Statistical Analysis Plan

A Randomized, Multicenter, Double-blind, Parallel, Active-control Study of the Effects of Sparsentan, a Dual Endothelin Receptor and Angiotensin Receptor Blocker, on Renal Outcomes in Patients with Primary Focal Segmental Glomerulosclerosis (FSGS)

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STATISTICAL ANALYSIS PLAN, VERSION 4.0

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A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PARALLEL, ACTIVE-CONTROL STUDY OF THE EFFECTS OF SPARSENTAN, A DUAL ENDOTHELIN RECEPTOR AND ANGIOTENSIN RECEPTOR BLOCKER, ON RENAL OUTCOMES IN PATIENTS WITH PRIMARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

Investigational Medicinal Product:	Sparsentan
Product Code:	RE-021
Protocol Number:	021FSGS16010 (DUPLEX)
Developmental Phase:	Phase 3
Based On:	021FSGS16010 Protocol Amendment 6
Sponsor:	Travere Therapeutics, Inc. 3611 Valley Centre Drive, Suite 300 San Diego, CA 92130 USA

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This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
ACE	Angiotensin Converting Enzyme
ACEI	Angiotensin-Converting Enzyme Inhibitor
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AEOI	Adverse Event of Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARB	Angiotensin II Receptor Blocker
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
CMH	Cochran Mantel-Haenszel
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology
CNI	Calcineurin Inhibitor
COVID-19	Coronavirus Disease 2019
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of Variation
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
EQ-5D-5L	EuroQol, 5-dimension QOL instrument, version 5L
EQ-5D-Y	EuroQol, 5-dimension QOL instrument, version Youth
ESRD	End-Stage Renal Disease
FAS	Full Analysis Set
FPRE	FSGS Partial Remission Endpoint
FSGS	Focal Segmental Glomerulosclerosis
IAS	Interim Analysis Set
IQR	Interquartile Range
IWRS	Interactive Web Response System
KDQOL	Kidney Disease Quality of Life
KM	Kaplan-Meier
LS	Least Squares

Abbreviation	Term
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMF	Mycophenolate Mofetil
MMRM	Mixed-Model Repeated Measures
MNAR	Missing Not At Random
N	Total Sample Size
NCS	Not Clinically Significant
OLE	Open-label Extension
OLEFAS	Open-label Extension Full Analysis Set
PCS	Physical Component Summary
PedsQL	Pediatric Quality of Life Inventory
PK	Pharmacokinetic
PP	Per Protocol
PRO	Patient-Reported Outcome
PT	Preferred Term
QOL	Quality of Life
RAAS	Renin-Angiotensin-Aldosterone System
RRT	Renal Replacement Therapy
SD	Standard Deviation
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SEM	Standard Error of the Mean
SF-12	Short Form Health Survey
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SSR	Sample Size Reassessment
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
UP/C	Urine Protein/Creatinine Ratio
US	United States
VAS	Visual Analogue Scale
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the statistical methods and technical specifications for the analysis of data collected for the 021FSGS16010 (DUPLEX) protocol within the double-blind period of the study. Specifications for analysis of data from the open-label extension (OLE) period of the study at the time of interim analysis are also included. A separate SAP will be written to detail the analysis of OLE results at final analysis and study completion.

Any deviation from this plan will be documented in the clinical study report.

Protocol Revision Chronology:		
Amendment 6	01 December 2020	Amendment
Amendment 5	23 January 2020	Amendment
Amendment 3	06 June 2019	Amendment
Amendment 2	07 January 2019	Amendment
Amendment 1	26 June 2018	Amendment
Original Protocol Version 1.2	19 January 2018	Original v1.2
Original Protocol	15 December 2016	Original

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Efficacy Objective

The efficacy objective of the study is to determine the long-term nephroprotective potential of treatment with sparsentan as compared to an angiotensin receptor blocker in patients with primary and genetic focal segmental glomerulosclerosis (FSGS).

3.1.2. Safety Objective

The safety objective of the study is to assess the safety and tolerability of sparsentan by double-blind monitoring of safety endpoints.

3.1.3. Open-Label Objective

The open-label objective of the study is to assess the long-term efficacy, safety, and tolerability of open-label sparsentan in patients with FSGS.

3.2. Study Endpoints

3.2.1. Primary and Surrogate Efficacy Endpoints

The primary efficacy endpoint is the slope of estimated glomerular filtration rate (eGFR) over approximately 2 years of randomized treatment assessed at the final analysis. The slope of eGFR is evaluated following the initial acute effect of randomized treatment (ie, from Week 6 to Week 108; chronic slope over 2 years) in non-United States (US) countries and following initiation of randomized treatment (ie, from Day 1 to Week 108; total slope over 2 years) in the US.

The surrogate efficacy endpoint is the proportion of patients achieving the FSGS partial remission endpoint (FPRE), defined as urine protein/creatinine ratio (UP/C) ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline of the double-blind period in UP/C at Week 36 at the interim analysis.

3.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are assessed at the final analysis and are part of a hierarchical (gate-keeping) testing procedure.

The secondary efficacy endpoints in non-US countries are:

- The percent change from Week 6 in eGFR at Week 108
- The percent change in eGFR from baseline of the double-blind period to 4 weeks post-cessation of randomized treatment at Week 112
- The slope of eGFR following the initiation of randomized treatment (ie, from Day 1 to Week 108; total slope over 2 years)

The secondary efficacy endpoints in the US are:

- The slope of eGFR following the initial acute effect of randomized treatment (ie, from Week 6 to Week 108; chronic slope over 2 years)
- The change in eGFR from baseline of the double-blind period to 4 weeks post-cessation of randomized treatment at Week 112

3.2.3. Exploratory Endpoints

Exploratory endpoints for the double-blind period are:

- The slopes of eGFR over approximately 1 year of randomized treatment evaluated following the initial acute effect of randomized treatment (ie, from Week 6 to Week 60; chronic slope over 1 year) and after initiation of randomized treatment (ie, from Day 1 to Week 60; total slope over 1 year)
- The absolute and percent change from baseline of the double-blind period in eGFR at each visit
- The percent change from Week 6 in eGFR at each visit
- The proportion of patients achieving FPRE, defined as UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline of the double-blind period in UP/C at each visit
- The percent change from baseline of the double-blind period in UP/C at each visit
- The time to achieve the target reduction in UP/C (ie, FPRE, as defined as ≤1.5 g/g [170 mg/mmol] and a >40% reduction)
- The proportion of patients reaching a confirmed 40% reduction in eGFR, end-stage renal disease (ESRD), or death. ESRD is defined as initiation of renal replacement therapy (RRT) or sustained eGFR <15 mL/min/1.73 m^2 during the study
- The proportion of patients reaching a confirmed 30% reduction in eGFR, ESRD, or death
- Changes from baseline of the double-blind period in blood pressure at each visit
- The proportion of patients requiring initiation of or intensification in immunosuppressive medication during the study
- The proportion of patients undergoing reduction in immunosuppressive medication during the study
- The time to initiation or intensification in immunosuppressive medication during the study
- Changes from baseline of the double-blind period in quality of life (QOL), measured via patient-reported outcome (PRO) at each visit beginning with Week 12
- Frequency and duration of hospitalizations (for any reason and for reasons related to the kidney)
- Trough plasma pharmacokinetic (PK) concentrations during the double-blind period

3.2.4. Safety Endpoints

Safety endpoints include:

- Changes from baseline of the double-blind period in body weight, vital signs, physical examination, peripheral edema, 12-lead electrocardiogram, and clinical laboratory parameters
- Changes from baseline of the double-blind period in lipid profile (total cholesterol and triglycerides, low-density lipoprotein cholesterol [LDL-C], very low-density lipoprotein cholesterol [VLDL-C], and high-density lipoprotein cholesterol [HDL-C])
- Changes from baseline of the double-blind period in serum albumin and serum potassium at each visit
- Incidence of treatment-emergent adverse events (TEAEs) during the double-blind period

3.2.5. OLE Endpoints

OLE endpoints will be described in the separate OLE SAP.

4. STUDY DESIGN

4.1. Summary of Study Design

This is a randomized, multicenter, double-blind, parallel, active-control study, with an open-label extension of up to 156 weeks, in patients with FSGS. Patients who meet inclusion criteria during screening and who are taking renin-angiotensin-aldosterone system (RAAS) inhibitors will undergo a 2-week washout period from these agents prior to randomization. Approximately 300 eligible patients will be randomized 1:1 to receive either sparsentan or an active control (irbesartan). Randomization will include stratification by screening eGFR and UP/C values. The strata will be as follow:

- eGFR strata:
  - ≥30 to <60 mL/min/1.73 m^2 (all patients)
  - ≥60 mL/min/1.73 m^2 (all patients)
- UP/C strata:
  - ≤3.5 g/g (396 mg/mmol; patients ≥18 years of age) or ≤2 g/g (226 mg/mmol; patients <18 years of age)
  - >3.5 g/g (396 mg/mmol; patients ≥18 years of age) or >2 g/g (226 mg/mmol; patients <18 years of age)

Additional antihypertensive agents are allowed during the study to maintain blood pressure ≤130/80 mmHg (patients ≥18 years of age) or ≤ the 75th percentile (patients <18 years of age), with the exception of those that inhibit the RAAS and endothelin systems.

Study visits in the double-blind period will be conducted at 2, 4, 6, 8, and 12 weeks after randomization and at 12-week intervals thereafter. Following the 108-week blinded treatment period, treatment with study medication will be discontinued. Patients will return to the clinical site for the final visit of the double-blind period 4 weeks after study medication has been discontinued.

Patients may be evaluated for eligibility in the open-label extension using values from the Week 108 visit (end of blinded treatment period) as screening assessments. Patients with an eGFR <30 (but >20) mL/min/1.73 m^2 will be eligible for participation in the open-label extension at the discretion of the Investigator but will require close monitoring of eGFR and serum potassium.

Open-label extension study visits will be conducted at 12-week intervals. A study visit 2 weeks after the start of the open-label extension will also be conducted to assess tolerability to sparsentan.

Patients will participate in the open-label extension for up to 156 weeks, for a total of 268 weeks in the study (ie, double-blind and open-label periods).

4.2. Definition of Study Drugs

4.2.1. Double-Blind Period

Sparsentan will be dispensed as 200-mg tablets overencapsulated (blinded) with size 00 capsules, and irbesartan (active control) will be dispensed as 75-mg tablets overencapsulated (blinded) with size 00 capsules.

For patients with screening body weight >50 kg, the initial starting dose for study drug is 2 capsules (sparsentan 400 mg or irbesartan 150 mg), whereas for patients with screening body weight ≤50 kg, the initial starting dose is 1 capsule (sparsentan 200 mg or irbesartan 75 mg). Weight will be measured at each study visit, and the dose may be increased at the Investigator's discretion if the patient's weight reaches >50 kg.

At the Week 2 visit, the Investigator will evaluate dose tolerance in a blinded manner prior to titrating up to the target dose of 4 capsules (sparsentan 800 mg or irbesartan 300 mg) for patients with screening weight >50 kg, or 2 capsules for patients with screening weight ≤50 kg. Patients may continue on the initial dose without titration or have dose reductions back to the initial (reduced) dose after dose titration based on tolerability as described in the protocol. At the Investigator's discretion, patients with screening weight >50 kg who do not tolerate the initial dose for any reason may continue at one-half the initial dose, 1 capsule (sparsentan 200 mg or irbesartan 75 mg).

4.2.2. Open-Label Extension

Sparsentan will be dispensed as 200-mg or 400-mg tablets.

Patients who are taking 2 capsules of study medication (ie, 400 mg sparsentan or 150 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at 200 mg sparsentan for the first 2 weeks of the open-label extension. Likewise, patients who are taking 4 capsules of study medication (ie, 800 mg sparsentan or 300 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at 400 mg sparsentan for the first 2 weeks of the open-label extension. Following 2 weeks at half the double-blind dose (ie, Week 114), the Investigator will evaluate dose tolerance prior to titrating up to the target dose.

Patients who are taking 1 capsule of study medication (ie, 200 mg sparsentan or 75 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at 200 mg sparsentan for the first 2 weeks of the open-label extension. Following 2 weeks at 200 mg sparsentan (ie, Week 114), the Investigator will evaluate dose tolerance. Patients who are tolerating the initial dose will continue on 200 mg sparsentan.

For patients who enter the open-label extension with an eGFR value <30 mL/min/1.73 m^2, any dose titration at Week 114 will be at the Investigator's discretion based on the results of the Week 114 assessments. Patients who do titrate to a higher dose at Week 114 will be contacted by the Investigator at Week 116 to assess tolerance of the higher dose.

Doses may be modified at any time throughout the open-label extension for safety/tolerability reasons at the Investigator's discretion. In addition, after titration to the target dose for the open-label extension, increases above the target doses of 200 mg or 400 mg sparsentan may be

considered for patients who, in the Investigator's opinion (and following consultation with the Medical Monitor), would benefit from an increased dose.

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

Approximately 300 patients will be randomized and allocated 1:1 to receive sparsentan or irbesartan. This sample size takes into consideration enrollment feasibility in this rare disease setting and was evaluated using simulations.

4.3.1.1. Surrogate Endpoint: FPRE

Based on the results at Week 8 of the sparsentan Phase 2 DUET study (RET-D-001) in FSGS patients and projected to Week 36, it is assumed that sparsentan will result in approximately 50% of patients achieving FPRE, and that irbesartan will result in approximately 20% of patients achieving FPRE. Based on these assumptions and using a Pearson chi-square test for 2 proportions and a 2-sided α level of 0.05, 190 patients (approximately 95 per treatment group) will yield at least 90% power to detect a difference in response proportions between sparsentan and irbesartan. The minimum treatment difference that could be declared statistically significant is approximately 13% with approximately 190 patients.

4.3.1.2. Primary Endpoint: Slope of eGFR

For the final analysis of the primary endpoint (eGFR slope) evaluated following the initial acute effect of randomized treatment (ie, eGFR chronic slope over 2 years) in non-US countries and following the initiation of randomized treatment (ie, eGFR total slope over 2 years) in the US, the ability of the study to distinguish between treatment groups was evaluated using the projected treatment difference in eGFR slopes given the treatment difference on the surrogate efficacy endpoint. The calculations assume that treatment difference in eGFR slope is equal to the treatment difference in UP/C response proportions multiplied by the difference in eGFR slopes among patients who achieved the UP/C response (ie, UP/C responders) and those who did not (ie, UP/C non-responders). Available data from the DUET and disease registry studies were used to model this relationship.

Using the available data, the modeling exercise yielded an estimated difference in eGFR slopes between UP/C responders and non-responders of approximately 8.4 mL/min/1.73 m^2 per year based on the eGFR chronic slope. With the assumed treatment difference in response proportions of 30%, the projected treatment difference in eGFR slopes is approximately 2.52 mL/min/1.73 m^2 per year. The model also estimated the residual variability (standard deviation [SD]) to be approximately 10.80 mL/min/1.73 m^2 per year. With 300 patients (approximately 150 per treatment group) and a 2-sided α level of 0.05, the study has at least 90% power to differentiate between treatments if the underlying eGFR slope difference is at least 2.5 mL/min/1.73 m^2 per year. With 300 patients, the minimum treatment difference in eGFR slope that can be declared statistically significant is approximately 1.40 mL/min/1.73 m^2/year. Power calculations follow the approach described in Dupont and Plummer (Dupont 1998).

Based on the eGFR total slope, the modeling exercise yielded a projected treatment difference in eGFR slopes of approximately 2.1 mL/min/1.73 m^2 per year, assuming a treatment difference in

response proportions of 30% for the surrogate endpoint. With 300 patients (approximately 150 patients per treatment group) and a 2-sided α of 0.05, the study has at least 90% power to differentiate between treatments. This power calculation is based on the Wald statistic using a standard deviation of the eGFR total slope of 5.50 mL/min/1.73 m^2 per year estimated from blinded interim data from the current study.

It should be noted that statistical testing can only be performed at the final analysis if a statistically significant difference is demonstrated at the interim analysis of the surrogate endpoint.

4.3.2. Sample Size Reassessment

A sample size reassessment (SSR) procedure is planned when the first 50 randomized patients have completed the Week 60 visit or discontinued study medication/study prior to Week 60. This procedure will be conducted and overseen by the Data Monitoring Committee. An analysis plan specific to the SSR will be approved prior to the SSR.

Using the methodology described by Mehta and Pocock (Mehta 2011), the conditional power for the endpoint of slope of eGFR over the treatment period will be computed. If the conditional power is in the range of 50% to 80%, the sample size will be increased to raise power, subject to a maximal increase in N of 35% (ie, total N will not exceed 300*1.35). In line with Gao, Mehta, and Ware (Gao 2008), there is no Type I error inflation with this approach. If the conditional power is not in the range 50% to 80%, the trial will proceed with no change in sample size. The same SSR methodology will be applied separately to both eGFR chronic and total slope endpoints, and the sample size will be increased according to the larger of the 2 results, subject to the same maximal increase of up to 35%. Note that in the SSR analysis plan, the eGFR total slope endpoint was labeled as starting from Week 2 to Week 108. While a more accurate label is from Day 1 to Week 108, the data and model used to estimate the eGFR total slope is the same as those described in this SAP.

4.4. Randomization

Randomization will be carried out using an interactive web response system (IWRS), with central randomization following a 1:1 ratio between the 2 treatment arms, based on a permuted-block randomization method. Randomization will be stratified by the following factors:

- eGFR value at Screening (≥30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2)
- UP/C at Screening
  - ≤3.5 g/g (396 mg/mmol; patients ≥18 years of age) or ≤2 g/g (226 mg/mmol; patients <18 years of age)
  - >3.5 g/g (396 mg/mmol; patients ≥18 years of age) or >2 g/g (226 mg/mmol; patients <18 years of age)

5. PLANNED ANALYSES

The following describes the timing of the planned analyses. For definitions of analysis populations, refer to Section 6.3.

5.1. Interim Analyses

An unblinded interim analysis will be conducted after 36 weeks following randomization of at least 190 patients (approximately 95 patients per treatment group) to determine whether the surrogate efficacy endpoint, FPRE, is statistically significant. The statistical evaluation of the surrogate efficacy endpoint will be performed using available data from all subjects at the time of interim analysis using a longitudinal mixed model with binary responses, ie, a generalized linear model with logit link function to model the probability of achieving FPRE, at a significance level of $\alpha = 0.05$. Unblinded analysis on select efficacy and safety endpoints will also be conducted.

The interim analysis will be conducted by the unblinded statistical subteam, and only limited analysis results will be disseminated publicly. Full results will not be disseminated among the investigators and those directly involved with ongoing study conduct until after study completion. Details on interim analysis procedures including formation of the unblinded subteam, interim database lock, unblinding procedures, management of unblinded analysis results, and management of documents containing unblinded analysis results will be finalized prior to interim analysis.

5.2. Final Analyses

The final analysis will be conducted when all randomized patients have completed the end of the double-blind study assessment (Week 112) or early terminated from the study, with the final database cleaned and locked.

5.3. Open-Label Extension Analyses

Select safety analyses of OLE results will be performed at the time of interim analysis and are specified in this SAP. No efficacy analyses of OLE results will be performed at the time of interim analysis. A separate SAP will be written to detail the analysis of OLE results at final analysis and study completion.

5.4. Changes from Planned Protocol Analyses

The analyses specified in this SAP are consistent with DUPLEX Protocol Amendment 6 with the following exception.

The primary statistical evaluation of the surrogate endpoint, FPRE, will be performed using the Interim Analysis Set (IAS) rather than the subset of patients in the FAS who are scheduled to have completed their Week 36 visit per Section 12.11 of the protocol. Statistical evaluation of FPRE using the subset of patients in the FAS who are scheduled to have completed their Week 36 visit will be performed as a sensitivity analysis.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. General Presentation Considerations

Individual patient data obtained from electronic case report forms (eCRFs), central laboratories, local laboratories, PROs, external sources, and derived data will be presented in data listings by patient. All data listings that contain an evaluation date will contain a relative study day.

All output will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the International Council for Harmonisation recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters.

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. Percentage calculations will be based on non-missing data unless otherwise specified. Percentages are rounded to 1 decimal place unless otherwise specified.

For continuous variables, the number of patients, mean (arithmetic), SD, standard error of the mean (SEM), median, interquartile range (IQR), minimum, and maximum values will be presented. Geometric mean and geometric coefficient of variation (CV%) will additionally be presented for key efficacy variables (eGFR and quantitative urinalysis, including UP/C). The precision of summary statistics, unless otherwise specified, will be as follows: mean, median, and IQR to 1 more decimal place than the raw data; and SD and SEM to 2 decimal places more than the raw data. In general, the decimal places should not exceed 3 decimal places unless appropriate. Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified in the table and listing shell.

Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% CIs as well as percentage of censored observations. In addition, time-to-event data will be summarized with descriptive statistics for those with an event. KM plots will generally be displayed as cumulative probability plots (ie, probability of event occurring prior to or at time x).

6.2. Data Conventions

The precision of original measurements will be maintained in summaries when possible.

For tables where rounding is required, rounding will be done at the final stage of the calculation, to the nearest round-off unit. For example, when rounding to the nearest integer, values ≥XX.5 will be rounded up to XX + 1 (eg, 97.5 will round up to 98), while values <XX.5 will be rounded down to XX (eg, 97.4 will round down to 97).

Percentages based on frequency counts will be based on available data, and denominators will generally exclude missing values, unless otherwise stated. For frequency counts of categorical variables, categories whose counts are 0 will be displayed for completeness. For example, if none of the patients discontinue due to “lost to follow-up,” this reason will be included in the table with a count of 0. Percentages based on frequency counts of eCRF collections

(eg, demographic categories) will be presented as a whole number (no decimal places), and nonzero values less than 0.5% will be presented as "<1%." Values less than 100% but that round up from 99.5% to 100% will be presented as ">99%."

Quantitative laboratory tests containing less than (<) and greater than (>) symbols are test results that are below and above quantifiable limits, respectively. In order to retain these values for analysis purpose, values will be imputed as the numeric portion of the result.

6.3. Analysis Populations

6.3.1. Full Analysis Set

All patients who are randomized and take at least 1 dose of double-blind study medication will be included in the Full Analysis Set (FAS). Patients in the FAS will be analyzed according to randomized treatment assignment. If a patient is incorrectly stratified (ie, randomized according to an incorrect stratification), the patient will be analyzed under the randomized treatment for the stratum recorded in the IWRS. All efficacy analyses for the double-blind period will be based on the FAS.

6.3.2. Interim Analysis Set

The IAS is the subset of the FAS at the time of the data extraction for interim analysis (per Section 5.1). Patients in the IAS will be analyzed according to randomized treatment assignment. All analyses conducted at the time of the interim analysis, including primary analysis of the surrogate endpoint and safety analysis, will be based on the IAS.

6.3.3. Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set is a subset of the FAS containing patients who met study eligibility requirements and had no major protocol deviations that might affect the validity of the efficacy measurements. Patients will be analyzed according to randomized treatment assignment. The PP Analysis Set will be used for sensitivity analyses related to efficacy.

The criteria for inclusion in the PP Analysis Set will be finalized prior to study unblinding (interim and final) as specified in Section 7.3. Evaluation of patient inclusion in the PP Analysis Set will occur for the interim analysis and final analysis.

6.3.4. Safety Analysis Set

The Safety Analysis Set includes all patients who are randomized and have taken at least 1 dose of study medication. Patients will be analyzed according to the double-blind randomized treatment. The Safety Analysis Set will be the primary population used for safety analyses.

6.3.5. Pharmacokinetic Analysis Set

The PK Analysis Set includes all patients who have received at least 1 dose of study medication and have at least 1 confirmed fasted analyzable sample. Patients must have been fasting for approximately 8 hours before the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK Analysis Set will be used for PK and PK/pharmacodynamic analyses.

6.3.6. OLE Full Analysis Set

The OLE Full Analysis Set (OLEFAS) includes all patients who have received at least 1 dose of sparsentan in the open-label extension. All analyses during the OLE will be based on the OLEFAS. For the purposes of the analyses outlined in this SAP, patients will be analyzed according to randomized treatment assignment in the double-blind period.

6.4. Baseline Definition

6.4.1. Double-Blind Baseline

Double-blind baseline is defined as the last non-missing assessment prior to and including the first administration of study medication (including unscheduled assessments) in the study. In the case where the last non-missing assessment and the study medication start date (and time if available) coincide, that assessment will be considered baseline. Unless explicitly stated, all baselines used in this SAP will refer to the double-blind baseline.

6.4.2. Open-Label Extension Baseline

Open-label extension baseline is defined as the last non-missing assessment prior to and including the first administration of sparsentan (including unscheduled assessments) in the open-label extension. In the case where the last non-missing assessment and the sparsentan start date (and time if available) coincide, that assessment will be considered baseline.

6.5. Derived and Transformed Data

6.5.1. Baseline Age

Age is captured in the electronic data capture system, as relative to the date of informed consent.

6.5.2. Study Day

Study day 1 is defined as the day on which the first dose of study mediation is administered (Day 1/Week 0). All other study days will be calculated relative to that date. The day before the start of study medication is Day -1 (there is no Day 0).

Study day will be calculated using the following formula:

study day = date – first dose date + 1, where date ≥first dose date

study day = date – first dose date, where date <first dose date

6.5.3. Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Days – A duration expressed in days between one date (*date1*) and another date (*date2*) will be calculated using the following formula:

  duration in days = date2 – date1 + 1

- Months – A duration expressed in months is calculated as the number of days divided by 365.25/12 (approximately 30.4)
- Years – A duration expressed in years is calculated as the number of days divided by 365.25
- Height – Height entries made in inches (in) are converted to centimeters (cm) using the following formula:

  height (cm) = height (in) × 2.54

- Weight – Weight entries made in pounds (lb) are converted to kilograms (kg) using the following formula:

  weight (kg) = weight (lb) / 2.2046

- Temperature – Temperature entries in degrees Fahrenheit are converted to degrees Celsius using the following formula:

  temp (degrees Celsius) = 5 / 9 × (temp [degrees Fahrenheit] – 32)

- Change from Baseline – Change from Baseline will be calculated as:

  Change = post Baseline value – Baseline value

- Percentage change from Baseline – Change from Baseline will be calculated as:

  Percentage change from Baseline = ([post Baseline value – Baseline value] / Baseline value) × 100

- Percent Change from Baseline of variables analyzed in natural log will be calculated as:

  Percent Change = [exp(change in natural log) – 1] × 100

For variables requiring log transformation, natural log will be used.

6.5.4. Visit Windows

A visit window method will be applied to determine analysis visits across the study for efficacy and safety endpoints based on laboratory results, including eGFR and quantitative urinalysis (including UP/C and FPRE). If a patient has multiple assessments (including unscheduled visits) within a visit window, the value closest to the target day for that visit will be selected for analysis. If more than 1 assessment is equidistant to the target day, then the latest value will be selected. For efficacy analysis visits on or prior to Week 108, only assessments while the patient is on randomized treatment should be included (see Section 8.1 for definition of on treatment).

For quantitative urinalysis endpoints that are derived as the geometric mean of replicates collected over several days, all replicates used to derive the average should be mapped to the same analysis visit per Table 2, should be within 5 days of each other, and should all have been collected while the subject was on study medication. For the derivation of baseline, all replicates must have been collected on or prior to the date of reference dose. The study day of the endpoint will be derived as the maximum study day of the replicates used in the derivation.

If a patient is missing a UP/C assessment at a given analysis visit due to only having 1 urine sample available within 5 days, the available single assessment closest to the target day for that visit will be selected for sensitivity analysis.

The following visit windows for the double-blind period are defined for endpoints based on laboratory results. Visit windows for the OLE will be defined in a separate SAP.

Table 2: Visit Windows (Study Days)

		Analysis Visit Window (Study Days)	
Analysis Visit	**Relative Target Day**	**eGFR and Safety Labs**	**Quantitative Urinalysis**
Week 2	15	2 – 22	N/A
Week 4	29	23 – 36	N/A
Week 6	43	37 – 50	2 – 71
Week 8	57	51 – 71	N/A
Week 12	85	72 – 127	72 – 127
Week 24	169	128 – 211	128 – 211
Week 36	253	212 – 295	212 – 295
Week 48	337	296 – 379	296 – 379
Week 60	421	380 – 463	380 – 463
Week 72	505	464 – 547	464 – 547
Week 84	589	548 – 631	548 – 631
Week 96	673	632 – 715	632 – 715
Week 108[1]	757	716 – 771	716 – 771
Week 112[1]	785	>771	>771
4-week after EOT[2]	785[1] or Last Dose Date + 28[3]	>771[1] or 2-12 weeks (14-84 days) after Date of Last Dose[3]	>771[1] or 2-12 weeks (14-84 days) of Date of Last Dose[3]

[1] For patients who completed the planned randomized treatment period.
[2] Efficacy endpoints only.
[3] For patients who discontinued the randomized treatment early.
eGFR = estimated glomerular filtration rate; EOT = End of Treatment; N/A = not applicable.

6.5.5. Kidney Disease Quality of Life (KDQOL) Survey

KDQOL-36 is a short form questionnaire that includes the Short Form Health Survey (SF-12) as generic core plus the burden of kidney disease, symptoms/problems with kidney disease, and effects of kidney disease scales from the KDQOL-SF v1.3. Below are the included items:

- Items 1-12: SF-12 v2
- Items 13-16: Burden of kidney disease (4 items)
- Items 17-28b: Symptoms/problems of kidney disease (12 items)
- Items 29-36: Effects of kidney disease (8 items)

Each question in KDQOL-36 is pre-coded with a numeric value, and out-of-range responses will be recorded as missing. Missing values will not be imputed. Survey responses will be scored based on adaptations from the KDQOL-SF v1.3 scoring manual (Hays 1997) and SF-12 scoring guide (Maruish 2012), as outlined below:

1. For items 13 to 36, raw pre-coded numeric values will be transformed to 0 to 100 possible range, with the higher transformed scores always reflecting better quality of life. Scores present the percentage of total possible scores achieved. Transformations per items are specified in Table 3 below.

Table 3: Transformations of Pre-coded Values for KDQOL-36

Applicable Items	Pre-coded Value	Transformed Score (0-100)
Items 13-16	1	0
	2	25
	3	50
	4	75
	5	100
Items 17-27, 28a, 28b, 29-36	1	100
	2	75
	3	50
	4	25
	5	0

KDQOL = Kidney Disease Quality of Life.

2. The following 3 subscales will be computed as the average of available items (transformed scores) within each subscale:

Table 4: KDQOL Subscales

Sub-scale	Average of Available Items (Transformed Scores)
Symptoms/Problems List	Items 17-28 (12 items)
Effects of Kidney Disease	Items 29-36 (8 items)
Burden of Kidney Disease	Items 13-16 (4 items)

KDQOL = Kidney Disease Quality of Life.

3. For items 1 to 12, scale scores and physical (PCS) and mental component summary (MCS) measures will be computed using a norm-based method in the following steps:

- Recode 4 items that require recoding; a higher score indicates better functioning:

Table 5: SF-12 v2 Items Recoding

Items	Response Choices	Pre-coded Item Value	Final Item Value
1 – General health	Excellent	1	5.0
	Very good	2	4.4
	Good	3	3.4
	Fair	4	2.0
	Poor	5	1.0
5 – How much did pain interfere with your normal work	Not at all	1	5
	A little bit	2	4
	Moderately	3	3
	Quite a bit	4	2
	Extremely	5	1
6a – Felt calm and peaceful 6b – Energy	All of the time	1	5
	Most of the time	2	4
	Some of the time	3	3
	A little of the time	4	2
	None of the time	5	1

SF-12 = Short Form Health Survey.

- After item recoding, a raw score is computed for each scale. This score is the simple algebraic sum of responses for all items in that scale, as shown below:

Table 6: SF-12 v2 Scale Items and Range of Possible Scores

Scale	Sum of Final Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Physical Functioning (PF)	Items 2a + 2b	2, 6	4
Role Physical (RP)	Items 3a + 3b	2, 10	8
Bodily Pain (BP)	Item 5	1, 5	4
General Health (GH)	Item 1	1, 5	4
Vitality (VT)	Item 6b	1, 5	4
Social Functioning (SF)	Item 7	1, 5	4
Role Emotional (RE)	Items 4a + 4b	2, 10	8
Mental Health (MH)	Items 6a + 6c	2, 10	8

SF-12 = Short Form Health Survey.

- Transform each raw scale score to a 0 to 100 scale using the formula shown below:

$$\text{Transformed scale} = \frac{(\text{Actual raw score} - \text{lowest possible raw score})}{\text{Possible raw score range}} * 100$$

- Next, standardize each scale using a z-score transformation by subtracting the mean 0 to 100 score observed in the 1998 general US population for each scale and dividing the difference by the corresponding scale standard deviation, as shown below:

Table 7: SF-12 v2 Z-Score Transformation Based on 1998 General US Population Means and Standard Deviations

Scale	Mean	Standard Deviation
Physical Functioning (PF)	81.18122	29.10558
Role Physical (RP)	80.52856	27.13526
Bodily Pain (BP)	81.74015	24.53019
General Health (GH)	72.19795	23.19041
Vitality (VT)	55.59090	24.84380
Social Functioning (SF)	83.73973	24.75775
Role Emotional (RE)	86.41051	22.35543
Mental Health (MH)	70.18217	20.50597

SF-12 = Short Form Health Survey; US = United States.

- Next, transform each scale z-score to the norm-based (50, 10) scoring. This is done by multiplying each z-score by 10 and adding the resulting product to 50. The norm-based scale scores will be used for analysis.
- To compute the PCS and MCS scores, multiply each scale z-score by its respective physical and mental factor score coefficient and summing the 8 products, as shown below:

Table 8: SF-12 v2 Factor Score Coefficients for PCS and MCS Derivation

Scale	Factor Score Coefficients	
	PCS	MCS
Physical Functioning (PF)	0.42402	-0.22999
Role Physical (RP)	0.35119	-0.12329
Bodily Pain (BP)	0.31754	-0.09731
General Health (GH)	0.24954	-0.01571
Vitality (VT)	0.02877	0.23534
Social Functioning (SF)	-0.00753	0.26876
Role Emotional (RE)	-0.19206	0.43407
Mental Health (MH)	-0.22069	0.48581

MCS = Mental Component Summary; PCS = Physical Component Summary; SF-12 = Short Form Health Survey.

- The final step for computation of PCS and MCS involves transforming the aggregate physical and mental summary scores to the norm-based (50, 10) scoring. This is done by multiplying each aggregate summary score from the previous step by 10 and adding the resulting product to 50. The norm-based scores will be used for analysis.

6.5.6. Pediatric Quality of Life Inventory (PedsQL)

The PedsQL (v4.0) instrument consists of developmentally appropriate modules: Child Self-Report (ages 8 to 12) and Teen Self-Report (ages 13 to 18). Each module is composed of 23 items comprising 4 dimensions:

- Physical Functioning: 8 items
- Emotional Functioning: 5 items
- Social Functioning: 5 items
- School Functioning: 5 items

The instrument will be scored in the following steps:

1. Transform each 0-4 scale items to 0 to 100 as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0.
2. Create scale score for each dimension, as the sum of the items over the number of items answered. If more than 50% of the items are missing, the scale score for that dimension should not be computed. If <50% of the items are missing, impute the missing score using the mean of the completed items.
3. Create Psychosocial Health Summary Score as the sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales.
4. Create Physical Health Summary Score, which is equivalent to the Physical Functioning Scale Score.

5. Create Total Score as the sum of all the items over the number of items answered on all the Scales.

The 4-dimension scores, 2 summary scores, and Total Score will be used for analysis.

6.5.7. EQ-5D-5L

EuroQol, 5-dimension QOL instrument, version 5L (EQ-5D-5L) is a 2-part instrument consisting of the following:

- Descriptive system is comprised of the following 5 dimensions:
  - Mobility
  - Self-care
  - Usual activities
  - Pain/discomfort
  - Anxiety/depression
- EQ Visual Analogue Scale (EQ VAS)

For each dimension, respondents select 1 of 5 statements that best describes their health on that day. Each statement/level is pre-coded with a 1-digit number (1 to 5). Missing responses will be coded as "9." The responses to the 5 dimensions are then concatenated to represent a patient's health state. For example, "12345" represents a Mobility response of 1, Self-care response of 2, Usual activities response of 3, Pain/discomfort response of 4, and Anxiety/depression response of 5. The health states can be converted into a single index value based on country-specific value sets by using the crosswalk link function (vanHout 2012).

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale. The scale is numbered from 0 to 100, with 0 labeled as "the worst health you can imagine" and 100 labeled as "the best health you can imagine."

6.5.8. EQ-5D-Y

EuroQol, 5-dimension QOL instrument, version Youth (EQ-5D-Y) is a child-friendly version of EQ-5D and consists of 2 parts: the same 5 dimensions as the EQ-5D-5L assessed with 3 levels, and the EQ VAS numbered from 0 to 100.

For each dimension, respondents select 1 of 3 statement best describes their health on that day. Missing responses will be coded as "9." The responses to the 3 dimensions are then concatenated to represent a patient's health state, similar to that in EQ-5D-5L. There is no value set available for EQ-5D-Y for conversion for a single index value.

6.5.9. eGFR Derivation

The eGFR for each baseline and post-baseline visit will be determined at the central laboratory using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration; Levey 2009) formula for patients ≥16 years of age at the time of screening, and the Modified Schwartz formula for patients <16 years of age at the time of screening (Schwartz 2009a; Schwartz 2009b).

Missing central laboratory eGFR from subject visits for which serum creatinine is available will be derived using the appropriate age-based formula. For the derivation of eGFR per the Modified Schwartz formula, if height is missing for the subject visit then the last reported height within the central laboratory results will be used in the derivation.

6.5.10. UP/C and Urine Albumin/Creatinine Ratio (UA/C) Derivation

Missing central laboratory UP/C from subject visits for which the corresponding urine protein or urine creatinine are reported with "<" or ">" will be derived. Urine protein or urine creatinine values reported as "<" or ">" will be imputed as the numeric portion of the result and the ratio will then be derived. If both urine protein and urine creatinine are reported with "<" or ">" then UP/C will not be derived.

The same derivation will be performed for missing central laboratory UA/C using the corresponding urine albumin and urine creatinine results.

6.6. Handling of Missing Data

Tabular summaries of missing data for efficacy endpoints will be prepared per Section 7.8.

6.6.1. Missing Efficacy Endpoints – eGFR and Quantitative Urinalysis

6.6.1.1. Primary Analysis

For the primary analysis of the primary, secondary, and exploratory efficacy endpoints of eGFR and quantitative urinalysis, missing central lab data may be derived per Section 6.5.9 and Section 6.5.10 but will not otherwise be imputed. The primary analysis will analyze all available data based on analysis visit window as described in Section 6.5.4, using the mixed-effects model with random slope and intercepts and the mixed-model repeated measures (MMRM) approaches described in Section 8.5.1, Section 8.8.1, and Section 8.8.2. These models implicitly adjust for missing data through a variance covariance structure.

For the primary analysis of the surrogate endpoint of FPRE, missing data will be imputed according to Section 6.6.2.

6.6.1.2. Sensitivity Analyses

6.6.1.2.1. Multiple Imputations

For the sensitivity analysis of primary and secondary efficacy endpoints of eGFR, missing data will be imputed using the multiple imputation (MI) procedure. Under the missing at random (MAR) assumption, a Bayesian multivariate normal model for the data (including the same covariates as for the primary analysis) will be fitted using a Markov Chain Monte Carlo (MCMC) approach. Quasi-independent samples will be drawn from the posterior distributions for the parameters of the multivariate normal distribution for each arm. A non-informative prior will be used. The MCMC approach allows all missing observations to be imputed, whether a patient has monotone or non-monotone pattern of missingness. Monotone missing pattern is when a data point is missing for an individual patient, all subsequent data points are missing for that patient, whereas a non-monotone missing pattern implies data points are missing in

intermediate visits for a patient. The seed number for the random generator will be defined and documented before study unblinding.

Following the approach described in Ouyang (2017), the following imputation procedures will be implemented:

1. Intermittent missing values before a discontinuation event (ie, discontinuation of randomized therapy or early permanent dropout): The MAR assumption is reasonable for intermittent missing values before a discontinuation event since the values of the endpoint before and after the intermittent missing value are known. Imputation of intermittent missing data will be accomplished using the MCMC option in SAS PROC MI by treatment group to impute intermittent missing data without a monotone missing pattern, prior to performing imputations of values following the discontinuation event.
2. Missing data following a discontinuation event (ie, discontinuation of randomized therapy or early permanent dropout): Impute the post-discontinuation missing data by treatment group under the assumption of MAR using the regression option from the monotone statement of SAS PROC MI. Baseline and post-baseline scheduled visits will be used in the regression option to impute the missing values.
3. Repeat steps 1 and 2 to generate 30 multiply imputed datasets.
4. The mixed-model (ie, the analytic model) analysis described for the endpoint will be performed on each set of the newly "complete" data (observed data plus imputed values).
5. Using Rubin's approach (Rubin 1987), the estimated treatment effects are combined across imputations. This will be accomplished using SAS PROC MIANALYZE.

6.6.1.2.2. Tipping Point Analysis

To assess the robustness of the results to the MAR assumption, additional sensitivity analyses using the tipping point approach will be used to assess how extreme and detrimental outcomes among patients with missing data must be to overwhelm the treatment effect attained in those patients who had complete data. In these analyses, the same basic analytic model will be used as in the primary analysis, but the MI approach will be expanded to allow for varying impact of missing data by incorporating a shift parameter in the imputation model. The range of values for the shift parameter will explore the varying missing data assumptions, from MAR to missing not at random, including the scenario where imputation model is completely based on the control group (ie, control-based imputation).

For the sparsentan-treated patients, the post-discontinuation imputed values from MI step 3 will be made worse by subtracting a delta defined as k times the treatment differences (means or slopes) obtained for the post-discontinuation visits obtained from the specified mixed model analysis (ie, the analytic model) of the endpoint. No adjustment from the MAR assumption will be implemented for the irbesartan-treated patients (ie, k = 0%).

Generate worse-case scenarios with varying values of k (eg, 100%, 120%, 140%…200%…) until the significance of the prespecified analysis assuming MAR is overturned (eg, from p-value <0.05 to p-value ≥ 0.05). The worsening by k times the treatment differences is applied to all the post discontinuation imputed values for each set of "complete" data from MI step 3. As an example, if a sparsentan patient had 2 post-discontinuation visits imputed, the values of both of

these 2 imputed visits would be made worse by subtracting k times the sparsentan versus irbesartan treatment differences at these 2 visits.

1. Note that when k = 0%, this approach produces an analysis that is consistent with MAR and is equivalent to the primary analysis with MI.
2. When k = 100%, this approach produces an analysis that is equivalent to "jump to reference," since the whole treatment differences were subtracted out from the imputations based on the trend of the control group.
3. When k >100%, the analysis reflects a "worse-than-control" specification.

6.6.1.3. Local Labs

The primary analyses will use central lab data only. As a sensitivity analysis, local lab data will be included with central lab data.

6.6.2. Missing Efficacy Endpoints – Responder Endpoints

6.6.2.1. Primary Analysis

For the primary analysis of the surrogate endpoint, missing FPRE will be imputed using the MI procedure outlined in Section 6.6.1.2.1 via imputation of the UP/C result in the natural log scale. Complete UP/C data sets will first be generated via the MI procedure and FPRE outcome for each post-baseline visit subsequently determined. Missing central lab UP/C may be derived per Section 6.5.10 prior to performing imputation via the MI procedure.

For the analysis of all other responder efficacy endpoints, in which patients are classified as either a responder or a nonresponder (binary outcome), any patient who does not have an assessment at the specified time point for the definition of response will be considered a nonresponder (ie, NRI, nonresponder imputation). That is, for the percentage of responders, the patient will be included in the denominator and will not contribute to the numerator.

6.6.2.2. Sensitivity Analysis

A sensitivity analysis will be performed for the surrogate endpoint using Week 36 results only for patients who would have been expected to complete Week 36 at the time of data cutoff (see Section 7.7 for the definition of this population). Any patient who did not have an assessment at the specified time point for the definition of response will be considered a non-responder (ie, NRI, nonresponder imputation). That is, for the percentage of responders, the patient will be included in the denominator and will not contribute to the numerator. A Cochran-Mantel-Haenszel (CMH) test, adjusting for the 2 randomization stratification factors to compare sparsentan with irbesartan, will be used for this analysis. This sensitivity analysis was the originally planned primary analysis.

As an additional sensitivity analysis for the surrogate endpoint, if a patient is missing a UP/C assessment at a given analysis visit due to only having 1 urine sample available within 5 days, the available single assessment closest to the target day for that visit will be selected for inclusion in analysis for FPRE response using a CMH test. Additionally, a tipping point analysis will also be performed to assess the robustness of the results to the MAR assumption.

For all responder endpoints, an "observed cases" sensitivity analysis will be conducted, excluding those patients who do not provide an assessment at the specified timepoint for the definition of response. That is, for the percentage of responders, the patient will not be included in the numerator or the denominator.

The primary analysis of the surrogate endpoint will use central lab data only. As a sensitivity analysis, local lab data will be included with all observed cases of central lab data and analyzed using the primary model generalized linear model.

6.6.3. Missing Adverse Event or Concomitant Medication Onset Date

Adverse events and concomitant medications with incomplete onset dates will be assumed to have started during the study in accordance with the following prioritized list of assumptions:

1. Missing year: event or medication assumed to have the same year as first dose of study medication or year of end date, whichever is earlier
2. Missing month: event or medication assumed to have started during the study if the year is the same or later than the year of the first dose of study medication. Event or medication assumed to have started at the same month of the first dose of study medication or same month as end date (if year of end date ≤year of event), whichever is earlier
3. Missing day: event or medication assumed to have the same day as first dose of study medication if the year and month of onset are the same as year and month of first dose of study medication or the same day as end date, whichever is earlier. Otherwise, the day is assumed to be the first of the month.

6.6.4. Missing Adverse Event or Concomitant Medication End Date

If the entire end date is unknown and the event or medication is not considered ongoing at the end of study or follow-up, the event will be assumed to have ended on the last date of contact for the patient.

If only the day of end date is unknown, the day will be assumed to be the last of the month or the last date of contact for the patient, whichever is earlier.

If both the day and month of end date are unknown, the event will be assumed to have ended on the last day of the year or the last date of contact for the patient, whichever is earlier.

6.6.5. Missing Adverse Event Severity or Relationship

An event with missing severity will be considered severe. An event with missing relationship will be considered related to study medication.

7. STUDY POPULATION

7.1. Patient Disposition

Patient disposition will be tabulated by treatment group and overall and will include the number of patients who screened, failed screening, enrolled/randomized, received study medication, completed double-blind treatment, discontinued study medication (including reasons), completed the double-blind period, and discontinued the study during the double-blind period (including reasons). At the interim analysis, the number of patients who enrolled in the OLE period, discontinued sparsentan in the OLE period (including reasons) and discontinued the study during the OLE period will also be tabulated.

The number and percentage of patients in each analysis set will be summarized.

Patient enrollment by study site and country will be tabulated by treatment group and overall.

A by-patient listing of inclusion into analysis sets and study completion information including reason for study drug discontinuation or early withdrawal from study, if applicable, will be presented.

7.2. Screen Failures

The reason for screen failures will be summarized by region or site, as appropriate.

7.3. Protocol Deviations

Protocol deviations for missed visits, missed assessments, out of window visits or assessments, and violations of inclusion/exclusion criteria (where possible) will be determined based on available data. All other protocol deviations will be collected through study monitoring.

Protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified and the assessment of determination of evaluable patients for analysis populations (PP Analysis Set and PK Analysis) will be performed and approved by the Study Statistician, Medical Monitor, and Clinical Study Manager prior to database lock and unblinding of individual patient treatment information.

Evaluability of patients will be based on the following:

- Compliance of study entry criteria (inclusion and exclusion)
- Correct stratification at randomization
- Received the randomized treatment
- Adequate study medication exposure (no extended dosing interruptions)
- Adequate treatment compliance based on prescribed dose level (within 80% to 120%)
- No prohibited concomitant medications or therapies during the study
- No accidental or intentional unblinding at the investigational site

- No other major protocol deviations that may affect efficacy or safety conclusions, may include:
  - Non-withdrawal although at least 1 withdrawal criterion was met
  - Extensive visit window violations
  - Extensive missing visits
  - Non-adherence to study procedures
  - Inadequate handling of study medication

Major protocol deviations will be summarized by deviation category (overall and due to coronavirus disease 2019 [COVID-19]) and presented in a by-patient data listing.

7.4. Demographic and Baseline Characteristics

Demographic variables will include the following:

- Age at informed consent
- Sex
- Race
- Ethnicity
- Geographic region and country

Other baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)
- Childbearing potential (for females only)
- Hemoglobin A1c (HbA1c)
- Baseline eGFR (mL/min/1.73 m^2), including the following categories:
  - <30 mL/min/1.73 m^2, ≥30 to <60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2
  - <30 mL/min/1.73 m^2, ≥30 to <45 mL/min/1.73 m^2, ≥45 to <60 mL/min/1.73 m^2, ≥60 to <90 mL/min/1.73 m^2, ≥90 mL/min/1.73 m^2
- Baseline UP/C (g/g), including the following categories:
  - Adults: ≤3.5 g/g, >3.5 g/g; Pediatrics: ≤2 g/g, >2 g/g
- Pretreatment medication use
  - Immunosuppressive agents (ie, steroids, calcineurin inhibitors [CNIs], mycophenolate mofetil [MMF], and other immunosuppressive agents including azathioprine and adrenocorticotropic hormone [ACTH]) and RAAS inhibitors (ie, angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers, aldosterone blockers, and aliskiren)

- Baseline concomitant medication use
  - Antihypertensive medications, lipid-lowering medications, diuretics, immunosuppressive agents (steroids, CNIs, MMF, azathioprine, ACTH)
- Documented history of nephrotic syndrome
  - A patient will be considered to have documented history of nephrotic syndrome if the term "Nephrotic syndrome" is present in medical history or if all of the following conditions are met at any visits prior to the first dose of randomized treatment:
  - UP/C >3.5 g/g (adults) or UP/C >2 g/g (pediatrics)
  - Serum albumin <3.0 g/dL
  - Abnormal edema from physical examination

Demographics and baseline characteristics will be summarized and presented by treatment group and overall for the FAS, IAS, and PP Analysis Set. Summaries by randomization stratum will also be presented. A by-patient listing will also be provided.

7.5. Baseline FSGS Information

Baseline FSGS information will be summarized using data collected from the Medical History and FSGS Confirmation and Genetic Testing History eCRFs. The following variables will be summarized:

- Age at FSGS diagnosis
- Age at FSGS diagnosis group (<18, ≥18)
- Duration from FSGS diagnosis in years at time of informed consent
- Years since FSGS diagnosis (≤10, >10)
- Genetic testing available (Yes/No)
- FSGS-related genetic mutation

Baseline FSGS disease characteristics will be summarized and presented by treatment group and overall for the FAS, IAS, and PP Analysis Sets. Summaries by randomization stratum will also be presented. A by-patient listing will also be provided.

7.6. Medical History

Verbatim terms on eCRFs will be mapped to preferred terms (PTs) and system organ classes (SOCs) using Medical Dictionary for Regulatory Activities (MedDRA).

Medical history will be summarized by system organ class, preferred term, and treatment group using the safety population. Summaries will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. A by-patient listing will also be provided.

7.7. Blinded Assessment of Comparability to Previous Study Populations

A statistical modeling exercise was conducted to support the design of this Phase 3 study. The modeling was performed using data from NEPTUNE, FSGS-CT, and DUET. The patient population included in the modeling was selected from these data sources to reflect the target patient population in DUPLEX. The modeling results (Statistical Analysis Plan Modeling Report [FSGS], v1.0) indicate that there is a relationship between eGFR slope and FPRE status across data sources. The exercise resulted in a model that reasonably predicts treatment difference in eGFR slopes given a treatment difference in FPRE response proportion, adjusting for potential prognostic factors. This relationship is key in establishing the utility of FPRE as a likely surrogate for early assessment of efficacy.

The applicability of the modeling results to the DUPLEX study lies in the comparability of the patient populations used in the modeling with that of the DUPLEX population. While it is reasonable to expect comparability due to the manner in which patients were selected for inclusion in the modeling, an assessment of population comparability is planned when approximately 190 patients have been randomized and while the study is still completely blinded. These 190 randomized patients constitute the same patient population used in the sensitivity analysis of the surrogate endpoint at the time of interim analysis described in Section 6.6.2.2.

The comparability assessment will focus on baseline and demographic characteristics explored as potential prognostic factors in the previous modeling exercise. Continuous variables (ie, age, log UP/C, and eGFR) will be compared using t-tests. Categorical variables (ie, sex, race, and eGFR $\leq$ or >120 mL/min/1.73m^2) will be compared using chi-square tests. The specified baseline and demographic characteristics from DUPLEX will be compared against the corresponding variables from each of the following analysis datasets: NEPTUNE, FSGS-CT, DUET, pooled NEPTUNE + FSGS-CT, pooled DUET + NEPTUNE, and pooled NEPTUNE + FSGS-CT + DUET. Comparability of the DUPLEX population with a specific analysis dataset will be concluded if the null hypotheses of no difference for any of the 6 variables are not rejected at 2-sided $\alpha = 0.05$ following the Benjamini-Hochberg procedure to control the family-wise error rate.

If comparability cannot be concluded, the previous modeling exercise will be replicated on a subset of patients from the previous studies that match those from DUPLEX. Matching will be based on propensity scores. Results of the comparability assessment and the revised modeling, as applicable, will be communicated to the Food and Drug Administration prior to performing the planned unblinded interim analysis.

7.8. Impact of the COVID-19 Pandemic

Targeted summaries and listings will be presented to assess the impact of the COVID-19 pandemic on study disruptions, including alternative methods of assessment, missed visits, and collection of central laboratory data for efficacy endpoints. Assessment of protocol deviations due to COVID-19 is described in Section 7.3.
The following will be summarized by treatment group and overall at the interim analysis and final analysis:

- Patient count of missed visits by visit (overall and due to COVID-19)
- Patient count of visit type (onsite, phone, video, home health care, medical record review, other) by visit
- Patient count of missed central laboratory eGFR and UP/C assessments by visit (overall and due to COVID-19)
- Patient count of missed edema assessments by visit (overall and due to COVID-19)
- Patient count of missed blood pressure assessments by visit (overall and due to COVID-19)
- Patient count of local laboratory collection (eGFR only, UP/C only, any local labs) by visit

By-patient listings will be presented for patients discontinuing treatment due to COVID-19 and patients discontinuing the study due to COVID-19. A by-patient listing of all COVID-19 study disruptions, including protocol deviations, will also be presented. COVID-19 study disruptions will be identified from eCRF pages, central laboratory data, and protocol deviations.

8. EFFICACY

8.1. General Considerations

All efficacy analyses will be based on the FAS or IAS, as described below. The primary, surrogate, and secondary endpoint analyses will also be performed on the PP Analysis Set as supportive analyses. All primary efficacy analyses based on laboratory data will use central lab data only. All efficacy analyses specified below refer to the double-blind period only.

UP/C will be determined using first morning void urine samples and will be calculated as the geometric mean of 3 first morning void urine samples collected within 5 days prior to the visit. If one of the samples is missing, the average of the other 2 samples will be used. As UP/C is a highly right-skewed variable, analyses will be performed on log-transformed data. For ease of interpretation, results will be presented in the original units.

The eGFR for each baseline and post-baseline visit will be determined using the CKD-EPI (Levey 2009) formula for patients ≥16 years of age at the time of screening and the Modified Schwartz formula for patients <16 years of age at the time of screening (Schwartz 2009a; Schwartz 2009b).

For the purposes of efficacy analyses, an assessment is considered "on treatment" if it occurs after the first dose of study medication and no more than 3 days after the date of last dose of randomized treatment.

For all least-squares (LS) means that include strata coefficients, the observed strata proportions will be used instead of assuming equal sizes of strata.

8.2. Statement of the Null and Alternative Hypotheses

The final analysis of the primary endpoint in non-US countries will test the following hypothesis using the FAS:

- H_0: Slope of eGFR over the blinded treatment period (after adjusting for early hemodynamic effects) is equal between sparsentan and irbesartan
- H_1: Slope of eGFR over the blinded treatment period (after adjusting for early hemodynamic effects) is different between sparsentan and irbesartan

The final analysis of the primary endpoint in the US will test the following hypothesis using the FAS:

- H_0: Slope of eGFR over the blinded treatment period is equal between sparsentan and irbesartan
- H_1: Slope of eGFR over the blinded treatment period is different between sparsentan and irbesartan

The interim analysis of the surrogate endpoint at Week 36 will test the following hypothesis using the IAS:

- H_0: Proportion of patients achieving FPRE at Week 36 is equal between sparsentan and irbesartan

- H_1: Proportion of patients achieving FPRE at Week 36 is different between sparsentan and irbesartan

The final analysis of secondary efficacy endpoints in non-US countries will test the following hypotheses using the FAS:

- H_{01}: Percent change from Week 6 in eGFR at Week 108 is equal between sparsentan and irbesartan
- H_{11}: Percent change from Week 6 in eGFR at Week 108 is different between sparsentan and irbesartan
- H_{02}: Percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112 is equal between sparsentan and irbesartan
- H_{12}: Percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112 is different between sparsentan and irbesartan
- H_{03}: Slope of eGFR over the blinded treatment period is equal between sparsentan and irbesartan
- H_{13}: Slope of eGFR over the blinded treatment period is different between sparsentan and irbesartan

The final analysis of secondary efficacy endpoints in the US will test the following hypotheses using the FAS:

- H_{01}: Slope of eGFR over the blinded treatment period (after adjusting for early hemodynamic effects) is equal between sparsentan and irbesartan
- H_{11}: Slope of eGFR over the blinded treatment period (after adjusting for early hemodynamic effects) is different between sparsentan and irbesartan
- H_{02}: Change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112 is equal between sparsentan and irbesartan
- H_{12}: Change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112 is different between sparsentan and irbesartan

The treatment effect refers to the effect of sparsentan minus irbesartan.

8.3. Examination of Subgroups

At the final analyses, select efficacy endpoints (primary, surrogate, and secondary efficacy endpoints; eGFR change and percent change from baseline; and UP/C percent change from baseline) will be analyzed for patient subgroups using the FAS. The surrogate endpoint, eGFR change and percent change from baseline through Week 60, and UP/C percent change from baseline through Week 60 will also be analyzed for patient subgroups at the interim analysis using the IAS. In addition, select safety analyses (TEAEs) will also be analyzed for patient subgroups using the Safety Analysis Set. Baseline subgroups will be assessed at baseline only if there are a sufficient number of patients in each subgroup (eg, >5 patients per group). Post-baseline subgroups will be assessed at the time of analysis.

Baseline subgroups of interest are as follows:

- Age categories: <18, ≥18
- Age categories at FSGS diagnosis: <18, ≥18
- Sex: Male, Female
- Race: White, Black, Asian, Others
- Baseline BMI (kg/m^2): <27, ≥27
- Randomization strata:
  - Screening eGFR ≥30 to <60 mL/min/1.73m^2 and non-nephrotic (Screening UP/C ≤3.5 g/g for patients ≥18 years of age and ≤2 g/g for patients <18 years of age)
  - Screening eGFR ≥30 to <60 mL/min/1.73m^2 and nephrotic (Screening UP/C >3.5 g/g for patients ≥18 years of age and >2 g/g for patients <18 years of age)
  - Screening eGFR ≥60 mL/min/1.73m^2 and non-nephrotic (Screening UP/C ≤3.5 g/g for patients ≥18 years of age and ≤2 g/g for patients <18 years of age)
  - Screening eGFR ≥60 mL/min/1.73m^2 and nephrotic (Screening UP/C >3.5 g/g for patients ≥18 years of age and >2 g/g for patients <18 years of age)
- Baseline eGFR (mL/min/1.73m^2):
  - <60, ≥60 to <120, ≥120
  - <120, ≥120
- Baseline UP/C (g/g):
  - Non-nephrotic (≤3.5 for patients ≥18 years of age and ≤2 for patients <18 years of age)
  - Nephrotic (>3.5 for patients ≥18 years of age and >2 for patients <18 years of age)
- Prior use of the following RAAS inhibitors: Yes, No
  - ACE inhibitors
  - Angiotensin II receptor blockers (ARB)
  - Aldosterone blockers
  - Aliskiren
  - Any RAAS inhibitors
- Baseline use of the following medications: Yes, No
  - Any immunosuppressive agents
  - Steroids
  - Other immunosuppressive agents including CNIs, MMF, azathioprine, ACTH

  - Antihypertensive medications (except RAAS inhibitors) including diuretics
  - Diuretics
  - Statins and other hypolipidemic drugs
- Years since FSGS diagnosis: ≤10, >10
- Geographic region: North America, Europe, Asia Pacific, South America
- Baseline cardiovascular history: Yes, No
- History of hypertension: Yes, No
- Known mutation in podocyte proteins: Yes, No
- Post-baseline subgroups of interest as follows: Yes, No
  - Achievement of FPRE at Week 36, Week 60, or Week 108
  - Concomitant use (and no baseline use) of antihypertensive medications (except angiotensin-converting enzyme inhibitors [ACEIs], aldosterone blockers, aliskiren, or ARBs)
  - Concomitant use (and no baseline use) of diuretics
  - Concomitant use (and no baseline use) of immunosuppressive medications

Subgroup characteristics will be summarized by treatment group. For efficacy endpoints analyzed by a statistical model, the overall effect of the prognostic factor will be assessed by including a main effect for prognostic factor and a treatment by prognostic factor interaction term in the model. The treatment by prognostic factor interaction effect will be evaluated at a 0.20 level of significance to assess whether treatment effects vary by levels of prognostic factor. If the p-value for the treatment by prognostic factor interaction effect is <0.20, descriptive and inferential statistics will be presented for each subgroup level.

Additional subgroup analyses may be performed (eg, based on genetic testing results, exploratory biomarkers).

8.4. Multiple Comparisons and Multiplicity

The overall family-wise Type I error rate will be controlled by a hierarchical (gatekeeping) testing procedure.

The surrogate efficacy endpoint (UP/C response at Week 36) will first be tested at the interim analysis at 2-sided $\alpha = 0.05$. If the test is not significant, hypothesis testing stops. If the test is significant, then the following country-specific hierarchical testing will be performed.

For non-US countries, the hierarchy for the hypothesis testing will be as follows, if the test of the surrogate efficacy endpoint (UP/C response at Week 36) is significant:

1. test the primary efficacy endpoint (eGFR chronic slope over 2 years) at the final analysis at 2-sided $\alpha = 0.05$. If the test is not significant, hypothesis testing stops. If the test is significant,

2. test the 3 secondary endpoints using a Bonferroni-Holm procedure to control for family-wise error rate at 2-sided $\alpha = 0.05$.

For the US, the hierarchy for the hypothesis testing will be as follows, if the test of the surrogate efficacy endpoint (UP/C response at Week 36) is significant:

1. test the primary efficacy endpoint (eGFR total slope over 2 years) at the final analysis at 2-sided $\alpha = 0.05$. If the test is not significant, hypothesis testing stops. If the test is significant,
2. test the efficacy endpoint of eGFR chronic slope over 2 years at the final analysis at 2-sided $\alpha = 0.05$. If the test is not significant, hypothesis testing stops. If the test is significant,
3. test the efficacy endpoint of change in eGFR from baseline of the double-blind period to 4 weeks post-cessation of randomized treatment at Week 112 at the final analysis at 2-sided $\alpha = 0.05$.

For planned statistical tests that are not formally performed as a result of the aforementioned multiplicity adjustment strategy, nominal 2-sided p-values (without adjustment for multiplicity) will be computed as a measure of the strength of association between the endpoint and the treatment effect rather than formal tests of hypothesis.

8.5. Analysis of the Primary Efficacy Endpoint

8.5.1. Primary Efficacy Analysis

8.5.1.1. eGFR Chronic Slope over 2 Years

The primary efficacy analysis will be based on the FAS. The eGFR chronic slope over 2 years, defined as the slope of eGFR following the initial acute effect of randomized treatment (ie, Week 6 to Week 108), will be analyzed via a mixed-effects model with linear spline (ie, a 2-slope model with knot or change point at Week 6) with available eGFR data at the final analysis. The response variable is the eGFR measured at on-treatment, post-baseline assessments during the randomized treatment period for each patient. The model will include the following fixed effects:

- Treatment group (2 levels: sparsentan, irbesartan)
- Baseline eGFR
- Time from baseline (analysis visit, in weeks)
- Time from change point (in weeks)
- Treatment group by time from baseline interaction
- Treatment group by time from change point interaction
- Randomization stratification variable (4 levels based on Screening eGFR and UP/C)

In addition, the model will also include a random intercept and random slopes (time from baseline and time from change point) for each patient. The mixed model will utilize restricted maximum likelihood estimation with Kenward-Roger method to compute the denominator

degrees of freedom for tests of fixed effects. An unstructured covariance matrix will be assumed. If convergence issues arise, the autoregressive-1 covariance structure will be used.

The associated slope estimates within treatment group, difference in slopes, 95% CI, and 2-sided p-value will be extracted from the model. The treatment effect for the slope following the change point at Week 6 (ie, difference in slopes) will be the sum of the coefficients for the treatment group by time from baseline interaction and treatment group by time from change point interaction estimated from the model. Slope and the difference in slopes will be annualized for ease of presentation and interpretation.

8.5.1.2. eGFR Total Slope over 2 Years

The primary efficacy analysis will be based on the FAS. The eGFR total slope over 2 years, defined as the slope of eGFR following the initiation of randomized treatment (ie, Day 1 to Week 108), will be analyzed via a mixed-effects model with available eGFR data at the final analysis. The response variable is the eGFR measured at on-treatment, post-baseline assessments during the randomized treatment period for each patient. The model will include the following fixed effects:

- Treatment group (2 levels: sparsentan, irbesartan)
- Baseline eGFR
- Time from baseline (analysis visit, in weeks)
- Treatment group by time from baseline interaction
- Randomization stratification variable (4 levels based on Screening eGFR and UP/C)

In addition, the model will also include a random intercept and random slope for each patient. The mixed model will utilize restricted maximum likelihood estimation with Kenward-Roger method to compute the denominator degrees of freedom for tests of fixed effects. An unstructured covariance matrix will be assumed. If convergence issues arise, the autoregressive-1 covariance structure will be used.

The associated slope estimates within treatment group, difference in slopes, 95% CI, and 2-sided p-value will be extracted from the model. The treatment effect will be the contrast between sparsentan and irbesartan marginal slope estimates. Slope and the difference in slopes will be annualized for ease of presentation and interpretation.

8.5.2. Sensitivity Analyses of the Primary Efficacy Endpoint

Robustness of the primary analysis of the primary efficacy endpoint due to missing data or premature treatment discontinuations (including the impact of COVID-19) will be explored by the following sensitivity analyses:

- Mixed-effects model (as described in Section 8.5.1.1 and Section 8.5.1.2) with multiple imputation
- Tipping point approach of the multiple imputation analysis, as described in Section 6.6.1.2.2

- Mixed-effects model (as described in Section 8.5.1.1 and Section 8.5.1.2) using treatment completers only (patients who completed blinded treatment)
- Mixed-effects model (as described in Section 8.5.1.1 and Section 8.5.1.2) including local lab data

To assess the robustness of choice of change point, the primary efficacy analysis of eGFR chronic slope over 2 years will be repeated using a different change point at Week 4 and Week 8.

To assess the impact of changes in immunosuppressive medications, the primary efficacy analysis will be repeated by excluding assessments after initiation or intensification of immunosuppressive medication in the blinded treatment period.

To assess the potential impact of patient evaluability and major protocol deviations, the primary efficacy analysis will be repeated using the PP Analysis Set.

8.6. Analysis of the Surrogate Efficacy Endpoint

8.6.1. Primary Analysis

The primary analysis of the surrogate endpoint will be based on the IAS. The proportion of patients achieving FPRE, defined as UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline, will be analyzed using a generalized linear model with logit link function (using SAS PROC GENMOD) to model the probability of achieving FPRE. The response variable will be FPRE outcome through Week 60 (ie, only FPRE results through Week 60 will be included in the model). Missing response variables will be imputed using the MI procedure prior to analysis (see Section 6.6.2.1). Fixed effects in the model will include baseline UP/C (natural log), treatment, time (categorical, in weeks), and treatment by time interaction. Analysis will be stratified by randomization stratification variable (4 levels based on Screening eGFR and UP/C). An unstructured covariance matrix within subject will be assumed. If convergence issues arise, the autoregressive-1 covariance structure will be used.

The probability of achieving FPRE at Week 36 (risk) for each treatment group, treatment effect at Week 36 (risk difference), standard errors of risk and risk difference, 95% CIs of risks and risk difference, and p-values will be extracted from the model. Relative risk ratios and odds ratios, along with 95% CIs, will also be presented. Relative risk will be obtained from the same model described above with the exception that a Poisson distribution with log link function will be used.

The primary analysis described above will also be performed using the FAS population at the final analysis using all data through Week 108.

8.6.2. Sensitivity Analyses of the Surrogate Efficacy Results

Robustness of primary analysis of the surrogate endpoint due to missing data and premature discontinuations (including COVID-19) will be explored by the following sensitivity analyses:

- CMH test, adjusting for the 2 randomization stratification factors to compare sparsentan with irbesartan, using Week 36 results only (without imputation), based on the same population used in the analysis per Section 7.7. Only patients who would have been expected to have completed Week 36 based on the date of first dose will be

included; that is, subjects who discontinue prior to Week 36 but would have been expected to have completed Week 36 will be included. Patients with missing data at Week 36 will be considered non-responders. This sensitivity analysis was the originally planned primary analysis.

- CMH test with inclusion of UP/C assessments from a single urine sample
- Tipping point approach of the multiple imputation analysis as described in Section 6.6.1.2.2
- Observed cases analyzed using the primary model generalized linear model (no imputation)
- Inclusion of local lab data with central lab data analyzed using the primary model generalized linear model (no imputation)

To assess the potential impact of patient evaluability and major protocol deviations, the primary efficacy analysis will be repeated using the PP Analysis Set.

8.7. Analysis of the Secondary Efficacy Endpoints

8.7.1. Percent Change of eGFR from Week 6 to Week 108

The percent change of eGFR from Week 6 to Week 108 will be analyzed at the final analysis based on the FAS, using MMRM. The dependent variable will be all available on-treatment natural log(eGFR) data from Week 2 to Week 108. The model will include the following fixed effects:

- Treatment group (2 levels: sparsentan, irbesartan)
- Baseline eGFR in log scale
- Visit (categorical)
- Treatment group by visit interaction
- Randomization stratification variable (4 levels based on Screening eGFR and total urine protein)

In addition, patient will be included as a random effect.

The model will utilize restricted maximum likelihood estimation with Kenward-Roger method used to compute the denominator degrees of freedom for tests of fixed effects. An unstructured covariance matrix will be assumed. If convergence issues arise, autoregressive-1 covariance structure will be used.

Statistical significance of the treatment effect at Week 108 will be assessed by comparing with the treatment effect at Week 6. The LS mean estimate from the MMRM model will be used to perform treatment group comparisons. Estimates and CIs will be converted to percentages via the following transformations:

$$[\exp(\text{least squares mean change from Week 6 in natural log(eGFR)}) - 1] \times 100$$

Robustness of the analysis due to missing data and premature treatment discontinuations will be explored by the following sensitivity analyses:

- MMRM using multiple imputation
- MMRM using treatment completers only (patients who completed blinded treatment)

To assess the impact of changes in immunosuppressive medications, the analysis will be repeated by excluding assessments after initiation or intensification of immunosuppressive medication in the blinded treatment period.

To assess the potential impact of patient evaluability and major protocol deviations, the analysis will be repeated using the PP Analysis Set.

8.7.2. Change in eGFR from Baseline to 4 Weeks Post-cessation of Randomized Treatment (Week 112)

The change from baseline to 4 weeks post-cessation of randomized treatment (Week 112) will be analyzed via an analysis of covariance (ANCOVA) model using the FAS at final analysis. Only subjects who completed the 108-week treatment period will be included. The dependent variable will be the eGFR at analysis visit Week 112, with treatment and baseline eGFR included as fixed effects. The analysis will be stratified by the randomization strata. The treatment effect will be the contrast between sparsentan and irbesartan LS means. The LS means, treatment effect estimate, 95% CI, and p-value will be presented.

Robustness of the analysis due to missing data and premature treatment discontinuations will be explored by assessing the change from baseline to 4 weeks post End of Treatment (EOT) analysis visit.

To assess the impact of changes in immunosuppressive medications, the analysis will be repeated by excluding assessments after initiation or intensification of immunosuppressive medication in the blinded treatment period.

To assess the potential impact of patient evaluability and major protocol deviations, the analysis will be repeated using the PP Analysis Set.

8.7.3. Percent Change in eGFR from Baseline to 4 Weeks Post-cessation of Randomized Treatment (Week 112)

The percent change from baseline to 4 weeks post-cessation of randomized treatment (Week 112) will be analyzed using the FAS at final analysis using an ANCOVA model analogous to the one described in Section 8.7.2, with the exception that the response variable and corresponding baseline will be in natural log scale. Only subjects who completed the 108-week treatment period will be included. Estimates and CIs will be converted to percentage via the following transformations:

$$[\exp(\text{least squares mean change from baseline in natural log(eGFR)}) - 1] \times 100$$

Robustness of the analysis due to missing data and premature treatment discontinuations will be explored by assessing the change from baseline to 4 weeks post EOT analysis visit.

To assess the impact of changes in immunosuppressive medications, the analysis will be repeated by excluding assessments after initiation or intensification of immunosuppressive medication in the blinded treatment period.

To assess the potential impact of patient evaluability and major protocol deviations, the analysis will be repeated using the PP Analysis Set.

8.8. Analysis of Other Efficacy Endpoints

8.8.1. eGFR Endpoints

8.8.1.1. eGFR Chronic Slope over 1 Year

The slope of eGFR over approximately 1 year of randomized treatment evaluated following the initial acute effect of randomized treatment (ie, from Week 6 to Week 60; chronic slope over 1 year) will be analyzed via the mixed model random coefficients analysis described in Section 8.5.1.1 using IAS at the time of interim analysis and FAS at final analysis. The response variable is the eGFR measured at on-treatment, post-baseline assessments during the randomized treatment period up to and including Week 60 for each patient.

8.8.1.2. eGFR Total Slope over 1 Year

The slope of eGFR over approximately 1 year of randomized treatment evaluated following initiation of randomized treatment (ie, from Day 1 to Week 60; total slope over 1 year) will be analyzed via the mixed model random coefficients analysis described in Section 8.5.1.2 using IAS at the time of interim analysis and FAS at final analysis. The response variable is the eGFR measured at on-treatment, post-baseline assessments during the randomized treatment period up to and including Week 60 for each patient.

8.8.1.3. eGFR Absolute Change from Baseline

For the analysis of eGFR absolute change from baseline by visit (Week 2 to Week 112), an MMRM approach analogous to the model described in Section 8.7.1 for percent change from Week 6 will be used, except that the response variable and corresponding baseline value is in original scale rather than natural log scale. Analysis will be performed using IAS at interim analysis and FAS at final analysis. At the interim analysis, only eGFR results through Week 60 will be included. Change from baseline will be derived at each visit by subtracting the coefficient for baseline used to derive the LS mean from the LS mean estimate for the visit. The LS mean estimate for $\beta_{\text{week j*treatment}}$ (ie, the treatment effect at the visit j of interest) from the MMRM model will be used to perform treatment group comparisons by visit.

8.8.1.4. eGFR Percent Change from Baseline

For the analysis of eGFR percent change from baseline by visit, an MMRM approach analogous to the model described in Section 8.7.1 will be used. Analysis will be performed using IAS at interim analysis and FAS at final analysis. At the interim analysis, only eGFR results through Week 60 will be included. Change from baseline will be derived at each visit by subtracting the coefficient for baseline used to derive the LS mean from the LS mean estimate for the visit. The LS mean estimate for $\beta_{\text{week j*treatment}}$ (ie, the treatment effect at the visit j of interest) from the MMRM model will be used to perform treatment group comparisons by visit. Estimates and CIs will be converted to percentages via the following transformations:

$$[\exp(\text{least squares mean change from baseline in natural log(eGFR))} - 1] \times 100$$

8.8.1.5. eGFR Percent Change from Week 6

For the analysis of eGFR percent change from Week 6 by visit, the estimates from the MMRM model used in the analysis of eGFR relative percent change from baseline by visit described in Section 8.7.1 will be utilized. Analysis will be performed using IAS at interim analysis and FAS at final analysis. At the interim analysis, only eGFR results through Week 60 will be included. Statistical significance of the treatment effect at each visit after Week 6 will be assessed by comparing with the treatment effect at Week 6. Treatment effect refers to the treatment difference of sparsentan minus irbesartan. The LS mean estimate from the MMRM model will be used to perform treatment group comparisons. Estimates and CIs will be converted to percentages via the following transformations:

[exp(least squares mean change from Week 6 in natural log(eGFR)) – 1] × 100

8.8.2. UP/C Endpoints

8.8.2.1. Proportion of Patients Achieving FPRE

For the analysis of the proportion of patients achieving FPRE, defined as UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline, the by-visit estimates from the model described in Section 8.6.1 will be utilized. Analysis will be performed using IAS at interim analysis and FAS at final analysis. At interim analysis, only FPRE results through Week 60 will be included. LS means for the probability of achieving FPRE (risk) for each treatment group and treatment effect (risk difference) at each visit will be extracted from the model. Relative risk ratio and odds ratio will also be presented.

8.8.2.2. UP/C Percent Change from Baseline

For the analysis of UP/C percent change from baseline by visit, an MMRM approach analogous to the model described in Section 8.8.1.4 for eGFR percent change from baseline will be used for IAS at interim analysis and FAS at final analysis. At interim analysis, only UP/C results through Week 60 will be included. Change from baseline will be derived at each visit by subtracting the coefficient for baseline used to derive the LS mean from the LS mean estimate for the visit. The LS mean estimate for $\beta_{\text{week j*treatment}}$ (ie, the treatment effect at the visit j of interest) from the MMRM model will be used to perform treatment group comparisons by visit. Estimates and CIs will be converted to percentages via the following transformations:

[exp(least squares mean change from baseline in natural log(UP/C)) – 1] × 100

8.8.2.3. Time to Achieve FPRE

The time to achieve FPRE (ie, time to first occurrence of FPRE), defined as UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline, will be analyzed for IAS at interim analysis and FAS at final analysis using a Cox proportional hazards model with treatment and baseline UP/C (natural log) as fixed effects and stratified by randomization stratification variables. Patients who discontinue randomized treatment prior to achieving FPRE will be censored at the time of randomized treatment discontinuation. Patients who never met FPRE will be censored at the time of analysis (ie, data cut-off date for interim analysis or time of study discontinuation for final analysis) or the time of treatment completion in the randomized treatment period (whichever is earlier).

8.8.3. Other Quantitative Urinalysis Parameters

For the analysis of change from baseline by visit for other quantitative urinalysis parameters, a MMRM approach analogous to the model described in Section 8.8.1.4 for eGFR percent change from baseline will be used for IAS at interim analysis and FAS at final analysis. At interim analysis, only quantitative urinalysis results through Week 60 will be included. Change from baseline will be derived at each visit by subtracting the coefficient for baseline used to derive the LS mean from the LS mean estimate for the visit. The LS mean estimate for $\beta_{\text{week j*treatment}}$ (ie, the treatment effect at the visit j of interest) from the MMRM model will be used to perform treatment group comparisons by visit. Estimates and CIs will be converted to percentages via the following transformations:

[exp(least squares mean change from baseline in natural log(UP/C)) – 1] × 100

8.8.4. Other Responder Endpoints

The following responder endpoints will be summarized descriptively for FAS at both the interim and final analysis and compared (at final analysis only) between treatment groups using a CMH test controlling for the randomization variables:

- The proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or death. ESRD is defined as initiation of RRT or sustained eGFR <15 mL/min/1.73^2 during the study (confirmed after repeat assessment of at least 14 days after initial assessment)
- The proportion of patients reaching a confirmed 30% reduction in eGFR, ESRD, or death
- The proportion of patients requiring initiation or intensification in immunosuppressive medication during the study
- The proportion of patients undergoing reduction in immunosuppressive medication during the study

Reduction of eGFR requires confirmation by a value at least 4 weeks after the initial value. If the last value on randomized treatment is the initial value for reduction or eGFR <15 mL/min/1.73^2 then the last value on randomized treatment is considered confirmed or sustained.

Initiation of RRT will be entered on the Concomitant Procedures eCRF as “chronic dialysis” or “kidney transplant” and on the Adverse Events eCRF as “progression of CKD leading to chronic dialysis” or “progression of CKD requiring kidney transplant”.

8.8.5. Other Continuous Endpoints

Changes from baseline to all post-baseline visits with respect to QOL scores (including KDQOL, PedsQL, EQ-5D-5L index value and VAS, EQ-5D-Y VAS) and blood pressure (including systolic and diastolic excluding Day 1 post-dose) values will be analyzed for FAS at final analysis using an MMRM model analogous to the one described in Section 8.8.1.4 for eGFR percent change from baseline will be used. Change from baseline for blood pressure will also be analyzed for IAS at interim analysis. Only blood pressure results through Week 60 will be included in the interim analysis.

8.8.6. Other Events Endpoints

The number of hospitalization days during the study will be analyzed descriptively, and the incidence of patient hospitalizations will be analyzed using Fisher's exact test, for FAS at final analysis. Separate analyses will be presented for hospitalizations due to any reason and due to reasons related to the kidney.

8.8.7. Other Categorical Endpoints

Shifts in EQ-5D-5L and EQ-5D-Y health states from baseline to worst value (scheduled or unscheduled), last value (scheduled or unscheduled), and at each scheduled post-baseline visit will be provided by treatment group for FAS at final analysis.

8.8.8. Other Time-to-Event Endpoints

For the time-to-event analyses, patients who do not experience an event will be censored at the time of analysis (if still on randomized treatment) or the time of randomized treatment discontinuation (whichever is earlier). Treatment groups will be compared using a log rank test stratified by the randomization stratification variables for FAS at both interim and final analysis. KM estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM estimate of the medians and corresponding 95% CIs, if the medians can be estimated.

8.8.9. Other Immunosuppressive Agent Endpoints

The following endpoints related to use of immunosuppressive agents will be analyzed for IAS at the time of interim analysis and FAS at final analysis and compared (at final analysis only) between treatment groups.

The number of days treated with immunosuppressive agents while on randomized treatment and the total number of episodes of immunosuppressive agent use while on randomized treatment will be analyzed using a negative binomial regression model, via PROC GENMOD in SAS. Specifically, the model will compare treatment groups, adjusted for the randomization stratification factors, and will include the natural log transformation of duration of exposure in the double-blind period as an offset term. Estimated event rates will be extracted from the model for each treatment. The treatment effect will be presented as the ratio of event rates, along with the associated 95% CI and 2-sided p-value.

The time to first post-baseline immunosuppressive agent use while on treatment in the randomized treatment period will be analyzed per Section 8.8.8. Patients with no on-treatment use of immunosuppressive agents will be censored at the time of analysis (if still on randomized treatment) or the time of discontinuation of randomized treatment, whichever is earlier.

9. PHARMACOKINETICS

The PK Analysis Set will be used for all PK analyses. Trough plasma levels of study medication will be summarized at both interim and final analysis with descriptive statistics over time by treatment group, including the geometric mean and geometric CV%. Analyte concentrations below the lower limit of quantification will be indicated by BLQ (below limit of quantitation) and set to missing. However, the number of BLQs at each time point will be provided in the summary table.

10. SAFETY AND TOLERABILITY

Safety analyses will be conducted using the Safety Analysis Set at both interim and final analysis. At the interim analysis, all available data will be summarized. Unless otherwise noted, all safety analyses will be conducted using on-study data. All safety analyses specified below refer to the double-blind period only, except where noted. If >5% of patients initiate RRT while on study, select summaries excluding results after initiation of RRT may be prepared.

10.1. Adverse Events

Adverse event (AE) data will be collected from the time that signed informed consent is obtained until the patient fully completes his/her participation in the study.

All AE summaries will be restricted to TEAEs, which is defined as any AE that newly appears, increases in frequency, or worsens in severity following the initiation of study medication. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as treatment emergent. Verbatim terms will be coded to PT and SOCs using MedDRA.

Each AE summary will be displayed by treatment group. Summaries that are displayed by SOC and PT will be ordered by descending order of incidence of SOC and PT within each SOC. Summaries of the following types will be presented:

- Overall summary of TEAEs
- Patient incidence of TEAEs and the total number of entries by SOC and PT
- Patient incidence of TEAEs and the total number of entries by PT in descending order
- Patient incidence of TEAEs by SOC, PT, and highest severity. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity will be considered severe for this summary.
- Patient incidence and total number of entries of severe TEAEs by SOC and PT. AEs with missing severity will be considered severe for this summary.
- Patient incidence of TEAEs by SOC, PT, and closest relationship to study medication (Related/Not Related). Related AEs are those with relationships reported as “Possibly Related” or "Related" and unrelated AEs are those with relationships reported as “Unlikely Related” or “Not Related.” At each level of patient summarization, a patient is classified according to the closest relationship to study medication if the patient reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Patient incidence and total number of entries of related TEAEs by MedDRA SOC and PT. AEs with a missing relationship will be considered related for this summary.
- Patient incidence of serious TEAEs and the total number of entries by SOC and PT
- Patient incidence of TEAEs leading to treatment discontinuation by SOC and PT
- Patient incidence and total number entries of treatment-emergent adverse events of interest (AEOIs) by SOC and PT

- Patients incidence and total number of entries of TEAEs associated with safety topics of interest by PT
- Patients incidence and total number of entries of related TEAEs associated with safety topics of interest by PT
- Patients incidence and total number of entries of serious TEAEs associated with safety topics of interest by PT

10.1.1. Adverse Events of Interest

Abnormal liver function tests that meet the below criteria are considered AEOIs:

- The abnormality represents new elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN), with or without an elevation of total serum bilirubin >2 times ULN
- The abnormality represents a 2-fold increase in ALT or AST above the baseline value in patients who had elevated values prior to starting study medication.

As described in Section 10.1, patient incidence of treatment-emergent AEOIs will be summarized by treatment group.

In order to explore the relationship between liver function abnormalities and study medication, the following time-to-event analysis will be performed:

- Time to first onset of treatment-emergent AEOI
  - The time to the start of the first occurrence will be calculated by the date of onset of first AEOI – date of first dose of study medication + 1
  - Patients who never reported an AEOI will be censored at the date of completion or discontinuation in randomized treatment period or data cut-off date of analysis, whichever is earlier
- Time to resolution of the most severe treatment-emergent AEOI
  - If multiple treatment-emergent AEOIs with the same preferred term with increasing severity were reported for the same patient, the time to resolution will be calculated by the date of resolution of the most severe event – start of the initial event + 1
  - Otherwise, the time to resolution will be calculated by the date of resolution of the event – start of the event + 1
  - Patients whose most severe treatment-emergent AEOI is ongoing will be censored at the date of completion or discontinuation in randomized treatment period or data cut-off date of analysis, whichever is earlier
  - Only patients who had reported a treatment-emergent AEOI are included in this analysis.

The analysis of time to event will include the number of patients with, the number of patients without event (censored), descriptive statistics of time for those with an event, and range in days for all patients. KM estimates will be calculated by treatment group. The quartiles, including the

median time-to-event and their respective 2-sided 95% CIs, will be presented. KM estimates will be plotted as a cumulative probability plot for each treatment group, with the number at risk identified.

10.1.2. Other Safety Topics of Interest

The following summaries of TEAEs associated with safety topics of interest will include incidence of TEAE, treatment related TEAE, and serious TEAEs by PT and will be prepared separately for TEAEs on-study and on-treatment. All Sponsor-defined terms will be identified prior to database lock for the interim analysis and will be included in the clinical study report.

- Cardiovascular System associated TEAEs comprised of terms in the Cardiac SOC, Vascular SOC, and Cardiac Arrythmias Standardized MedDRA query (SMQ). Separate summaries of terms in the Cardiac Arrythmias SMQ will also be prepared.
- Hypotension associated TEAEs comprised of Sponsor-defined terms
- Hepatic associated TEAEs comprised of terms in the Hepatic Disorders SMQ, excluding the following sub-SMQs: alcohol related sub-SMQ, congenital, familial, neonatal and genetic disorders of the liver; liver infections; and pregnancy-related hepatic disorders
- Pancreatic associated TEAEs comprised of terms in the Acute Pancreatitis SMQ
- Fluid Retention associated TEAEs comprised of terms in the Haemodynamic Oedema, Effusions, and Fluid Overload SMQ
- Anemia associated TEAEs comprised of Sponsor-defined terms

10.1.3. On-Treatment Summaries

Select summaries for TEAEs while on-treatment will additionally be prepared. On-treatment will be defined as TEAEs starting ≤30 days from date of last dose in randomized treatment period for patients who discontinue treatment or any TEAE prior to first dose in OLE for patients who complete the randomized treatment period. Summaries will be prepared for TEAEs associated with safety topics of interest in Section 10.1.2. Patient incidence of on-treatment TEAEs and the total number of entries by PT will also be provided.

10.1.4. Adverse Events during OLE

At the interim analysis, summaries of adverse events with onset on or after the first dose of sparsentan in the OLE will be presented for the OLEFAS by randomized treatment group and overall. Time-to-event analyses will not be performed due to the anticipated small sample size.

10.2. Extent of Exposure and Compliance

The following extent of exposure parameters will be summarized both continuously using descriptive statistics and categorically using counts and percentages by treatment group and overall:

- Duration of treatment (weeks)
- Duration of treatment with initial/reduced dose (weeks)

- Duration of treatment with target dose (weeks)
- Time to titration to target dose (weeks)
- Total duration of study medication interruptions (days)

Duration of treatment (weeks) will be calculated as follows:

- Duration of treatment = (Date of last dose of study medication – Date of first dose of study medication + 1) / 7

Duration of treatment with initial/reduced dose and duration of treatment with target dose will be calculated similarly. For patients who received the target dose on Day 1, the duration of treatment with initial/reduced dose will be set to 0.

For patients who titrated to the target dose, the time to titration to target dose (weeks) will be calculated as follows:

- Time to titration to target dose = (Date of first dose of target dose – Date of first dose of study medication + 1) / 7

The duration of each incidence of study medication interruption will be calculated as follows:

- Duration of study medication interruption = (Date of restart of study medication – Date of temporary discontinuation)

The total duration of study medication interruptions is the sum of duration of study medication interruption over each incidence of interruption. For patients with no study medication interruption, the total duration is considered 0 days.

A summary of patients who had dose modifications will be presented by frequency count and percentages:

- Titration to target dose
- Dose reductions after titration to target dose

Patient's compliance rate (%) with study medication during the treatment period will be calculated as follows at the final analysis:

- 100 × {(Total number of capsules dispensed – Total number of capsules returned)/(Expected number of capsules to be taken based on the patient's titration schedule)}

Compliance rates will be summarized both continuously using descriptive statistics and categorically using counts and percentages by treatment group and overall.

Compliance will also be derived from the dose log to supplement the assessment using drug dispensation and return. Compliance based on the dose log for each patient will be determined as follows:

- Total number of capsules taken = sum over all actual dose intervals, where an actual dose interval is defined as any dose log record where actual dose > 0 capsules and derived as number of days × number of capsules

- Total number of capsules missed = sum over all missed dose intervals defined as any record where dose = 0 capsules and eCRF indicates missed dose; derived as number of days × number of expected capsules
- Total number of capsules taken over prescribed dose = sum of all dose intervals where dose log indicates overdose and derived as number of days × number of capsules
- Dose log compliance = 100 × (Total number of capsules taken)/(Total number of capsules taken + Total number of capsules missed – Total number of capsules taken over prescribed dose)

10.3. Prior and New Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be collected from 3 months prior to screening through the patient's final study visit. In addition, a lifetime history of medications previously used for treatment of FSGS, including systemic corticosteroids or other systemic immunotherapeutic agents, will be collected. For medications, verbatim terms on eCRFs will be mapped to Anatomical Therapeutic Chemical (ATC) class and preferred name using the World Health Organization (WHO) Drug Dictionary Enhanced. For procedures, verbatim terms will be mapped to PT and SOC using MedDRA.

Pretreatment concomitant medications are those medications with start and stop dates prior to the initial dose of study medication. Prior concomitant medications are those medications started prior to and continued after the initial dose of study medication. New concomitant medications are those medications that were started after the initial dose of study medication. If it cannot be determined whether the medication was a new concomitant medication due to a partial start or stop date or if the medication is taken on the same date as the initial dose of study medication, then it will be counted as a new concomitant medication.

Similarly, prior procedures are those procedures with a start date prior to initial dose of study medication. Concomitant procedures are those procedures that were started after the initial dose of study medication.

Select pretreatment medications, including ACEIs, aldosterone blockers, aliskiren, ARBs, corticosteroids, immunosuppressive medications, diuretics, any other antihypertensives, and lipid-lowering medications will be summarized for each treatment group by WHO ATC level 2, WHO ATC level 4, and preferred name. All other pretreatment medications will be listed only.

Prior and new concomitant medications will be summarized for each treatment group by WHO ATC level 2, WHO ATC level 4, and preferred name. In addition, prior and new concomitant medications will be summarized separately. These summaries will present the number and percentage of patients using each medication. Patients may have more than 1 medication per ATC level and preferred name. At each level of patient summarization, a patient is counted once if he/she reported 1 or more medications at that level. Each summary will be ordered by descending order of incidence of ATC level and preferred name within each ATC level.

Prior and concomitant procedures will be summarized for each treatment group by SOC and PT.

10.4. Clinical Laboratory Evaluations

Laboratory parameters will be summarized in the standard international system of units. Quantitative laboratory results will be summarized by treatment group using descriptive statistics at baseline and each post-baseline scheduled visit. Both absolute and percentage change from baseline will also be summarized.

10.4.1. Shifts in Normal Range

Shift tables (ie, low-normal-high at baseline versus low-normal-high at post-baseline visit in a 3-by-3 contingency table) from baseline to worst (including scheduled or unscheduled) and last value (scheduled or unscheduled) will be provided for hematology, serum chemistry, and coagulation by treatment group. For urinalysis parameters, a shift table depicting shifts to/from positive/negative from baseline to worst and last value will be provided.

10.4.2. Shifts in CTCAE Toxicity Grade

Shifts in Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade of laboratory tests from baseline to worst value (scheduled or unscheduled), last value (scheduled or unscheduled), and at each scheduled post-baseline visit will be provided by treatment group. The toxicity grades are in the CTCAE Version 4.03.

Summaries will present the number and percentage of patients with shifts in laboratory toxicity grade by treatment group.

10.4.3. Incidence of Liver Function Abnormalities

The incidence of patients with abnormalities in liver function tests (ALT, AST, alkaline phosphatase [ALP], and total bilirubin) will be summarized overall for the following categories:

- ALT and AST:
  - >1 × ULN
  - >2 × ULN
  - >3 × ULN
  - >5 × ULN
  - >8 × ULN
- ALP:
  - >1 × ULN
  - >1.5 × ULN
  - >2.5 × ULN
  - >5 × ULN

- Total bilirubin:
  - >1 × ULN
  - >1.5 × ULN
  - >2 × ULN
  - >3 × ULN

Scatterplots of ALT versus AST, ALT versus total bilirubin, and AST versus total bilirubin maximum post-baseline values will be presented. If appropriate, evaluation of drug-induced serious hepatotoxicity plots of ALT or AST >3 × ULN accompanied with total bilirubin by treatment group will be presented for assessment of potential drug-induced liver injury. A listing of patients with >2 × ULN total bilirubin and >3 × ULN ALT or AST at any time on study will be provided.

10.4.4. Incidence of Clinically Significant Local Labs

The incidence of patients with clinically significant local labs will be summarized by treatment group and overall at each baseline and post-baseline visit for each local lab parameter collected. Percentage will be based on the number of patients with local lab results for each parameter and visit.

10.5. Vital Signs

The results and change from baseline to each post-baseline scheduled visit will be summarized for blood pressure (systolic and diastolic), heart rate, respiration rate, temperature, and weight.

The number and percentage of patients meeting the following criteria at any time during the study will also be summarized:

- Systolic Blood Pressure:
  - ≤100 mmHg
  - A decrease from baseline more than 30 mmHg
  - >180 mmHg
  - An increase from baseline more than 40 mmHg
- Diastolic Blood Pressure:
  - ≤60 mmHg
  - A decrease from baseline more than 20 mmHg
  - >105 mmHg
  - An increase from baseline more than 20 mmHg
- Heart Rate:
  - <45 beats per minute
  - A decrease from baseline more than 20 beats per minute

- >120 beats per minute
- An increase from baseline more than 20 beats per minute

For the analysis of orthostatic hypotension, the number and percentage of subjects with >20 mmHg decrease in systolic blood pressure at any time and the number and percentage of subjects with >10 mmHg decrease in diastolic blood pressure at any time will be presented.

10.6. Electrocardiogram

The results and change from baseline to each post-baseline scheduled visits will be summarized by descriptive statistics for heart rate, PR, RR, QRS, QT, and QTcF.

The number of patients with QTcF intervals >450 msec, >480 msec, and >500 msec, as well as increases from baseline >30 msec and >60 msec, will be presented overall and by scheduled visit.

Shift tables (ie, normal-abnormal not clinically significant [NCS]-abnormal clinically significant [CS] at baseline versus normal-abnormal NCS-abnormal CS at post-baseline visit in a 3-by-3 contingency table) from baseline to worst (including scheduled or unscheduled), last value (scheduled or unscheduled), and at each scheduled visit will be presented by treatment group.

A by-patient listing will also be provided.

10.7. Physical Examination

The number and percentage of patients with physical examination abnormalities at each visit will be summarized and presented by body system.

10.7.1. Peripheral Edema

The presence and staging of peripheral edema will be summarized by frequency counts and percentages based on the following grade scale: 0, 1+ (trace), 2+ (mild), 3+ (moderate), and 4+ (severe), where 0 denotes no presence of edema. A shift table indicating changes in edema severity from baseline to worst (including scheduled and unscheduled), last value (scheduled and unscheduled), and at each scheduled post-baseline visit will be provided by treatment group.

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