Statistical Analysis Plan

A Randomized, Multicenter, Double-blind, Parallel-group, Active-control Study of the Efficacy and Safety of Sparsentan for the Treatment of Immunoglobulin A Nephropathy

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STATISTICAL ANALYSIS PLAN, VERSION 3.0

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A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PARALLEL-GROUP, ACTIVE-CONTROL STUDY OF THE EFFICACY AND SAFETY OF SPARSENTAN FOR THE TREATMENT OF IMMUNOGLOBULIN A NEPHROPATHY

Investigational Medicinal Product:	Sparsentan
Product Code:	RE-021
Protocol Number:	021IGAN17001 (PROTECT)
Developmental Phase:	Phase 3
Based On:	021IGAN17001 Protocol Amendment 5 (06 April 2021)
Sponsor:	Travere Therapeutics, Inc. 3611 Valley Centre Drive, Suite 300 San Diego, CA 92130 USA

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1. LIST OF ABBREVIATIONS

Abbreviation	Term
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse event
AEOI	Adverse events 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 limit of quantification
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
EQ-5D-5L	EuroQol 5-dimension, 5-level quality of life
ESRD	End-stage renal disease
FAS	Full Analysis Set
IgAN	Immunoglobulin A nephropathy
IQR	Interquartile range
IRT	Interactive response technology
KDQOL	Kidney Disease Quality of Life
KM	Kaplan-Meier
LS	Least squares
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MCS	Mental component summary

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MI	Multiple imputation
MLD	Maximum labeled dose
MMRM	Mixed Model Repeated Measures
OLE	Open-label extension
PAS	Primary Analysis Set
PCS	Physical component summary
PK	Pharmacokinetic
PP	Per Protocol
PPFA	Per Protocol at Final Analysis
PPPA	Per Protocol at Primary Analysis
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
TEAE	Treatment-emergent adverse event
UA/C	Urine albumin/creatinine ratio
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 021IGAN17001 (PROTECT) 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 primary 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 (CSR).

Protocol Revision Chronology		
Amendment 5	06 April 2021	Amendment
Amendment 4	13 July 2020	Amendment
Amendment 3	10 March 2020	Amendment
Amendment 2	07 May 2019	Amendment
Amendment 1	07 March 2019	Amendment
Original Protocol (US-specific)	10 September 2018	Original
Original Protocol	06 April 2018	Original

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Double-Blind Period

3.1.1.1. Efficacy Objective

The efficacy objective of the double-blind period of the study is to determine the effect of sparsentan on proteinuria and preservation of renal function as compared to an angiotensin receptor blockers in patients with immunoglobulin A nephropathy (IgAN).

3.1.1.2. Safety Objective

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

3.1.2. Open-Label Extension Period

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

3.2. Study Endpoints

3.2.1. Efficacy Endpoints – Double-Blind Period

3.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline (Day 1) in the urine protein/creatinine ratio (UP/C), based on a 24-hour urine sample, at Week 36.

3.2.1.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are listed below:

- The rate of change in estimated glomerular filtration rate (eGFR) over a 52-week (approximately 1-year) period following the initial acute effect of randomized therapy (the initial acute effect of randomized therapy is defined as the first 6 weeks of randomized treatment with study medication; thus, the analysis is from 6 weeks post randomization to 58 weeks post randomization; eGFR chronic slope at 1 year)
- The rate of change in eGFR over a 104-week (approximately 2-year) period following the initial acute effect of randomized therapy (the initial acute effect of randomized therapy is defined as the first 6 weeks of randomized treatment with study medication; thus, the analysis is from 6 weeks post randomization to 110 weeks post randomization; eGFR chronic slope at 2 years)
- The rate of change in eGFR over a 110-week (approximately 2-year) period following the initiation of randomized therapy (thus, the analysis is from Day 1 to 110 weeks post randomization; eGFR total slope at 2 years)

3.2.1.3. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints are listed below:

- The mean change from baseline over time in eGFR and selected proteinuria variables, based on a 24-hour urine sample (eg, urine protein excretion, urine albumin excretion, urine albumin/creatinine ratio [UA/C], and UP/C) up to Week 110
- 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

3.2.2. Exploratory Endpoints – Double-Blind Period

Exploratory endpoints are listed below:

- The rate of change in eGFR over a 58-week (approximately 1-year) period following the initiation of randomized therapy (thus, the analysis is from Day 1 to 58 weeks post randomization; eGFR total slope at 1 year)
- The change from baseline in eGFR at 6 weeks post randomization (ie, the acute effect of randomized therapy)
- The change from end of treatment (EOT, ie, Week 110) in eGFR 4 weeks following cessation of treatment (ie, at Week 114)
- Change in eGFR from baseline to 4 weeks post cessation of randomized treatment (Week 114)
- Achievement of urinary protein excretion of <0.3 g/day up to Week 110
- Achievement of urinary protein excretion of <1.0 g/day up to Week 110
- The proportion of patients with hematuria at each visit
- Changes from baseline in blood pressure at each visit
- The proportion of patients requiring systemic immunosuppressive medication during the study
- Mean changes from baseline in quality of life (QoL), measured via patient-reported outcome (PRO) at each visit
- Frequency and duration of hospitalizations (for any reason and for reasons related to the kidney)
- Trough plasma pharmacokinetic (PK) concentrations

3.2.3. Safety Endpoints – Double-Blind Period

Safety endpoints include the following:

- Changes from baseline in body weight, vital signs, physical examination, peripheral edema, and clinical laboratory parameters
- The incidence of treatment-emergent adverse events (TEAEs)

3.2.4. Open-Label Extension Period Endpoints

Endpoints for the OLE will be described in the separate OLE SAP.

4. STUDY DESIGN

4.1. Summary of Study Design

This is a 114-week randomized, multicenter, double-blind, parallel-group, active-control study, with an OLE period of up to 156 weeks, for a total study duration of up to 270 weeks in patients with IgAN who have persistent overt proteinuria and remain at high risk of disease progression despite being on a stable dose (or doses) of an angiotensin converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) that is (are) a maximum tolerated dose that is at least one-half of the maximum labeled dose (MLD) (according to approved labeling). The dose must have been stable for at least 12 weeks prior to study entry.

Approximately 380 patients aged ≥18 years will be enrolled into the study.

4.1.1. Double-Blind Period Design

Patients who meet eligibility criteria and provide written informed consent will undergo comprehensive baseline evaluations and clinical laboratory tests and will be randomly assigned in a 1:1 ratio to receive either

- sparsentan or
- irbesartan (active control)

Randomization will include stratification by eGFR value (30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and urine protein excretion (≤1.75 g/day and >1.75 g/day).

Standard-of-care treatment (ACEI and/or ARB therapy) and any other prohibited concomitant medications will be discontinued before the randomization (Day 1) visit. The final dose of an ACEI and/or ARB should be taken on the day before the randomization (Day 1) visit. The study medication (sparsentan or irbesartan) will be initiated on Day 1. Throughout the study (including the OLE period), patients will be maintained on the maximum allowed dose of study medication they can tolerate while secondarily maintaining blood pressure as close as possible to a target level of 125/75 mmHg. Treatment with additional antihypertensive agents is encouraged during the study, with the exception of those that inhibit the renin-angiotensin-aldosterone system (RAAS) and endothelin systems.

Study visits in the double-blind period will be conducted at 2, 4, 6, and 12 weeks after randomization and at approximately 12-week intervals thereafter. Following the 110-week blinded treatment period, treatment with study medication will be discontinued for 4 weeks. At this time, standard-of-care treatment should be resumed. Patients will return to the site for the double-blind period final visit 4 weeks after study medication has been discontinued.

Patients who complete the double-blind period may be eligible to enroll in the open-label extension period.

4.1.2. Open-Label Extension Period Design

Patients may be evaluated for eligibility to participate in the OLE period using assessments from the Week 110 visit as Screening assessments. Patients with an eGFR <30 (but >20) mL/min/1.73 m^2 will be eligible for participation in the OLE period at the discretion of the Investigator but will require close monitoring of eGFR and serum potassium.

For patients who agree to participate in the OLE period and meet the eligibility criteria, the Week 114 visit will also serve as the baseline visit (Day 1). Standard-of-care treatment (ACEI and/or ARB therapy) and any other prohibited concomitant medications will be discontinued before the Week 114 visit. The final dose of an ACEI and/or ARB therapy should be taken on the day before the Week 114 visit. At Week 114, patients will sign a new informed consent (if not completed previously at Week 110) for the OLE and will begin taking open-label sparsentan. All Week 114 (baseline visit) evaluations must be completed prior to the first dose of open-label sparsentan.

Patients will participate in the OLE period for up to 156 weeks, for a total of 270 weeks in the study (ie, double-blind and open-label periods). If sparsentan becomes commercially available during the OLE period, patients may transition out of the study and onto commercial product before the end of the OLE period.

4.2. Definition of Study Medication

4.2.1. Double-Blind Period

The investigational product doses to be administered in the double-blind period of the study will be dispensed as 200 mg sparsentan tablets over-encapsulated (blinded) with size 00 capsules. The active control doses to be administered in the double-blind period of the study will be dispensed as 150 mg irbesartan tablets over-encapsulated (blinded) with size 00 capsules.

The initial starting dose for study drug is 1 capsule (sparsentan 200 mg or irbesartan 150 mg). At the Week 2 visit, the Investigator will evaluate dose tolerance in a blinded manner prior to titrating up to the target dose of 2 capsules (sparsentan 400 mg or irbesartan 300 mg). Patients may continue on initial dose without titration or have dose reductions back to the initial dose (reduced dose) after dose titration based on tolerability as described in the protocol.

4.2.2. Open-Label Extension Period

The doses of sparsentan to be administered in the OLE period will be dispensed as 200 mg sparsentan tablets. Irbesartan will not be administered in the OLE period.

At Week 114, the starting dose is 1 tablet (200 mg) for all patients. At Week 116, the patient's dose will be titrated to 2 tablets (400 mg) if tolerated and determined safe by the Investigator. If the patient tolerates the initial dose, the patient's dose will be titrated to the target dose at Week 116. Patients who display asymptomatic blood pressure values ≤100/60 mmHg or who present with clinical symptoms of orthostatic hypotension but otherwise tolerate the initial dose will continue without titrating up to the target dose after the Week 116 visit.

For patients who enter the OLE period with an eGFR value <30 (but >20) mL/min/1.73 m^2 (ie, at Week 110), any dose titration at Week 116 will be at the Investigator's discretion based on the results of the Week 116 assessments. Patients whose dose is titrated to the 400 mg dose at Week 116 will be contacted by the Investigator at Week 118 to assess tolerance of the higher dose; at the Investigator's discretion, these patients may also come in for an additional visit at Week 118.

Doses may be modified (either 200 mg or 400 mg) at any time throughout the open-label extension period for safety or tolerability reasons at the Investigator's discretion.

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

The hypothesis to be tested relating to the change in proteinuria at Week 36 post randomization is

$$H0: \Delta = 0 \text{ versus } H1: \Delta \neq 0$$

where Δ is the true difference between sparsentan and irbesartan in the log change from baseline in proteinuria at Week 36. Based on data from the Leicester University Hospital Registry of IgA nephropathy patients (Leicester IgAN Patient Registry) in over 350 IgAN patients (who were not treated with steroid therapy) provided by Dr. Jonathan Barratt, together with proteinuria data published by Inker et al (Inker 2016), the standard deviation (SD) of the log change from baseline in proteinuria at Week 36 is estimated to be 0.92. A total of 280 randomized patients will therefore provide at least 90% power to test that the true relative treatment effect on proteinuria, sparsentan versus irbesartan, is at least 30%. Based on the data published in Inker et al (Inker 2016), this degree of treatment effect is predicted to reflect a treatment effect on clinical outcomes (doubling of serum creatinine, ESRD, or death) with a hazard ratio of 0.36 and a 95% confidence interval (CI) of (0.22, 0.61). In addition, Dr. Barratt's IgAN patient registry database indicates that a 30% treatment effect on proteinuria at the patient level predicts a difference in the slope of eGFR decline that translates to an estimated difference in eGFR at 104 weeks (approximately 2 years) of 6.64 mL/min/1.73 m^2, with a 95% CI of (0.83, 12.44).

Approximately 380 patients will be required to detect an underlying treatment effect in the rate of change in eGFR over 110 weeks following the initiation of randomized therapy (eGFR total slope at 2 years) of 2.9 mL/min/1.73 m^2 per year with 90% power. In addition, approximately 380 patients provide 80% power to detect a smaller treatment effect on eGFR slope at 2 years of 2.55 mL/min/1.73 m^2 per year. Consequently, approximately 380 patients provide more than 90% power to detect an underlying treatment effect in the rate of change in eGFR over 104 weeks following the initial acute effect of randomized therapy (eGFR chronic slope at 2 years) of 3.15 mL/min/1.73 m^2 per year. With this sample size, the observed annualized treatment difference to yield a p-value <0.02 is 1.8 mL/min/1.73 m^2 per year. These sample size and power calculations follow the method described by Dupont (Dupont 1998), with 1-sided $\alpha = 0.02$ and residual error of 5.8 mL/min/1.73 m^2 estimated from a random coefficient analysis of the Leicester University Hospital Registry. The projected treatment effects on the rate of change in eGFR were based on a meta-analysis of clinical studies in IgAN using the methodology presented by Inker (Inker 2019).

4.4. Randomization

Randomization will be carried out using an interactive response technology (IRT) system, 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)
- Urine protein excretion at Screening (≤1.75 g/day and >1.75 g/day)

5. PLANNED ANALYSES

5.1. Primary Analysis - Double-Blind Period

The primary analysis of proteinuria will be conducted on the Primary Analysis Set (PAS) after 36 weeks following randomization of approximately 280 patients to determine whether the primary efficacy endpoint, the change from baseline in UP/C, is statistically significant. As UP/C is a highly right-skewed variable, analyses will be performed on log-transformed data. The statistical evaluation of the primary efficacy endpoint will be performed using available data from all patients at the time of primary analysis, which will use a mixed model repeated measures (MMRM) analysis, at the significance level of $\alpha = 0.05$.

Unblinded analysis on select efficacy and safety endpoints will also be conducted.

The primary analysis will be conducted by the unblinded statistical subteam, and analysis results will not be disseminated among the Investigators and those directly involved with ongoing study conduct. Details on primary 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 primary analysis.

5.2. Final Analysis (Confirmatory Analysis) - Double-Blind Period

The final analysis (confirmatory analysis) of the double-blind period will be conducted when all randomized patients have either completed the end of the double-blind study assessment (Week 114) or have early terminated from the study, with the final database cleaned and locked.

5.3. Open-Label Extension Period Analysis

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

5.4. Change from Planned Protocol Analyses

The analyses specified in this SAP are consistent with PROTECT Protocol Amendment 5.

This SAP also clarifies which visits will contribute to the longitudinal analyses for efficacy if model convergence issues arise due to sparsity of data at later visits at the time of the primary analysis (Section 8.1).

The following analyses are included to address the recent Food and Drug Administration recommendations in the 27 May 2021 Advice letter (Reference ID: 4802510):

- Additional sensitivity analysis of the key secondary efficacy endpoint of the eGFR chronic slopes, defined as the slopes of eGFR following the initial acute effect of randomized treatment, at 1 year and 2 years via a mixed-effects model with linear spline with knot or change point at Week 6 with available eGFR data at primary analysis for 1 year and at the final analysis for 2 years as described in Section 8.6.3.1.

- Additional sensitivity analyses for the primary and key secondary endpoints using data during the double-blind period including after premature treatment discontinuation (ie, a treatment policy approach) as described in Section 8.5.2 and Section 8.6.3.

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 outputs 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 nonmissing 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.

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 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 zero 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 case report form (CRF) 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

The Full Analysis Set (FAS) includes all patients who are randomized and take at least 1 dose of randomized therapy. 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 IRT. All efficacy analyses for the double-blind period will be based on the FAS at the time of final analysis.

If a total of at least 10% of randomized patients did not receive any dose of randomized therapy, analysis of the primary and key secondary endpoints will be repeated based on all randomized patients as a sensitivity analysis.

6.3.2. Primary Analysis Set

The PAS is the subset of the FAS at the time of the data extraction for primary analysis (per Section 5.1). Patients in the PAS will be analyzed according to randomized treatment assignment. Primary analysis of proteinuria at Week 36 will be based on the PAS, unless the study is fully enrolled in which case the FAS will be used.

6.3.3. Per Protocol Analysis Set

The Per Protocol at Primary Analysis (PPPA) Analysis Set is a subset of the FAS containing patients who met study eligibility requirements and have no protocol deviations that might impact the assessment of efficacy measurements. Patients will be analyzed according to randomized treatment assignment. The PPPA Analysis Set will be used for sensitivity analyses related to efficacy at Primary Analysis.

The Per Protocol at Final Analysis (PPFA) Analysis Set is a subset of the FAS containing patients who met study eligibility requirements and have no protocol deviations that might impact the assessment of efficacy measurements. Patients will be analyzed according to randomized treatment assignment. The PPFA Analysis Set will be used for sensitivity analyses related to efficacy at Final Analysis.

The criteria for inclusion in the PPPA and PPFA Analysis Sets will be finalized prior to study unblinding (primary and final), as specified in Section 7.4. Evaluation of patient inclusion in the PPPA and PPFA Analysis Sets will occur for the primary 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 randomized therapy. Safety analyses will be based upon 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, and analyzable sample. Patients must have been fasting for approximately 8 hours before the visit and must not have had any major protocol deviations that potentially affect exposure levels. The PK Analysis Set will be used for PK 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 study medication in the OLE. All efficacy and safety analyses during the OLE will be based on the OLE FAS. 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 nonmissing assessment prior to and including the first administration of study medication (including unscheduled assessments) in the study. In the case where the last nonmissing assessment and the study medication start date (and time if available) coincide, that assessment will be considered baseline. Unless explicitly stated, all baseline used in this SAP will refer to the double-blind baseline.

6.4.2. Open-Label Extension Period Baseline

OLE baseline is defined as the last nonmissing assessment prior to and including the first administration of sparsentan (including unscheduled assessments) in the open-label extension. In the case where the last nonmissing 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 1 date (*date1*) and another later date (*date2*) will be calculated using the following formulas:
  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). 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 latest value will be selected. For efficacy analysis visits on or prior to Week 110, only assessments while the patient is on randomized treatment should be included (see Section 8.1 for definition of on treatment).

The visit windows for the double-blind period shown in Table 1 are defined for endpoints based on laboratory results. Visit windows for the OLE will be defined in a separate SAP.

Table 1: 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	2 – 36
Week 6	43	37 – 64	37 – 64
Week 12	85	65 – 127	65 – 127
Week 24	169	128 – 211	128 – 211
Week 36	253	212 – 295	212 – 295
Week 48	337	296 – 372	296 – 372
Week 58	407	373 – 449	373 – 449
Week 70	491	450 – 533	450 – 533
Week 82	575	534 – 617	534 – 617
Week 94	659	618 – 701	618 – 701
Week 106	743	702 – 757	702 – 757
Week 110[1]	771	758 – 785	758 – 785
Week 114[1]	799	>785	>785
4-week After EOT[2]	799[1] or Last Dose Date + 28[3]	>785[1] or >Last Dose Date[3]	>785[1] or >Last Dose Date[3]

eGFR = estimated glomerular filtration rate; EOT = end of treatment.
[1] For patients who completed the planned randomized treatment period.
[2] Efficacy endpoints only.
[3] For patients who discontinued the randomized treatment early.

6.5.5. Kidney Disease Quality of Life Survey

Kidney Disease Quality of Life (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 to 12: SF-12 v2
- Items 13 to 16: Burden of kidney disease (4 items)
- Items 17 to 28: Symptoms/problems of kidney disease (12 items)
- Items 29 to 36: Effects of kidney disease (8 items)

Each question in KDQOL-36 is precoded 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 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 a possible range of 0 to 100, with the higher transformed scores always reflecting better QoL. Scores present the percentage of total possible scores achieved. Transformations per items are specified in Table 2 below.

Table 2: 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 3 subscales shown in Table 3 will be computed as the average of available items (transformed scores) within each subscale:

Table 3: KDQOL Subscales

Subscale	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 steps shown in Table 4:

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

Table 4: 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 in Table 5 below:

Table 5: 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:

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

- Next, standardize each scale using a z-score transformation by subtracting the mean 0 to 100 score observed in the 1998 general United States (US) population for each scale and dividing the difference by the corresponding scale SD, as shown in Table 6 below:

Table 6: 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 measures, multiply each scale z-score by its respective physical and mental factor score coefficient and sum the 8 products, as shown in Table 7 below:

Table 7: 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. EQ-5D-5L

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

- Descriptive system composed of the following 5 dimensions:
  - Mobility
  - Self-care
  - Usual activities
  - Pain/discomfort
  - Anxiety/depression
- EQ visual analogue scale (EQ VAS)

For each dimension, respondent will select 1 of 5 statements that best describe 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 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 (van Hout 2012).

The EQ VAS records the respondent's self-rated health on a vertical, VAS. 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."

6.6. 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 – Proteinuria and eGFR Slope

6.6.1.1. Primary Analysis

For the primary analysis of primary endpoint of proteinuria and key secondary efficacy endpoints of eGFR slopes, missing central laboratory data will be imputed using the multiple imputation (MI) procedure (Ouyang 2017, Rubin 1987). Under the missing at random (MAR) assumption, a Bayesian multivariate normal model for the data 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 then 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 (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 (SAS, 2008) 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. Sensitivity 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 2 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%).

1. 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.
2. Note that when k = 0%, this approach produces an analysis that is consistent with MAR and is equivalent to the primary analysis with MI.
3. 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.
4. When k >100%, the analysis reflects a "worse-than-control" specification.

6.6.1.3. Local Laboratories

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

6.6.2. Missing Adverse Event or Concomitant Medication Onset Date

Adverse events (AEs) 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.

6.6.3. Missing Adverse Event or Concomitant Medication End Date

If the entire end date is unknown and the event or concomitant medication is not considered ongoing at the end of study or follow-up, the event or medication 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 or medication 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.

6.6.4. 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 primary analysis, the number of patients who enrolled in the OLE period, discontinued sparsentan in the OLE period, and discontinued the study during the OLE period (including reasons for treatment discontinuation) 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 by the clinical research associates.

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 (PPPA, PPFA and PK Analysis Set) 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 the following:
  - Non-withdrawal although at least 1 withdrawal criterion was met
  - Extensive visit window violations
  - Extensive missing visits
  - Nonadherence 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
- 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
- UP/C (g/g), including the following category
  - ≤1.25 g/g, >1.25 g/g
- Urine protein excretion (g/day), including the following category
  - ≤1.75 g/day, >1.75 g/day

- Pretreatment medication use
  - Immunosuppressive agents with renal indication (ie, steroids, calcineurin inhibitors, mycophenolate mofetil and other immunosuppressive agents). renal indication will be determined via medical review of concomitant medications and associated indications and be done prior to each database lock and unblinding
- Current RAAS Inhibitors at Screening
  - Any RAAS Inhibitors
  - ACEI at MLD
  - ARB at MLD
  - ACEI and ARB at MLD
- Baseline concomitant medication use
  - Antihypertensive medications, lipid-lowering medications

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

7.5. Baseline IgAN Disease Characteristics

Baseline IgAN disease characteristics will be summarized using data collected from the IgAN History CRFs and central scoring from renal biopsy slides. The following variables will be summarized:

- Age at IgAN diagnosis
- Years since renal biopsy to time of informed consent
- Oxford classification of IgAN (if available)

Baseline IgAN disease characteristics will be summarized and presented by treatment group and overall for the FAS, PAS, and PP Analysis Set. 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 Terminology (MedDRA).

Medical history will be summarized by SOC, PT, and treatment group using the Safety Analysis Set. Summaries will be ordered by descending order (based on total) of incidence of SOC and PT within each SOC. A by-patient listing will also be provided.

7.7. Baseline Electrocardiogram

Twelve-lead electrocardiograms (ECGs) will be conducted at Screening for the double-blind period and at Week 114 for the OLE period. ECG parameters including heart rate, PR, RR, QRS, QT, and QTcF will be summarized and presented by treatment group and overall for the FAS,

PAS, and PP Analysis Set. Descriptive statistics will be provided, and a categorical summary of overall ECG interpretation (normal, abnormal clinically significant, or abnormal not clinically significant) and abnormal QTcF values will be presented.

The number of patients with >450 msec, >480 msec, and >500 msec will be presented.

A by-patient listing will also be provided.

7.8. Impact of Coronavirus Disease 2019 (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 **parameters** will be summarized by treatment group and overall at the primary 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, or 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, or any local laboratories) 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 CRF pages, central laboratory data, and protocol deviations.

8. EFFICACY

8.1. General Considerations

All efficacy analyses will be based on the FAS or PAS as described below. The primary and key 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 laboratory data only. All efficacy analyses specified below refer to the double-blind period only.

Proteinuria (UP/C) will be determined based on a 24-hour urine sample. 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 Chronic Kidney Disease Epidemiology Collaboration (Levey 2009) formula for adults based on serum creatinine values from the visit.

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 the patient.

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

Longitudinal analyses of UP/C and eGFR (eg, via MMRM for continuous endpoints or generalized linear mixed models for binary endpoints) will consider data from post-baseline visits through Week 110 of the double-blind period. At the primary analysis, if there are issues with model converge due to sparsity of measurements at the later visits (ie, Week 106 or Week 110), then the longitudinal analyses will include only data through an earlier visit (ie, Week 94) to enable the analyses. The last visit to be included in the analyses will be appropriately documented in a note to file prior to unblinding for the primary analysis.

8.2. Statement of the Null and Alternate Hypotheses

The primary analysis of the primary efficacy endpoint at Week 36 will be ascertained first at primary analysis using the PAS.

The primary analysis of the primary efficacy endpoint will be summarized again at final analysis using the FAS, but will not test hypothesis.

The primary analysis of the primary efficacy endpoint at Week 36 will test the following hypotheses using the PAS at primary analysis:

- H_0: Change from baseline in proteinuria (UP/C) is equal between sparsentan and irbesartan
- H_1: Change from baseline in proteinuria (UP/C) is different between sparsentan and irbesartan

For non-US countries, the primary analysis of the key secondary endpoint will test the following hypotheses using the subset of patients in the FAS who had completed the Week 58 visit or early

terminated (for those who early terminated, patients need to expect to have visits at least through Week 58):

- H_0: Rate of change in eGFR following acute effect over 52 weeks (Week 6 to Week 58) is equal between sparsentan and irbesartan
- H_1: Rate of change in eGFR following acute effect over 52 weeks (Week 6 to Week 58) is different between sparsentan and irbesartan

The final analysis of the key secondary endpoints will test the following hypotheses using the FAS:

- H_{01}: Rate of change in eGFR following acute effect over 104 weeks (Week 6 to Week 110) is equal between sparsentan and irbesartan
- H_{11}: Rate of change in eGFR following acute effect over 104 weeks (Week 6 to Week 110) is different between sparsentan and irbesartan
- H_{02}: Change in eGFR from initiation of randomized therapy to 110 weeks is equal between sparsentan and irbesartan
- H_{12}: Change in eGFR from initiation of randomized therapy to 110 weeks is different between sparsentan and irbesartan

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

8.3. Examination of Subgroups

At both the primary and final analyses, select efficacy endpoints (primary and secondary efficacy endpoints) will be analyzed by patient subgroups using the PAS and FAS. 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 (years): ≤45, >45
- Age categories at IgAN diagnosis (years): ≤18, >18 to ≤40, >40
- Sex: Male, Female
- Race: White, Black, Asian, Others
- Baseline BMI (kg/m^2): <27, ≥27
- Randomization strata
  - Screening eGFR ≥30 to <60 mL/min/1.73 m^2 and Screening urine protein ≤1.75 g/day,
  - Screening eGFR ≥30 to <60 mL/min/1.73 m^2 and Screening urine protein >1.75 g/day,
  - Screening eGFR ≥60 mL/min/1.73 m^2 and Screening urine protein ≤1.75 g/day,
  - Screening eGFR ≥60 mL/min/1.73 m^2 and Screening urine protein >1.75 g/day

- Baseline eGFR (mL/min/1.73 m^2):
  - <60, ≥60 to <90, ≥90
  - <45, ≥45 to <60, ≥60 to <90, ≥90
- Baseline urine protein excretion (g/day): ≤1.75, >1.75
- Baseline use of antihypertensive medications include diuretics (except ACEIs, aldosterone blockers, aliskiren, or ARBs): Yes, No
- Years since renal biopsy to time of informed consent: ≤5, >5
- Geographic region: North America, Europe, Asia Pacific
- History of hypertension: Yes, No.

Post-baseline subgroups of interest are as follows: Yes, No

- Achievement of urinary protein excretion <0.3 g/day at Week 36, Week 58, and Week 110
- Concomitant use (and no baseline use) of systemic immunosuppressive medications

Subgroup characteristics will be summarized by treatment group.

Additional subgroup analyses may be performed.

Subgroup analyses will use models analogous to the primary analyses of respective endpoint (eg, MMRM, eGFR slope, etc.) without imputation and based on the MAR assumption.

8.4. Multiple Comparisons and Multiplicity

The overall family-wise Type I error rate will be controlled by a combination of a gatekeeping and fixed sequence procedure. If the analysis of UP/C at Week 36 at the primary analysis yields a 2-sided p-value <0.05, formal testing of key secondary endpoints will proceed.

8.4.1. Procedure for Non-US Countries

Analysis of key secondary endpoints will proceed as follows:

1. At the time of the primary analysis of proteinuria, the key secondary endpoint of rate of eGFR rate of change over 6 to 58 weeks will be tested at a significance level of $\alpha = 0.01$.
2. If significant at Step 1, $\alpha = 0.01$ will be recycled and the next key secondary efficacy endpoint, eGFR rate of change over 6 to 110 weeks, will be tested at a significance level of $\alpha = 0.05$ at the final analysis.
3. Otherwise (not significant at Step 1), eGFR rate of change over 6 to 110 weeks will be tested at a significance level of $\alpha = 0.04$ at the final analysis.
4. The next key secondary efficacy endpoint of eGFR rate of change over 110 weeks from initiation of randomized therapy will be tested at a significance level of $\alpha = 0.05$ (if significant at Step 1 and 2) or $\alpha = 0.04$ (if significant at Step 3).

If at Step 2 or 3, the statistical comparison of treatment group is not statistically significant at the specified significance level, then the remaining comparisons will be considered descriptive and exploratory.

8.4.2. Procedure for the US

At the time of the primary analysis, no formal testing will be conducted on the endpoint of eGFR rate of change over 6 to 58 weeks. Analysis of key secondary endpoints will proceed as follows at the final analysis:

1. The key secondary endpoint of eGFR rate of change over 110 weeks following initiation of randomized therapy will be tested at a significance level of $\alpha = 0.05$.
2. If significant at Step 1, eGFR rate of change over 6 to 110 weeks will be tested at a significance level of $\alpha = 0.05$.

If at Step 1, the statistical comparison of treatment group is not statistically significant at the specified significance level, then the remaining comparisons will be considered descriptive and exploratory.

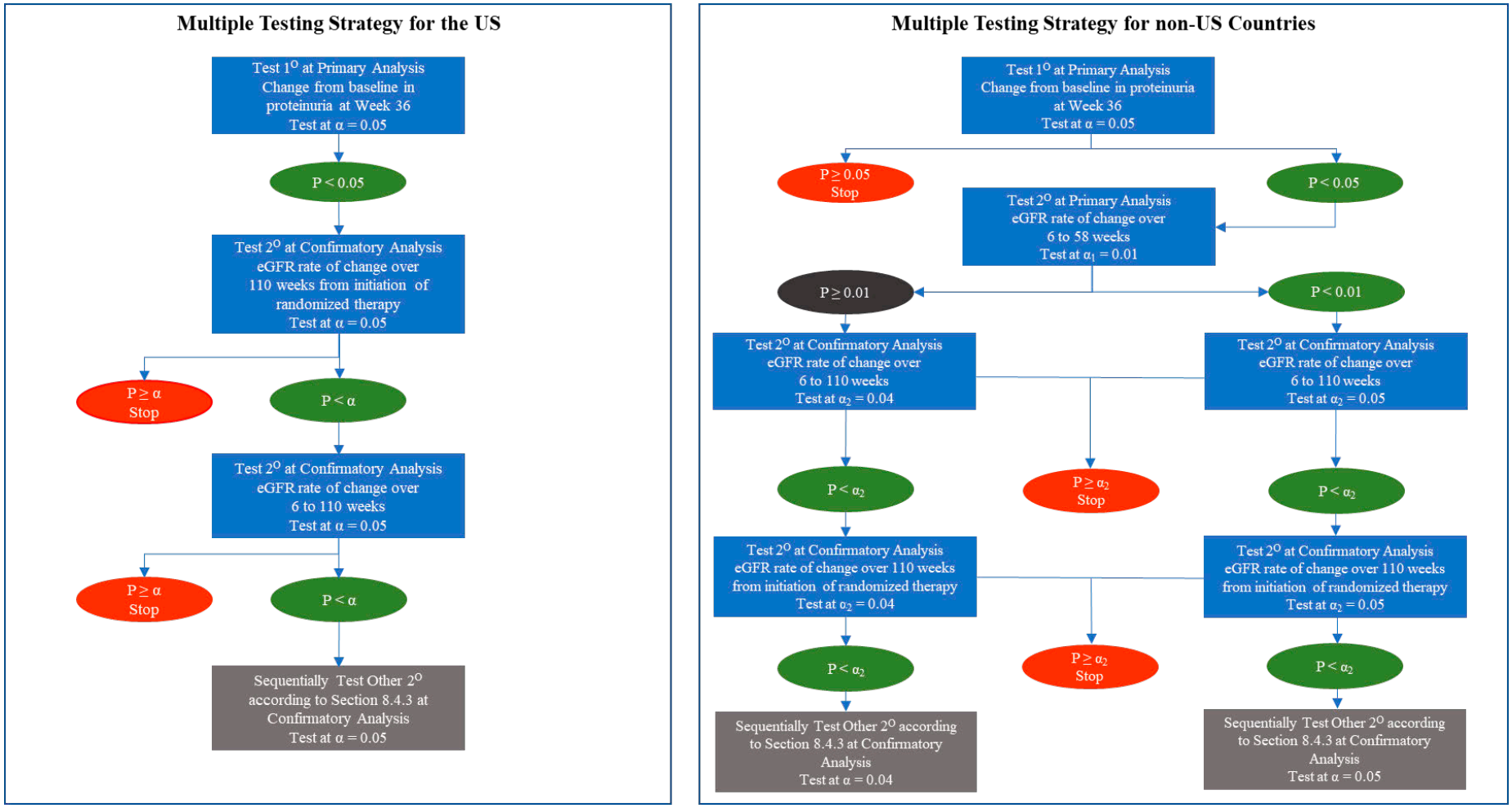
8.4.3. Procedure for Testing Other Secondary Endpoints Within the US and Non-US Countries

At the time of the final (confirmatory) analysis, if all the key secondary endpoints achieve statistical significance within the US or non-US countries, the other secondary endpoints will be statistically tested at the available alpha in the order specified below:

1. The mean change from baseline in UP/C at Week 110
2. The mean change from baseline in urine protein excretion at Week 110
3. The mean change from baseline in UA/C at Week 110
4. The mean change from baseline in urine albumin excretion at Week 110
5. The proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or death
6. The mean change from baseline in eGFR at Week 110

The multiple testing strategies for the US and for non-US countries are shown in Figure 1.

Figure 1: Multiple Testing Strategies for US and Non-US Countries



eGFR = estimated glomerular filtration rate; US=United States.

8.5. Analysis of the Primary Efficacy Endpoint

8.5.1. Primary Efficacy Analysis

The primary efficacy analysis will be based on the PAS (at primary analysis) and FAS (at final analysis) and change from baseline (Day 1) in proteinuria (UP/C) will be analyzed via an MMRM analysis. The dependent variable will be UP/C change from baseline. As UP/C is a highly right-skewed variable, analyses will be performed on log-transformed data. The model will include the following fixed effects:

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

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

Under the assumption of MAR, missing data will be imputed using the MI procedure (Ouyang 2017; Rubin 1987) for the UP/C result in the natural log scale. Specific imputation procedures are provided in Section 6.6.1.1.

An unstructured covariance matrix will be used. If the computational algorithm fails to converge, the following structures will be executed: heterogeneous Toeplitz, heterogeneous Compound Symmetry, heterogeneous first-order autoregressive, Toeplitz, Compound Symmetry, and first-order autoregressive.

The treatment effect will be the contrast between sparsentan and irbesartan LS means at Week 36. The LS means, treatment effect estimate (difference in LS means), 95% CI, and 2-sided p-value will be extracted from the model. Results will be back-transformed to present treatment effects on the ratio scale.

Estimates and CIs will be converted to percentages via the following transformations:

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

8.5.2. Sensitivity Analyses of the Primary Efficacy Results

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:

- Tipping point approach of the MI analysis as described in Section 6.6.1.2
- MMRM analysis using observed data (with no imputation of missing data)
- MMRM analysis using completers only (patients with non-missing UP/C values at Week 36 (212 to 295 days)

- MMRM analysis using observed data (with no imputation of missing data) during the double-blind period including after premature treatment discontinuation (treatment policy estimand). Additional analysis exploring potential intercurrent events that could impact the primary analysis (eg, premature discontinuation of study drug, use of immunospresssive agents, loss to follow-up, withdrawal of consent, need for RRT, or death) may be performed to examine their impact.

To assess the impact of changes in systemic immunosuppressive medications, the primary efficacy analysis will be repeated by excluding assessments after initiation of renal indication of systemic 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 Key Secondary Efficacy Endpoints

8.6.1. Rate of Change in eGFR Following Acute Effect of Randomized Therapy

The rate of change in eGFR over 52 weeks and 104 weeks following acute effect will each be analyzed via a mixed model random coefficients analysis. The dependent variable will be eGFR measured over 52 weeks (Week 6 to Week 58) or over 104 weeks (Week 6 to Week 110). The model will include the following fixed effects:

- Treatment group (2 levels: sparsentan, irbesartan)
- Baseline eGFR
- Time (ie, analysis visit in weeks)
- Treatment group by time interaction
- Randomization stratification variable (4 levels based on Screening eGFR and urine protein excretion)

In addition, the model will also include a random intercept and random slope for each patient.

Under the assumption of MAR, missing data will be imputed using the MI procedure (Ouyang 2017, Rubin 1987). Specific imputation procedures are provided in Section 6.6.1.1.

An unstructured covariance matrix will be assumed; if convergence issues arise, a first order autoregressive structure will be used.

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

8.6.2. Rate of Change in eGFR over 110 Weeks Following Initiation of Randomized Therapy

The rate of change in eGFR over 110 weeks following the initiation of randomized therapy will be analyzed via a mixed model random coefficients 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 (ie, analysis visit in weeks)
- Treatment group by time interaction
- Randomization stratification variable (4 levels based on Screening eGFR and urine protein excretion)

In addition, random intercept and random slope will be included for each patient.

Under the assumption of MAR, missing data will be imputed using the MI procedure (Ouyang 2017, Rubin 1987). Specific imputation procedures are provided in Section 6.6.1.1.

An unstructured covariance matrix will be assumed; if convergence issues arise, a first order autoregressive structure will be used.

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

8.6.3. Sensitivity Analyses of the Key Secondary Efficacy Results

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

- Tipping point approach of the MI analysis as described in Section 6.6.1.2
- Mixed model random coefficients analysis using observed data (with no imputation of missing data)
- Mixed model random coefficients analysis using completers only (patients who completed treatment through 1-year and 2-year blind treatment period)
- Mixed model random coefficients analysis including local laboratory data with central laboratory data
- Mixed model random coefficients using observed data (with no imputation of missing data) during the double-blind period including after premature treatment discontinuation (treatment policy estimand). Additional analysis exploring potential intercurrent events that could impact the primary analysis (eg, premature discontinuation of study drug, use of immunospresssive agents, loss to follow-up, withdrawal of consent, need for RRT, or death) may be performed to examine their impact.

To assess the impact of changes in immunosuppressive medications, the key secondary efficacy analysis will be repeated by excluding assessments after initiation of renal indication of systemic immunosuppressive medication in the blinded treatment period.

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

8.6.3.1. Sensitivity Analysis of the eGFR Chronic Slopes

Sensitivity analysis of the key secondary efficacy endpoints of the eGFR slopes over 52 weeks and 104 weeks, defined as the slopes of eGFR following the initial acute effect of randomized treatment (ie, Week 6 to Week 58 and to Week 110), 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 primary analysis for 1 year and at the final analysis for 2 years. The response variable is the eGFR measured at on-treatment, post-baseline assessments during the randomized treatment period up to and including Week 58 (and Week 110) 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 urine protein excretion)

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.

8.7. Analysis of Other Secondary and Exploratory Endpoints

All other secondary and exploratory endpoints will be evaluated using the FAS.

Use of systemic immunosuppressive medication for renal indication will be determined via medical review of concomitant medications and associated indications, and be done prior to each database lock and unblinding.

Kidney-related hospitalizations will be determined via medical review of serious AEs and be performed prior to each database lock and unblinding.

8.7.1. Rate of Change in eGFR over 58 Weeks Following Initiation of Randomized Therapy

The rate of change in eGFR over 58 weeks following the initiation of randomized therapy will be analyzed via a mixed model random coefficients analysis using the PAS at the time of primary analysis and the 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 58 for each patient. The model will include the following fixed effects:

- Treatment group (2 levels: sparsentan, irbesartan)
- Baseline eGFR
- Time (ie, analysis visit in weeks)
- Treatment group by time interaction
- Randomization stratification variable (4 levels based on Screening eGFR and urine protein excretion)

In addition, random intercept and random slope will be included for each patient.

Under the assumption of MAR, missing data will be imputed using the MI procedure (Ouyang 2017, Rubin 1987). Specific imputation procedures are provided in Section 6.6.1.1.

An unstructured covariance matrix will be assumed; if convergence issues arise, a first order autoregressive structure will be used.

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

8.7.2. Change in eGFR from Baseline to 4 Weeks Post-cessation of Randomized Treatment (Week 114)

The change from baseline to 4 weeks post-cessation of randomized treatment (114 weeks) will be analyzed via analysis of covariance (ANCOVA). The dependent variable will be the change from baseline eGFR at the analysis visit at Week 114. The model will include the following fixed effects:

- Treatment group (2 levels: sparsentan, irbesartan)
- Baseline eGFR
- Randomization stratification variable (4 levels based on Screening eGFR and urine protein excretion)

The treatment effect will be the contrast between sparsentan and irbesartan LS means. The LS means, treatment effect estimate (difference in LS means), 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 EOT analysis visit.

8.7.3. Other Continuous Endpoints

The following exploratory endpoints will be analyzed using an MMRM as described for the primary efficacy endpoint (Section 8.5.1). Missing data will not be imputed using the MI procedure:

- The mean change from baseline in eGFR and selected proteinuria variables, based on a 24-hour urine sample (eg, urine protein excretion, urine albumin excretion, UA/C, and UP/C), up to Week 110
- Mean changes from baseline in QoL, measured via PRO at each visit
- Change from baseline for blood pressure will also be analyzed at both primary analysis and at final analysis.

The following exploratory endpoints will be analyzed using an ANCOVA analysis:

- The change from baseline in eGFR at 6 weeks post randomization (ie, the acute effect of randomized therapy)
- The change from EOT (ie, Week 110) in eGFR 4 weeks following cessation of treatment (ie, at Week 114)
- Duration of hospitalizations (for any reason and for reasons related to the kidney)

Specifically, the change from baseline or EOT or duration (as applicable) will be the dependent variable, treatment group, and randomization stratification strata as fixed effects and baseline value as covariate. 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.

8.7.4. Other Responder Endpoints

Responder endpoints will be summarized at both the primary and final analysis. For these responder endpoints, patients are classified as either a responder or a non-responder.

The following endpoints will be analyzed via a logistic regression model with a fixed effect for treatment and baseline eGFR (baseline urinary protein excretion for complete remission defined as urinary protein excretion <0.3 g/day, partial remission defined as urinary protein excretion <1.0 g/day) as a covariate, stratified by the randomization strata:

- The proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or death
- The proportion of patients achieving urinary protein excretion <0.3 g/day up to Week 110

- The proportion of patients achieving urinary protein excretion <1.0 g/day up to Week 110

The treatment effect estimate from the model will be the contrast between sparsentan and irbesartan log odds. The treatment effect estimate and its 95% CI will be back-transformed to provide results on the odds ratio scale, and the associated 2-sided p-value will be presented.

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 m^2, then the last value on randomized treatment is considered confirmed or sustained. ESRD is defined as initiation of RRT or sustained eGFR <15 mL/min/1.73 m^2 during the study (confirmed after repeat assessment of at least 14 days after initial assessment).

The following endpoint will be analyzed using a generalized mixed model repeated measure analysis using PROC GLIMMIX in SAS:

- Proportion of patients with hematuria at each visit as determined by presence of blood in urinalysis
- Proportion of patients with use of systemic immunosuppressive medication during each 12-week time bucket.

Specifically, the model will include treatment, time (ie, nominal visit in weeks), treatment by time interaction, and stratification strata factors as fixed effects, and patient as a random effect. A logit link function will be used with distribution set to binomial. An unstructured covariance matrix will be assumed; if convergence issues arise, a first order autoregressive structure will be used. Treatment effect estimates will be extracted from the model at each visit in terms of the difference between treatments in log odds, together with the associated 95% CI and 2-sided p-values. Treatment effects and CIs will be back transformed to provide results on the odds ratio scale.

At the primary analysis, analysis models without stratification by randomization strata or other simpler models may be used if sparsity of data causes model convergence issues.

8.7.4.1. Time-to-Event Analyses

The time to occurrence of the following endpoints will be also analyzed at both the primary and final analyses:

- First confirmed 40% reduction in eGFR, ESRD, or death
- Initiation of systemic immunosuppressive medication (all and renal indication only)

Time-to-event data will be analyzed using a Cox regression model, stratified by randomization strata, via PROC PHREG in SAS. The tabulation will also include the KM estimates of the medians and corresponding 95% CIs if the medians can be estimated. The number and percent of patients censored and with events will be presented. Patients without any documentation of events will be censored at the time of analysis (if still on randomized treatment) or the time of discontinuation of randomized treatment, whichever is earlier.

For patients with an event for the first confirmed 40% reduction in eGFR, ESRD, or death endpoint, the minimum of the following event dates will be used:

- Death
  - Date of death
- ESRD
  - Date of initiation of RRT
  - Date of first occurrence of eGFR <15 mL/min/1.73 m^2 (confirmed after repeat assessment of at least 14 days after initial assessment)
- Confirmed 40% reduction from baseline in eGFR
  - Date of first assessment meeting criteria

Reduction of eGFR requires confirmation by a value at least 4 weeks after the initial value. If a patient experiences more than one of these events, only the event that occurs first will be included in the analysis.

Additional sensitivity analysis may be performed at final analysis if there are sufficient events after premature treatment discontinuation during the double-blind period.

8.7.5. Analyses of Events Rates

The following efficacy endpoints, considered event rate endpoints, will be analyzed using a negative binomial regression model, via PROC GENMOD in SAS:

- Number of systemic immunosuppressive medications over the treatment period
- Number of days treated with systemic immunosuppressive medications
- Number of hospitalizations (for any reason and for reasons related to the kidney)

Specifically, the model will compare treatment groups, adjusted for the randomization stratification factors, and will include the natural log transformation of duration of exposure 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.

9. PHARMACOKINETICS

The PK Analysis Set will be used for all PK analyses. Trough plasma PK concentrations of study medication will be summarized at both the primary and final analyses 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 below limit of quantification (BLQ) 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 the primary and final analysis. At the primary 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

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 are 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 PTs and SOC 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
- Patient incidence and total number of entries of TEAEs associated with safety topics of interest by PT
- Patient incidence and total number of entries of related TEAEs associated with safety topics of interest by PT
- Patient incidence and total number of entries of serious TEAEs associated with safety topics of interest by PT

10.1.1. Adverse Events of Interest (AEOIs)

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

- The abnormality represents a new elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × ULN, with or without an elevation of total serum bilirubin >2 × 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 PT 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 an event, the number of patients without an 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 TEAEs, treatment-related TEAEs, 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 primary analysis and will be included in the CSR.

- Cardiovascular system-associated TEAEs comprised of terms in the Cardiac SOC, Vascular SOC, and Cardiac Arrhythmias Standardized MedDRA Query (SMQ). Separate summaries of terms in the Cardiac Arrhythmias 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, 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
- Hyperkalemia-associated TEAEs comprised of PTs “Hyperkalemia,” “Hyperkalaemia,” and “Blood potassium increased”

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 primary analysis, summaries of AEs with onset on or after first dose of sparsentan in the OLE will be presented for the OLE FAS 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 weeks.

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 the following dose modifications will be summarized 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 CRF 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 comprehensive history of medications previously used for treatment of IgAN, 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 PTs and SOC using MedDRA.

Pretreatment 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 on or 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, and all antihypertensives, 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 separately for each treatment group by WHO ATC level 2, WHO ATC level 4, and preferred name. These summaries will present the number and percentage of patients using each medication. Patients may have more than one medication per ATC level and preferred name. At each level of patient summarization, a patient

is counted once if he/she reported one 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, coagulation, quantitative urinalysis, and lipids 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 vs AST, ALT vs total bilirubin, and AST vs total bilirubin maximum post-baseline values will be presented. If appropriate, evaluation of drug-induced serious hepatoxicity 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 and >3 × ULN ALT or AST at any time on study will be provided.

10.4.4. Incidence of Clinically Significant Local Laboratory Assessments

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 laboratory parameter collected. Percentage will be based on the number of patients with local laboratory results for each parameter and visit.

10.5. Vital Signs

The results and change from baseline to each post-baseline scheduled visits 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 patients with >20 mmHg decrease in systolic blood pressure at any time and the number and percentage of patients with > 10 mmHg decrease in diastolic blood pressure at any time will be presented.

10.6. Physical Examination

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

10.6.1. Peripheral Edema

The presence and staging of peripheral edema will be summarized by frequency counts and percentages based on the following grades: 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.

11. REFERENCES

Dupont W, Plummer W. Power and sample size calculations for studies involving linear regression. Control Clin Trials. 1998;19:589-601.

Hays RD, Kallich J, Mapes D, et al. *Kidney Disease Quality of Life Short Form (KDQOL-SF™), Version 1.3: A Manual for Use and Scoring*. Santa Monica, CA: RAND; 1997..

Inker LA, Mondal H, Greene T, et al. Early change in urine protein as a surrogate end point in studies of IgA nephropathy: an individual-patient meta-analysis. Am J Kidney Dis. 2016;68(3):392-401.

Inker LA, Heerspink HJL, Tighiouart H, et al. GFR slope as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of randomized controlled rrials. J Am Soc Nephrol. 2019;30(9):1735-45.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Maruish ME (Ed.). (2012). *User's Manual for the SF-12v2 Health Survey (3rd ed.)*. Lincoln, RI: Quality Metric Incorporated.

Ouyang J, Carroll KJ, Koch G, Li J. Coping with missing data in phase III pivotal registration trials: Tolvaptan in subjects with kidney disease, a case study. Pharm Stat. 2017;16(4):250-66.

Rubin DB. *Multiple Imputation for Nonresponse in Surveys.* New York, NY: John Wiley & Sons Inc.; 1997.

van Hout B, Janssen MF, Feng YS et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.

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