only sample weight is supplied, a specific gravity of 1 g/mL will be assumed, and it will be considered equivalent to volume. If necessary, dialysate volume at each time point may be calculated using the flow rate and the actual elapsed time from start of dialysis; if this approach is utilized, it will be described in report.

A total cumulative $Ae_{x\text{-}y\ h}$ will be calculated by summing the $Ae_{t1\text{-}t2}$ values over the x-y h interval, where x = the start of the collection time interval and y = end of the last collection time interval.

The fraction of the dose administered recovered as avacopan over the time interval t1 to t2 in dialysate (fe_d) will be calculated for each collection interval as follows:

$fe_{t1\text{-}t2} = (Ae_{t1\text{-}t2} / \text{dose}) \times 100$

The $fe_{t1\text{-}t2}$ excreted as M1 will be calculated for each collection interval as follows:

$fe_{t1\text{-}t2} = (Ae_{t1\text{-}t2}\ \text{M1} / [\text{parent dose} \times (\text{MW of M1} / \text{MW of avacopan})]) \times 100$

MW avacopan: 581.64 g/mol

MW M1: 597.65 g/mol

Cumulative $fe_{0\text{-}x}$ will be calculated by summing the $fe_{t1\text{-}t2}$ values over the 0-x h period in the same manner as cumulative $Ae_{0\text{-}x}$.

Dialysate clearance (CL_D) will be calculated for avacopan and M1 over the interval of hemodialysis (approximately 4 to 8 h after Day 1 drug administration for Group 2, Period 1) according to the following formula:

$CL_D = Ae_d / AUC_{pre\text{-}dialyzer}$

9.5.1.4. Criteria for Handling Concentration Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first quantifiable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a predose plasma concentration is missing, it will be set to zero by default within Phoenix WinNonlin.

Dialysate concentrations that are BLQ will be set to zero for the calculation of $Ae_{t1\text{-}t2}$.

9.5.1.5. Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable predose concentration value in the first treatment period will be considered anomalous and set to missing for the PK analysis. This will be set to 0 by default in Phoenix WinNonlin.

If the predose concentration is >5% of C_{max} in the second treatment period, all PK concentration and parameter data will be excluded from the summary statistics and statistical analysis for that period.

9.5.2. Presentation of Pharmacokinetic Data

Summary tables, arithmetic mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by renal function group and time postdose will be provided for plasma PK concentrations. All figures will be produced on both linear-linear and linear-logarithmic scales. The +SD bars will only be displayed on the linear--linear scale. Nominal scheduled times will be used in the mean figures and actual elapsed times will be used in the individual figures and by-subject plots.

Summary tables by renal function group and time postdose will also be provided for protein binding results.

Summary tables by renal function group will be provided for all PK parameters, with the exception of diagnostic regression-related PK parameters. Separate summary tables by renal function and time interval will be provided for excretion parameters, cumulative excretion parameters and dialysate parameters.

A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times the median t_{max} or diarrhea within 24 hours of dosing.

If the actual time of sample collection deviates from the nominal time by more than ±20%, the plasma concentration will be flagged and excluded from the summary statistics. Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

Individual plasma concentrations of avacopan and its metabolite M1 will be listed by renal function group, subject, period (for Group 2), and nominal time point.

Plasma concentration data will be summarized by renal function group and period at nominal time points using the number of subjects (N), n, arithmetic mean, arithmetic CV, SD, geometric mean, geometric CV, median, minimum and maximum as appropriate.

For plasma concentration data the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, geometric mean and CV% of geometric mean will be reported as not calculated (NC).

For PK parameters the following rule will apply:

- Geometric mean and coefficient of variation will not be calculated for t_{last} or t_{max}.

9.5.3. Pharmacokinetic Statistical Methodology

A statistical analysis will be conducted to investigate the renal impairment effect on the PK of avacopan by comparing ESRD (off-HD) (test renal functions) to normal renal function (reference renal function).

The hypothesis testing will be 2-sided and carried out on 0.1 significance level.

A scatterplot (only include normal renal function and ESRD [off-HD]) of the natural log (ln)-transformed[5] $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}48}$, $AUC_{0\text{-inf}}$, and C_{max} versus baseline eGFR (mL/min/1.73m^2 with the linear regression[6] line and 90% confidence interval (CI) fitted, will be provided. The Spearman's rank correlation coefficient and p-value will also be calculated.

The natural log (ln)-transformed $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}48}$, $AUC_{0\text{-inf}}$, and C_{max} will be analyzed using a mixed model.[7] The model will include renal function group and sex as fixed effects, body weight as a covariate, and subject as a random effect.

For each PK parameter separately, the least squares mean (LSM) for each renal function, difference in LSMs between the test and reference renal functions, and corresponding 90% confidence interval (CI) will be calculated; these values will then be back transformed to give the geometric least square mean (GLSM), ratio of GLSMs, and corresponding 90% CI.

Similar analysis will be conducted to compare the effect of hemodialysis on the PK of avacopan, ESRD (on-HD) (test renal function) will be compared to ESRD (off-HD) (reference renal function). The model will include renal function group and period as fixed effects, and subject as a random effect.

Similar analysis may also be conducted to investigate the renal impairment effect on the PK of M1.

Examples of the SAS code that will be used are as follows:

9.6. Safety and Tolerability Assessments

9.6.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0 (or higher if a new version is issued during the study; see the DMP for more details). All AEs will be assigned a severity grade using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.00.

A TEAE will be defined as any AE that starts on or after the first dose of investigational product and up to EOS.

A treatment related TEAE will be defined as a TEAE with a relationship of related to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of dosing (most recent dose for group 2) for TEAEs only.

A separate listing will be provided for the other safety findings/special situations (medication errors, misuse, or abuse).

The frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by renal function group
- TEAEs by severity and renal function group
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by renal function group
- Treatment-related TEAEs by severity and renal function group

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and renal function group
- Preferred term and renal function group

For the AE data the following rules will apply:

- For the derivation of treatment-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to the first dose.
- For the derivation of treatment-related status (applicable to TEAEs only): If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.
- For the derivation of onset time (applicable to TEAEs only): If the start date/time of a TEAE is missing, onset time will not be calculated. If the start date/time of a TEAE is

incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of dosing is 01MAY2019/08:00 and recorded start date/time of a TEAE is 03MAY2019, then the minimum possible onset time will be calculated by assuming a TEAE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing). If the start date of a TEAE is the same as the date of dosing but the start time of a TEAE is missing, an onset time will be presented as '≥00:00:01'. Any clock changes will be accounted for in the derivation.

- For the derivation of duration (applicable to all AEs): If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming an AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing). Any clock changes will be accounted for in the derivation.

- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category.

- For the calculation of TEAE summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as separate TEAE under each severity category.

9.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters, and their changes from baseline, will be listed, as applicable; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

Summary tables and spider plots by renal function group and timepoint will be provided for clinical chemistry, and hematology parameters, and their changes from baseline, as applicable.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, all calculations, and presentation in the figures, <x and ≤x values will be set to lower limit of quantification, whereas >x and ≥x values will be set to x.

9.6.3. Vital Signs Parameters

All vital signs parameters, and their changes from baseline, will be listed, as applicable; any value outside the clinical reference range will be flagged.

Summary tables and spider plots by renal function group and timepoint will be provided for all vital signs parameters, and their changes from baseline, as applicable.

9.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters, and their changes from baseline, will be listed; any value outside the clinical reference range will be flagged.

Summary tables and spider plots by renal function group and timepoint will be provided for all 12-lead ECG parameters, and their changes from baseline.

An outlier analysis will be performed for QT interval corrected for heart rate using Fridericia's formula (QTcF). The analysis will include all individual original, repeat, and unscheduled postdose values.

The maximum postdose values will be summarized by renal function group according to the following categories:

- ≤450 ms
- >450 and ≤480 ms (all instances flagged in the listing)
- >480 and ≤500 ms (all instances flagged in the listing)
- >500 ms (all instances flagged in the listing)

The maximum increases from baseline will be summarized by renal function group according to the following categories:

- ≤30 ms
- >30 and ≤60 ms (all instances flagged in the listing)
- >60 ms (all instances flagged in the listing)

9.6.5. Child-Pugh Score (Group 2)

Child-Pugh assessment data will be listed.

9.6.6. Hepatotoxicity

If a participant experiences elevated laboratory parameters, as detailed in Appendices 7 and 8 of the protocol, additional tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

Any additional vital signs or laboratory data recorded due to the potential drug-induced liver injury (DILI) will be listed. Values outside the reference ranges will be flagged on the individual subject data listings. The subjects' substance use and liver disease history data will be listed. Results from any hepatic monitoring procedures, such as a liver imaging or biopsy, will be listed, if performed.

Results from a echocardiogram or multigated acquisition (MUGA) scan will also be listed, if performed.

9.6.7. Other Assessments

Medical history will be listed.

All other safety and tolerability assessments not detailed in the above sections will be listed only.

9.6.8. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim analyses are planned for this study.

11. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol-specified analyses.

12. REFERENCES

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13. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.

NA = not applicable