STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of the NOX1/4 Inhibitor Setanaxib in Patients with Alport Syndrome
Protocol Number:	GSN000500
Protocol Version/Date:	3.0/ 22 April 2024
Investigational Product:	Setanaxib
Sponsor:	Calliditas Therapeutics Suisse SA Chemin des Aulx 16 1228 Plan-les-Ouates Switzerland Calliditas Therapeutics Suisse SA is a subsidiary of Calliditas Therapeutics AB
SAP Version/Date:	V1.0/ 21 JULY 2025

SIGNATURE PAGE

Protocol Title:	A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of the NOX1/4 Inhibitor Setanaxib in Patients with Alport Syndrome
Protocol Number:	GSN000500
SAP Version/Date:	V1.0/21 JULY 2025

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
PPD PPD ***Senior Biostatistician*** ***Medpace, Inc.***	
PPD PPD ***Medical Director*** ***Medpace, Inc.***	
PPD PPD ***Principal Biostatistician*** ***Calliditas Therapeutics AB***	

VERSION HISTORY

Version	Version Date	Description
1.0	21 July 2025	Final Version

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical therapeutic chemical
BQL	Below quantification limit
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case report form
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
eGFR	Estimated glomerular filtration rate
ET	Early termination
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measurement
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
RAS	Renin-angiotensin system
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System organ class
TEAE	Treatment-emergent adverse event
TFLs	Table, figures and listings
UPCR	Urine protein to creatinine ratio
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number GSN000500. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective and Endpoint

Primary	
Objective	**Endpoint**
To evaluate the safety and tolerability of setanaxib compared to placebo in patients with Alport syndrome.	• Percentage of patients with treatment-emergent serious adverse events (SAEs); and • Percentage of patients with treatment-emergent adverse events of special interest (AESIs), i.e., anemia.

2.1.2 Safety Objectives and Endpoints

Safety	
Objective	**Endpoint**
To assess the effect of setanaxib on vital signs compared to placebo.	Percentage of patients with clinically significant changes in heart rate and blood pressure.
To evaluate the effect of setanaxib on 12-lead ECGs compared to placebo.	Percentage of patients with clinically significant changes in 12-lead ECG.
To evaluate the effect of setanaxib on physical examinations compared to placebo.	Percentage of patients with clinically significant changes in physical examination.
To evaluate the effect of setanaxib on clinical laboratory parameters compared to placebo.	Percentage of patients with clinically significant changes in hematology, serum chemistry, urinalysis, and thyroid function.
To evaluate the effect of setanaxib on hearing compared to placebo.	Percentage of patients with clinically significant changes in hearing audiometric testing (bone- and air-conduction).

2.1.3 Secondary Objectives and Endpoints

Secondary	
Objective	**Endpoint**
To assess the effect of setanaxib on urine protein to creatinine ratio (UPCR) compared to placebo.	• The ratio of UPCR at 24 weeks compared to baseline; and • Percentage of patients with a 25% reduction in UPCR at 24 weeks, compared to baseline.
To assess the effect of setanaxib on estimated glomerular filtration rate (eGFR) compared to placebo.	The ratio of eGFR at 24 weeks compared to baseline.
To assess the plasma exposure of setanaxib and its active metabolite GKT138184.	Pre-dose and post-dose plasma concentrations of setanaxib and GKT138184 at a steady state. The following PK properties will be calculated: • Area under the concentration-time curve over 24 hours at steady state ($AUC_{0\text{-}24\text{-}ss}$); • Minimum plasma concentration at steady state ($C_{min\text{-}ss}$); and • Maximum plasma concentration at steady state ($C_{max\text{-}ss}$).

2.1.4 Exploratory Objectives and Endpoint

Exploratory	
Objective	**Endpoint**
To assess the effect of setanaxib on biomarkers of inflammatory pathways, fibrosis, or disease progression compared to placebo.	Change from baseline at 24 weeks in the following parameters: **Urine-based biomarkers:** MCP-1/Cr, EGF, Cystatin-C, TGF-β1, NGAL, KIM-1, B2-M, and osteopontin; **Serum-based biomarkers:** MCP-1, BUN, Cystatin-C, B2-M, TGF-β1, CCL3, IL1B, TIMP1, TNFα, VEGF, and YKL-40; and **Plasma-based biomarkers:** NGAL, MMP9, SPP1, and CCN2.
Potential optional future analysis to assess the effect of setanaxib on additional biomarkers of inflammatory pathways, fibrosis, or disease progression compared to placebo.	Where allowed per local regulations, IEC approval and patient consent (and assent, where applicable), optional exploratory blood and urine samples will be collected. The samples will be used to assess additional biomarkers of Alport syndrome, inflammatory

	pathways, fibrosis, or disease progression compared to placebo. This may include, but will not be limited to, ADMA, TIMP-2, IGFBP7, and COL1A1.

2.2 Study Design

2.2.1 Overview

This is a randomized, double-blind, placebo-controlled Phase 2a study assessing oral setanaxib in patients with Alport syndrome. The safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of setanaxib will be assessed over 24 weeks of treatment. Patients are required to have persistent proteinuria (UPCR ≥90 mg/mmol [0.8 g/g]) despite treatment with a stable dose of RAS (Renin-angiotensin system) inhibitor therapy (ACEis and/or ARBs) at the maximum allowed dose or maximum-tolerated daily dose for at least 8 weeks prior to consent/assent. Patients should remain on their regimens of RAS inhibitors for the whole duration of the study.

This study aims to assess the safety of setanaxib as an add-on treatment to current RAS inhibitor treatment, in patients with Alport syndrome at risk of disease progression and with limited treatment options available. The double-blind, placebo-controlled design is chosen to provide safety data and preliminary efficacy for setanaxib in addition to the standard of care treatment in this patient population with a standard of care (with placebo) arm as reference. This will help to guide the design of further Phase 2/3 studies of setanaxib in Alport syndrome.

The study is planned to enroll and treat approximately 18 patients, eligible patients will be randomized in a 2:1 ratio, respectively to the following treatment groups:

- Setanaxib group:
    - For patients aged 12 to 17 years: 1200 mg/day (800mg morning + 400mg evening) for 24 weeks.
    - For patients aged ≥18 years: 1600mg/day (800mg twice daily) for 24 weeks.
- Placebo group: matching placebo tablets daily.

Up to 6 patients should be in the age group of 12 to 17 years old at the time of consent/assent, and a minimum of 12 patients should be ≥18 years of age. To ensure balance among treatment groups, randomization will be stratified by age group (12 to 17 year of age and ≥18 years of age) at the time of consent/assent.

Patients must take the first dose of study drug in the presence of site staff during Study Visit 3 (Day 1). Similarly, the morning dose at the week 2, week 12, and week 24 visit should be taken at the study site, to allow for proper PK sampling.

The estimated study duration for an individual patient is up to approximately 32 weeks. Following a 4-week screening period (Note: the screening period may be longer than 4 weeks, as needed, to complete genetic testing), patients will receive setanaxib or placebo for a 24-week treatment period, followed by a 4-week follow-up period.

Refer to Table 2 Schedule of Procedures in the protocol for a complete list of procedures to be completed at each study visit.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the Case Report Form (CRF). Unscheduled and early termination (ET) visits will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1 (Visit 3)	1	NA	NA
Week 2 (Visit 4)	15	2	29
Week 6 (Visit 5)	43	30	64
Week 12 (Visit 6)	85	65	106
Week 18 (Visit 7)	127	107	148
Week 24 (EOT) (Visit 8)	169	149	183
Week 28 (Safety FUP)	197	184	197+

For each analysis visit, if a scheduled visit occurs within the analysis day window, then the measurement from this scheduled visit will be used as the measurement for the analysis visit. If no scheduled visit occurs within the analysis day window, the unscheduled measurement closest to the target day will be used. If measurements are equidistant to the target day, the latter will be used. If no visits occur within the analysis day window, the measurement for this analysis visit will be treated as missing.

3.1.3 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study drug, unless otherwise stated.

Liver tests (Alanine aminotransferase, Aspartate aminotransferase, and total bilirubin) baseline values are determined by averaging the values obtained at screening visits 1 and 2 to obtain the arithmetic mean.

UPCR and eGFR baseline values are defined as the geometric mean of 2 assessments prior to randomization.

3.1.4 Change and Percent Change from Baseline

Change from baseline will be derived as visit value minus baseline value. Percent change from baseline will be defined as [(visit value minus baseline value) divided by baseline value] multiplied by 100. In case where baseline value equal 0, baseline value of 0.001 will be used to calculate percent change from baseline.

3.1.5 Summary Statistics

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.1.6 Hypothesis Testing

No formal hypothesis testing will be conducted.

3.1.7 Evaluation of Site Effect

The number of patients at each site is expected to be small. Site effect will not be considered.

3.1.8 Handling of Dropouts and Missing Data

Date Values

In cases of incomplete dates (e.g., AE, concomitant medication, and medical history start and/or stop dates), the missing component(s) will be assumed as the most conservative value possible. For example, if the start date is incomplete, the first day of the month will be imputed for the missing day and January will be imputed for the missing month. If a stop date is incomplete, the last day of the month will be imputed for the missing day and December will be imputed for the missing month. If it is not possible to determine whether an AE is or is not treatment emergent due to completely or partially missing dates, the dates will be imputed in a conservative way so that the AE will be considered as treatment emergent, i.e., starting in the on-treatment period. Incomplete start and stop dates will be listed as collected without imputation.

In cases of incomplete date for Alport syndrome genetic testing or Alport diagnosis, the 15th day of the month will be imputed for missing day and June will be imputed for missing month.

Date imputation will only be used for computational purposes such as treatment-emergent status. Actual date values, as they appear in the original CRFs, will be presented within the data listings.

Non-Date Values

For the secondary endpoint, to assess the effect of setanaxib on eGFR compared to placebo, missing values will be imputed using multiple imputation methods (see Section 3.5.1). For the analyses of all other endpoints, no imputation will be made for missing values. Safety data will be used according to availability, with no imputation for missing data.

3.1.9 Laboratory Values Above or Below Limits of Quantification

For continuous laboratory values less than the lower limit of quantification (LLQ), half of the lower limit value (i.e. LLQ/2) will be used in the analysis. For values greater than the upper limit of quantification (ULQ), the upper limit value (i.e. ULQ) will be used in the analysis.

3.2 Analysis Populations

3.2.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will include all patients who are randomized into the study.

3.2.2 Safety Analysis Set (SAS)

The Safety Analysis Set (SAS) is defined as all randomized patients who take at least 1 dose of the study drug.

3.2.3 Pharmacokinetic (PK) Analysis Set

The Pharmacokinetic Analysis Set will be defined as all randomized patients who take at least 1 dose of the study drug and have at least one measured concentration, including any BQL, at a scheduled PK time point post-dose.

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Counts and percentages of patients who were screened (signed informed consent), discontinued early during screening (screen failures), randomized and received at least one dose of study drug will be summarized in total based on all screened patients. Reasons for early discontinuation will also be summarized.

Counts and percentages of patients who were randomized, received at least one dose of study drug, discontinued early from the study, and completed the study will be summarized by treatment and in total based on all randomized patients. Reasons for early discontinuation will also be summarized.

3.3.2 Protocol Deviations

Protocol deviations will be identified based on clinical data as defined in the Protocol Deviation Plan, where all protocol deviations will be defined as either CSR reportable or non-CSR reportable. The CSR reportable protocol deviations will be categorized and separated by treatment group. The CSR reportable deviations will include all randomized patients using counts and percentages.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized by treatment and in total based on all randomized patients. Reasons for exclusion from each analysis population will also be summarized.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment and overall, for the FAS:

- Age (years) and age categories (12 to 17, ≥18 years) at the time of consent
- Sex
- Childbearing potential
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)

- Time since genetic diagnosis
- Gene and inheritance pattern
- Time since clinical diagnosis.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version v26.1. Counts and percentages of patients with medical history by system organ class (SOC) and preferred term (PT) will be summarized by treatment group and in total based on randomized patients.

3.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary version March 2023. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).Counts and percentages of patients taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment group and in total based on the SAS.

3.3.7 Study Drug Exposure and Compliance

Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Note that the exposure calculation is intended to describe the length of time a patient was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by treatment group based on the SAS with descriptive statistics and with counts and percentages of patients with exposure in the following categories:

- <4 weeks
- 4 - <8 weeks
- 8 - <12 weeks
- 12 - <16 weeks
- 16 - <18 weeks
- 18 - <24 weeks
- ≥24 weeks

Percent compliance to the study drug will be calculated using the following formula:

$$\frac{\#\ tablets\ dispensed - \#tablets\ returned}{\#\ expected\ tablets\ taken} \times 100$$

If study drug is not returned, the number of tablets returned will be considered 0 for the compliance calculation. The expected tablets taken will be calculated as the earliest date between the end of treatment date and the date of early termination – the date of first dose +1 (multiply by 3 if patient 12 to 17 years old and multiply by 4 if patient ≥18 years old).

Percent compliance to the study drug will be summarized by treatment group based on the SAS with descriptive statistics and with counts and percentages of patients with compliance in the following categories:

- <80%
- 80-120%
- >120%

3.4 Safety Assessment

The SAS will be the primary population for the safety analysis.

3.4.1 Adverse Events -Primary Endpoint

The primary endpoints are:

- Percentage of patients with treatment-emergent SAEs;
- Percentage of patients with treatment-emergent AESIs.

All adverse events (AEs) will be coded to SOC and PT using MedDRA version v 26.1. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug and up to 30 days post-last dose of study drug. Pre-treatment AEs are defined as AEs that started prior the first dose of study drug and post-treatment AEs are defined AEs that started more than 30 days after last dose of study drug.

AESI is defined as CTCAE Grade ≥2 anemia, defined as hemoglobin <10g/dL, and absolute reticulocyte counts of <50% of the baseline value (Screening Study Visit 2), which are confirmed by repeat testing.

Estimand

To assess the primary endpoint for treatment-emergent SAE, the safety estimand is defined by the following key attributes, according to the framework provided in International council for Harmonization (ICH) E9 (R1) [1]:

- **Treatment**: Setanaxib treated patients compared to placebo
- **Population**: The SAS comprised of all randomized patients who took at least 1 dose of the study drug.
- **Variable of interest**: Treatment-emergent SAEs
- **Intercurrent event handling**: All events will be counted regardless of early discontinuation of treatment, up to 30 days post-last dose of study drug
- **Summary measures**: Count and percentage of patients experiencing SAEs during the Treatment Period up to 30 days post-final dose.

The number and percentage of patients with SAEs will be presented by treatment group, system organ class (SOC), and preferred term (PT). Similar summaries will be presented for treatment emergent AESIs. The number and percentage of patients with study drug related treatment-emergent SAEs and AESIs will be presented by treatment group, SOC and PT.

3.4.2 Other Adverse Events

The number and percentage of patients by treatment group, SOC and PT will be presented for the following:

- Any AEs
- Any TEAEs (overall and by maximum severity)
- Any TEAEs with CTCAE Grade ≥3
- Any study drug related TEAEs (overall and by maximum severity)
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to discontinuation of study
- Any AEs leading to death

The AEs described above will be summarized separately by system organ class and preferred term. Listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study drug.

3.4.3 Clinical Laboratory Tests

Clinical laboratory evaluations (including serum chemistry, hematology, endocrinology/thyroid function, and urinalysis) will be obtained as indicated in Table 2 Schedule of Procedures in the protocol and processed by a central laboratory. A list of laboratory tests to be performed are included in Appendix B in the protocol.

Laboratory values and changes from baseline will be presented at each visit and baseline by laboratory test. In addition, the number and percentage of patients with parameters outside the normal range (below the lower limit of normal (<LLN) or above the upper limit of normal (>ULN)) will be presented by visit and treatment group. The count and percentage of patients with clinically significant changes will be tabulated by treatment group. Clinically significant changes will be identified as any TEAEs related to significant change in laboratory test. Medical review of AE will be performed by Medpace to identify any clinically significant changes. The provided classifications will be used in analysis.

3.4.4 Vital Signs

Vital signs, including systolic and diastolic blood pressure and heart rate, will be measured at timepoints specified in Table 2 Schedule of Procedures in the protocol.

Vital signs will be summarized descriptively, including the change and percent change from baseline at each visit by treatment group and overall. Number and percentage of patients with any clinically significant change from baseline will be summarized at each visit by treatment group.

3.4.5 Electrocardiograms

A standard 12-lead ECG will be performed at timepoints specified in Table 2 Schedule of Procedures in the protocol. Continuous ECG parameters will be summarized with descriptive statistics by treatment group for each visit. The number and percentage of patients with clinically significant changes will be tabulated by treatment group. In addition, a summary of QTcF measurements will be summarized by treatment group for the following predefined criterion:

- QTcF>450 for male

- QTcF>470 for female.

QTcF will be calculated according to the following formula:

$$QTcF = \frac{QT}{\sqrt[3]{RR/1000}}$$

3.4.6 Physical Examinations

A physical examination will be performed at timepoints specific in Table 2 Schedule of Procedures in the protocol.

Physical examination parameters will be recorded as normal, abnormal or not done. Abnormal values will be assessed as clinically significant or not clinically significant. Count and percentages for physical parameters will be summarized by treatment group and in total. The number and percentage of patients with clinically significant changes from baseline will be tabulated by treatment group.

3.4.7 Hearing Examination

A hearing examination will be performed at timepoints specific in Table 2 Schedule of Procedures in the protocol.

Hearing examination, including bone- and air-conduction, will be recorded as no change from baseline, no significant change from baseline or clinically significant change from baseline. All values will be summarized by treatment group and by visit. The number and percentage of patients with clinically significant change from baseline will be tabulated by treatment group.

3.5 Efficacy Assessment

Efficacy data will be summarized using the FAS Population.

3.5.1 Urine Protein to Creatinine Ratio (UPCR)

The ratio of UPCR at 24 weeks compared to baseline will be analyzed using a mixed model repeated measurement (MMRM) approach and incorporate UPCR data from 6 weeks, 12 weeks and 24 weeks. Baseline and 24 weeks UPCR will be calculated as the geometric mean of 2 assessments and log-transformed prior to inclusion in the analysis model. The model will include fixed effects for treatment, visit, and treatment by visit interaction, along with the log-transformed baseline value as a covariate. Patient will be included as a random effect. An unstructured covariance matrix will be used to model the within patient correlation of data. If the model does not converge, other covariance structures may be considered. The Kenward-Roger approximation to estimate the degrees of freedom will be used. Model assumptions will be assessed using residual plots (such as q-q plots, histograms) and, if not met, other data transformations or non-parametric approaches may be considered. The LS mean and 2-sided 95% confidence intervals will be estimated.

The analysis will be implemented using SAS® Proc Mixed. Sample SAS code below:

```
*************************************************************************************************************
** TRT          = treatment group
** VISIT        = Visit name
** USUBJID      = Patient ID
** CHG_UPCR     = Change of log-UPCR at each visit from baseline
** BASE         = log-baseline UPCR
```

```
**********************************************************************************************************

proc mixed data=data;
  class TRT USUBJID VISIT;
  model CHG_UPCR = TRT VISIT BASE TRT*VISIT/ddfm=kr;
  repeated VISIT/ sub = USUBJID type = un;
  estimate 'Week 24 effect' TRT -1 1;
  lsmeans TRT*VISIT/cl pdiff;
run;
```

The proportions of patients achieving a 25% reduction in UPCR at 24 weeks from baseline in the setanaxib group will be compared to placebo group using a Fischer's exact test.

3.5.2 Estimated Glomerular Filtration Rate

The eGFR data will be log-transformed prior to analysis. Data included at baseline and at 24-weeks will be the log of the geometric mean of 2 assessments, collected at least 1 week apart. eGFR data are such that it is possible there will be a small number of patients with extreme outlying data. Therefore, the analysis of the ratio of eGFR at 24 weeks compared to baseline will be based on a Robust Regression approach. In order to handle missing data, the analysis will be performed over 3 phases: an imputation, analysis, and pooling phase, as described below.

Imputation phase

During the imputation phase, missing data for eGFR will be imputed 25 times to generate 25 datasets. Multiple imputation will be performed in as follows:

- If missing data follows non-monotone pattern:
  (a) First, non-monotone missing values will be imputed to create a monotone missing pattern.
  (b) Then, the remaining monotone missing values will be imputed using a regression method sequentially imputing data across successive visits.
- If missing data follows monotone pattern:

  (c) Monotone missing values will be imputed using a regression method sequentially imputing data across successive visits.

Sample SAS code below:

```
**********************************************************************************************************
** TRT                  = treatment group
** VAL2, VAL6, VAL12, VAL18, VAL24a, VAL24b = eGFR value at 2, 6, 12, 18
                                              and 24 weeks, respectively
** SCR1               = Screening Visit 1 eGFR value
** SCR2               = Screening Visit 2 eGFR value

**********************************************************************************************************

   (a)      proc mi data=data nimpute=25 seed=483794 out=mono;
               mcmc chain=single impute=monotone;
               by TRT;
               var SCR1 SCR2 VAL2 VAL6 VAL12 VAL18 VAL24a VAL24b;
            run;
```

```
(b)      proc mi data=mono nimpute=1 SEED=2019301 OUT=imputed;
            class TRT;
            var SCR1 SCR2 VAL2 VAL6 VAL12 VAL18  VAL24a VAL24b;
            monotone regression;
            by _imputation_;
         run;

(c)     proc mi data=data nimpute=25 SEED=2019301 OUT=imputed;
            by TRT;
            monotone regression;
            var SCR1 SCR2 VAL2 VAL6 VAL12 VAL18 VAL24a VAL24b;
        run;
```

Analysis phase

In the analysis phase, the ratio of eGFR at 24 weeks compared to baseline will be calculated for each patient within each imputed dataset. The ratio of eGFR of the log-transformed data will be analysed using Robust Regression with independent variables of treatment and log-transformed baseline eGFR. M-estimation will be used with Huber weights. Sample SAS code below:

```
*************************************************************************************************************
** TRT = treatment group
** CHG = Change of log-eGFR baseline ratio at 24 weeks
** BASE = log-baseline eGFR
*************************************************************************************************************

proc robustreg data=chg method=m (wf=huber) outest=chg1 covout;
  by _imputation_;
  class TRT;
  model CHG = BASE TRT;
run;
```

Pooling phase

In the pooling phase, the results from these 25 analyses will be combined using Rubin's method to construct the treatment estimate using the parameter estimates and associated standard errors. Sample SAS code below:

```
proc mianalyze data=chg1;
   modeleffects estimate;
   stderr stderr;
   ods output ParameterEstimates=est2;
run;
```

If the multiple imputation approach is such that the model convergence is questionable and the given parameter estimates cannot be obtained, then the ratio of eGFR at 24 weeks compared to baseline will be evaluated using similar MMRM model as for UPCR, otherwise, MMRM analysis will be considered as sensitivity analysis.

3.6 Exploratory Assessment

Blood and urinary samples for exploratory biomarkers will be collected at visits as specified in Table 2 Schedule of Procedures in the protocol. Exploratory biomarkers parameters will be summarized with descriptive statistics by treatment group for each visit.

3.7 Pharmacokinetic Assessment

The PK Analysis Set will be used for PK analyses.

3.7.1 Sample Collections for Pharmacokinetic Analysis

PK samples will be collected at Week 2 (pre-dose and 1, 2, 3, 4, and 6 hours post-dose), at Week 12 (pre-dose), and at Week 24 (pre-dose).

The PK sampling windows are as follows:

- Pre-dose: within 90 minutes prior to dose;
- 1, 2, 3, and 4 hours post-dose: ±5 minutes; and
- 6 hours post-dose: ±15 minutes.

3.7.2 Handling Missing or Below the Lower Limit of Quantification Data

For PK concentration data, if the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged,In cases of missing pre-dose concentrations for each treatment on Day 1, the missing components may be assumed as zero. For the other cases beyond the first pre-dose, the missing data will not be imputed.

For the concentration summary and mean concentration plot preparation of each treatment, the following rules will be applied:

- Mean concentration at any individual time point will only be calculated if at least half of the subjects have valid values (i.e. quantifiable and not missing) at this time point for each treatment.
- In cases where a mean value is not calculated due to the above criterion not being met, the value will be set to “NC”.
- BLQ values will be set to zero.

3.7.3 Pharmacokinetic Concentration

Observed plasma concentrations of setanaxib and GKT138184, along with blood sampling dates and actual blood sampling time relative to last dose, will be listed by patient, actual treatment given and nominal sampling time. The listing would display the concentrations side-by-side together with the nominal time and actual time.

Observed plasma concentrations of setanaxib and GKT138184 will be summarized by actual treatment, nominal time point and analyte (setanaxib or GKT138184) using univariate statistics (mean, geometric mean, median, standard deviation, standard error of the mean, coefficient of variation, minimum, maximum and the number of available observations).

Individual plasma concentrations will be plotted by treatment on a linear and semi-log scale against actual sampling time points relative to dosing time. Mean (±SD) concentration will be plotted on a linear and semi-logarithmic scale against nominal time points by treatment, when available. LLOQ will be plotted as a reference line in both instances.

Individual and Mean (±SD) trough concentration will be plotted for each treatment group on linear and semi-log scale.

Actual sampling times that are outside the sampling time windows will be excluded from concentration summary and mean concentration plotting but will still be used in the calculations of PK parameters and individual concentration plotting.

Individual values for PK concentration data will be reported to the same level of precision as received from bioanalytical laboratory. For PK data, N will be reported as integer, CV% and geometric CV% will be reported with 1 decimal place, and all other summary statistics will be reported with 3 significant digits. Geometric mean and geometric CV% will be calculated excluding 0 values.

3.7.4 Pharmacokinetic Parameters

The derivation and summary of the pharmacokinetic parameters will be performed by the sponsor.

The PK parameters AUC(0-24)-ss, Cmin-ss and Cmax-ss will be derived for each individual patient using non-linear mixed effect methodology and prior PK knowledge of the compound, and summarized as appropriate. More details regarding the PK analysis analyses will be provided in a separate pharmacokinetic analysis plan. The pharmacokinetic analysis results will be reported separately from the main CSR. A summary of the methods and results will be reported in the main CSR. The pharmacokinetic analysis plan should be referred to along with this present SAP.

4 INDEPENDENT DATA MINITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will monitor the safety of patients over the course of the study. The IDMC will meet once or more during the patient enrollment period to examine the unblinded accumulated safety data. Patients, investigators, site staff and in general all personnel directly involved in the conduct of the study will remain blinded to the patients' treatment assignment until the completion of the study.

Details related to the IDMC responsibilities, authorities, and procedures will be documented in a IDMC charter which will be finalized prior the first patient being enrolled in the study.

5 ANALYSIS TIMING

5.1 Interim Analysis

No interim analysis is planned.

5.2 Final Analysis

After the database is locked, final analysis will be generated. Final tables, figures, and listings (TFLs) will be provided approximately 3 weeks after database lock. In addition to TFLs, SDTM (Study Data Tabulation Model) data and ADaM (Analysis Data Model) data along with associated files will be provided. Associated files may include annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There have been two changes from the protocol v3.0:

The first change is the clarification of the primary endpoint: only treatment-emergent serious adverse events will be included in the analysis of the primary endpoint.

The second change is the inclusion of MMRM analysis for the ratio of eGFR at 24 weeks compared to baseline, if the model convergence, from multiple imputation approach, is questionable and the given parameter estimates cannot be obtained.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

1. ICH E9 (R1). ICH Harmonised Guideline Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statisical Principles for Clinical Trials E9(R1). International Conference on Harmonisation [online], Available at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf