Statistical Analysis Plan

A Multicentered, Single-Group Phase 2, Exploratory, Open-Label, Study to Investigate Safety and Effect of Sparsentan in Combination with Sodium-Glucose Cotransporter-2 (SGLT2) Inhibition in the Treatment Adult Participants with Immunoglobulin A Nephropathy (IgAN)

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STATISTICAL ANALYSIS PLAN, VERSION 1.0

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A MULTICENTERED, SINGLE-GROUP PHASE 2, EXPLORATORY, OPEN-LABEL STUDY TO INVESTIGATE SAFETY AND EFFECT OF SPARSENTAN IN COMBINATION WITH SODIUM GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITION IN THE TREATMENT OF ADULT PARTICIPANTS WITH IMMUNOGLOBULIN A NEPHROPATHY (IGAN)

Investigational Medicinal Product:	Sparsentan
Product Code:	RE-021
Protocol Number:	TVTX-RE021-204 (SPARTACUS)
Developmental Phase:	Phase 2
Based On:	Protocol TVTX-RE021-204 Original (13 February 2023)
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
AR(1)	first-order autoregressive
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	Blood pressure
CI	Confidence interval
CS	Compound symmetry
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
FMV	First morning void
IgAN	Immunoglobulin A nephropathy
IQR	Interquartile range
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MLD	Maximum labeled dose
MMRM	Mixed model repeated measures
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PPAS	Per Protocol Analysis Set
PT	Preferred term
RAASi	renin-angiotensin-aldosterone system inhibitor
SD	Standard deviation
SAP	Statistical analysis plan
SEM	Standard error of the mean
SGLT2	sodium glucose cotransporter-2
SMQ	Standardized MedDRA Query

Abbreviation	Term
SOC	System organ class
TEAE	Treatment-emergent adverse event
UA/C	Urine albumin-to-creatinine ratio
ULN	Upper limit of normal
UP/C	Urine protein-to-creatinine ratio
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 sparsentan in combination with sodium glucose cotransporter-2 (SGLT2) inhibition in the treatment of adult participants with immunoglobulin A nephropathy (IgAN).

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

Protocol Revision Chronology		
Original Protocol	13 February 2023	Original

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Efficacy Objective

The primary efficacy objective of the study is to evaluate the effect of sparsentan on albuminuria in participants with IgAN on SGLT2 inhibitor medication.

3.1.2. Secondary Efficacy Objective

The secondary efficacy objective of the study is to evaluate the effect of sparsentan on proteinuria variables, estimated glomerular filtration rate (eGFR) and blood pressure (BP), in participants with IgAN on SGLT2 inhibitor medication over the duration of the study.

3.1.3. Safety Objective

The safety objective of the study is to assess the safety and tolerability of sparsentan in participants with IgAN on chronic stable treatment with an SGLT2 inhibitor.

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is

- The change from baseline in urine albumin-to-creatinine ratio (UA/C) at Week 24.

3.2.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints including the following:

- Achievement of UA/C of <0.2 g/g at Week 24.
- Achievement of 30% and 50% reduction from baseline in UA/C at Week 24.
- The change from baseline in UA/C, urine protein-to-creatinine ratio (UP/C), eGFR, and BP at each visit.

3.2.2. Safety Endpoints

Safety endpoints include the following:

- The incidence of treatment-emergent adverse events (TEAEs), serious adverse events (AEs), AEs leading to treatment discontinuation, and adverse events of interest (AEOI).
- Changes from baseline in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters.

4. STUDY DESIGN

4.1. Summary of Study Design

This is a 28-week, open-label, multicenter, single-group, Phase 2 exploratory study to determine the safety and effect of sparsentan in participants with IgAN who are at risk of disease progression despite being on both stable renin-angiotensin-aldosterone system inhibitor (RAASi) and SGLT2 inhibitor treatment for at least 12 weeks prior to study entry.

Approximately 60 participants aged ≥18 years will be enrolled into this study.

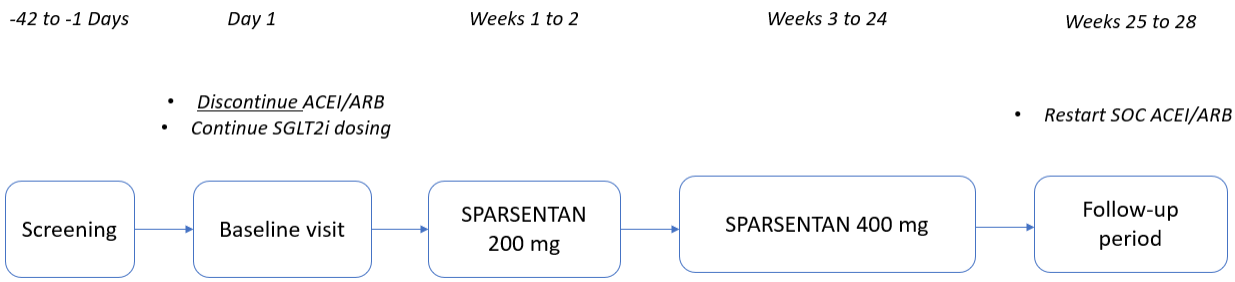
Participants who provide written informed consent will be assessed for eligibility and will undergo baseline evaluations including clinical laboratory tests. Per the eligibility criteria, all participants are required to be on a stable dose(s) of angiotensin converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB) and on a stable dose of a SGLT2 inhibitor at screening and will continue their stable treatments through the screening period. Eligible participants entering the study will remain on the stable dose of the SGLT2 inhibitor for the duration of the study, however, they will discontinue ACEI and/or ARB therapy before the Day 1 visit. The final dose of an ACEI and/or ARB should be taken on the day before the Day 1 visit. Baseline evaluations will be taken on Day 1 prior to administration of the first dose of the study medication (sparsentan).

Study medication will be administered daily for a treatment period of 24 weeks with study visits conducted at weeks 2-, 4-, 12-, and 24- following Day 1. Following the 24-week treatment period, study medication will be discontinued for 4 weeks. At this time, the Investigator should resume standard of care treatment, including RAASi treatment. Participants will return to the site for a visit at Week 28 for the safety follow-up visit.

UA/C and UP/C will be determined using first morning void (FMV) samples and will be calculated as the average of 2 FMV samples collected within 3 days prior to each visit. If 1 of the samples is missing, UA/C and UP/C from the single sample will be used.

The overall study design is summarized in Figure 1 (below). For individual participants, the total duration of participation from the screening visit to the safety follow-up visit (Week 28) will be a maximum 34 weeks.

Figure 1: Study Design



Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; mg = milligrams; SGLT2i = sodium glucose cotransporter-2 inhibitor; SOC = standard of care.

4.2. Definition of Study Medication

Study interventions are all pre-specified, investigational, and non-investigational medicinal products, medical devices, and other interventions (eg, surgical, and behavioral) intended to be administered to the study participants during the study conduct.

At the Week 1 the starting dose will be 1 tablet (1 × 200 mg) taken prior to the morning meal.

Starting at week 3 the dose will be titrated to 1 tablet (1 × 400 mg) taken prior to the morning meal, if tolerated and determined safe by the Investigator.

Patients can continue 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.

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

Approximately 60 participants will be enrolled in the study. The sample size of the study is determined empirically without formal statistical assumptions. A sample size of 60 is sufficient to detect at least 1 AE with probability 95%, assuming an expected AE incidence of 5% using the binomial distribution.

4.4. Randomization

This is a single-arm study; therefore, randomization is not applicable in this study.

5. PLANNED ANALYSES

5.1. Primary Analysis

The primary analysis will be conducted on the Full Analysis Set (FAS) after all participants complete their safety follow-up visit (Week 28) or have discontinued study.

All analysis on efficacy and safety endpoints will be conducted.

5.2. Interim Analysis

An interim analysis will be performed 24 weeks after approximately 20 participants have been enrolled to evaluate select safety and efficacy endpoints.

5.3. Change from Planned Protocol Analyses

The analyses specified in this SAP are consistent with Original Protocol. There are no changes from the planned protocol analyses.

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, external sources, and derived data will be presented in data listings by patient.

All outputs will be incorporated into Microsoft Word rich text format 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.

For continuous variables, the number of patients, mean (arithmetic), standard deviation (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 will additionally be presented for key efficacy variables (eGFR and quantitative urinalysis, including UP/C and UA/C). The precision of summary statistics, unless otherwise specified, will be as follows: mean, median, and IQR to 1 more decimal place than the raw data and SD and SEM to 2 decimal places more than the raw data. In general, the decimal places should not exceed 3 decimal places unless appropriate.

Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified in the table and listing shell.

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 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 zero. Percentages will be presented as a whole number (no decimal places), and nonzero values less than 0.5% will be presented as “<1%.” Values <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. To retain these values for analysis purpose, values will be imputed as the numeric portion of the result.

6.3. Analysis Population

6.3.1. Full Analysis Set

All participants who take at least 1 dose of sparsentan will be included in the FAS. All efficacy and safety analyses will be based on the FAS.

6.3.2. Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) is a subset of the FAS containing participants who meet study eligibility requirements and have no protocol deviations that might impact the assessment of efficacy measurements. The PPAS will be used for sensitivity analyses relating to efficacy.

6.4. Baseline Definition

6.4.1. General

Unless otherwise defined, study baseline is defined as the last nonmissing assessment prior to first dose of study medication and including the baseline (Day 1) visit.

6.4.2. Quantitative Urinalysis Parameters

Baseline for quantitative urinalysis parameters, including UA/C and UP/C, will be calculated as the average of the 2 FMV samples collected within 3 days prior to the Day 1 visit. If one of the samples is missing, the single sample will be used.

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. Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Days – A duration expressed in days between 1 date (*date 1*) and another later date (*date 2*) will be calculated using the following formulas:
  duration in days = date2 – date1 + 1
- Weeks – A duration expressed in weeks is calculated as the number of days divided by 7
- 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:
  temperature (degrees Celsius) = 5 / 9 × (temp [degrees Fahrenheit] – 32)
- Change from baseline – Change from baseline will be calculated as:
  Change = post baseline value – baseline value
- Percent change from baseline – Percent change from baseline will be calculated as:
  Percent change = ([post baseline value – baseline value]/baseline value) × 100

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

6.5.3. Visit Windows

A visit window method will be applied to determine the record to be used for analysis across the study period for efficacy and safety endpoints based on laboratory results, including eGFR and quantitative urinalysis (including UP/C and UA/C). If a patient has multiple assessments (including unscheduled visits) within the 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.

The visit window shown in Table 1 is defined for endpoints based on laboratory results.

Table 1: Visit Window

Analysis Visit	Relative Target Day	Analysis Visit Window (Study Days)	
		eGFR and Safety Labs	Quantitative Urinalysis
Week 2	15	2 – 22	N/A
Week 4	29	23 – 57	2 – 57
Week 12	85	58 – 127	58 – 127
Week 24	169	128 – 183	128 – 183
Week 28	197	>183	>183

eGFR = estimated glomerular filtration rate; N/A = Not applicable

6.6. Handling of Missing Data

The study will have processes and procedures in place to minimize missing data and to collect information on participants even after discontinuing study medication. Missing values will not be imputed.

6.6.1. Primary Analysis

UA/C and other quantitative urinalysis measures such as UP/C will be determined using FMV samples and will be calculated as the average of 2 FMV samples collected within 3 days prior to each visit. If 1 of the samples is missing, UA/C and UP/C from the single sample will be used.

6.6.2. Local Laboratories

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

6.6.3. Missing Adverse Event or Concomitant Medication Onset Date

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.

6.6.4. 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.

6.6.5. Missing Adverse Event Severity or Relationship

An event with missing severity will be considered severe. An event with missing relationship will be considered related to study medication and SGLT2 inhibitor.

7. STUDY POPULATION

7.1. Patient Disposition

Patient disposition will be tabulated and will include the number of patients who screened, failed screening, enrolled, received study medication, completed study medication, discontinued study medication (including reasons), completed the study, and discontinued the study (including reasons). Percentages will be calculated out of the number of patients enrolled. Percentages will not be displayed for the number of patients screened or the number of patients who failed screening.

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.

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

A Kaplan-Meier plot of time to study termination or early withdrawal will be presented. Patients who withdrawal early from study will be considered an event at the time (weeks) of study withdrawal. Patients who do not discontinue will be censored at the time (weeks) of study completion as follows:

Weeks until completion= (date of completion - date of treatment initiation + 1)/7.

Weeks until early withdrawal = (date of early withdrawal - date of treatment initiation + 1)/7.

Similarly, a plot of time to treatment discontinuation will be presented. Patients with treatment for at least 162 days will be considered to have completed treatment.

7.2. Screen Failures

The reason for screen failures will be summarized by 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. The clinical research associates will collect all other protocol deviations. Protocol deviations will be classified as critical, important, major, or minor as follows:

- Critical: A deviation from Protocol-related procedures that threatens integrity of data, adversely affects subjects and/or could invalidate acceptability of a project (or part of it). Such deviations require immediate action. This classification will only be used for a confirmed Serious Breach or a serious quality issue. Both circumstances will involve Quality Assurance.
- Important: A subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of key study data or that may significantly affect a subject's rights, safety or well-being.

- Major: A deviation from Protocol-related procedures that could affect integrity of the data or adversely affect subjects. Such deviations require timely action.
- Minor: A deviation from accepted procedures that will not adversely affect subjects or data integrity but should be dealt with appropriately.

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 the PPAS will be performed and approved by the Study Statistician, Medical Monitor and Clinical Study Manager prior to database lock.

Evaluability of patients will be based on the following:

- Compliance of study entry criteria (inclusion and exclusion)
- Adequate study medication exposure (no extended dosing interruptions)
- Adequate treatment compliance based on prescribed dose level (withing 80% to 120%)
- No prohibited concomitant medications or therapies during the study
- No other major protocol deviations that may affect efficacy or safety conclusions, including 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

Critical/Important/Major protocol deviations will be summarized by deviation category 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

Other baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- Body mass index (kg/m^2)
- BP (systolic and diastolic)
- Childbearing potential (for females only)

- Hemoglobin A1c (%)
- Blood glucose (mmol/L)
- Glycosuria (Urine glucose values of "Trace", '1+', '2+', '3+', 'Present', etc)
- Hematuria (Urine Blood/Hgb values of "Trace", '1+', '2+', '3+', 'Present', etc)
- UA/C
- eGFR (mL/min/1.73 m^2), continuously and including the following categories:
  - <25 mL/min/1.73m^2, ≥25 to <60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2
  - <15 mL/min/1.73 m^2, ≥15 to <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), continuously and including the following category.
  - ≤1.25 g/g, >1.25 g/g
- Current RAASi at Screening and at Day -1
  - Any RAASi
  - RAASi at maximum labeled dose (MLD)
  - ACEI at MLD
  - ARB at MLD
  - ACEI and ARB at MLD
  - ACEI or ARB at MLD
- Baseline concomitant medication use*
  - Antihypertensive medications, lipid-lowering medications, 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.

* Medication lists will be reviewed and documented prior to the database lock to finalize the list of medications to be included in each category.

Demographics and baseline characteristics will be summarized and presented for both the FAS and PPAS. All baseline characteristics will use the last available data prior first dose of study medication except UA/C and UP/C will use the definition described in Section 6.4.2. 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 eCRFs. The following variables will be summarized:

- Age at IgAN diagnosis

- Years since renal biopsy to time of informed consent
- Time in weeks on SGLT2 inhibitor prior to enrollment (start of sparsentan treatment) is calculated as defined in Section 6.5.2

Baseline IgAN disease characteristics will be summarized and presented for both the FAS and PPAS. 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 and PT using the FAS. Summaries will be ordered by descending order of incidence of SOC and PT within each SOC. A by-patient listing will also be provided.

8. EFFICACY

8.1. General Considerations

All efficacy analyses will be done descriptively on the FAS using observed data only. Change from baseline (or percent change from baseline, as appropriate) will be summarized with mean and 95% CI, as appropriate. For categorical efficacy endpoints, the proportion of participants in the category will be presented along with corresponding 95% CI.

The primary and secondary efficacy endpoint analyses based on the PPAS will be performed as sensitivity analyses. All primary efficacy analyses based on laboratory data will use central laboratory data only.

Albuminuria (UA/C) and proteinuria (UP/C) will be determined based on a FMV samples. As UA/C and UP/C are highly right-skewed variables, 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 last dose of study medication for the patient. Additionally, efficacy analyses may be repeated using all on-study data.

8.2. Analysis of the Efficacy Endpoints

8.2.1. Primary Efficacy Analysis

Target Population: Adult patients with IgAN who are on a stable dose of SGLT2 inhibitor. The primary efficacy analysis will be based on the FAS.

Variable: Change from baseline to Week 24 in UA/C

Treatment Conditions: Sparsentan + SGLT2 inhibitor QD for 24 weeks

Intercurrent events: The following intercurrent events could impact the UA/C values of patients:

- Non-compliance with study drug
- Receipt of immunosuppressive steroids for renal indications
- Death or renal transplant

For all intercurrent events, an on-treatment policy will be used. Sensitivity analyses may be performed using the treatment policy (all on-study data used).

Population-level summary: The change from baseline (Day 1) UA/C at Week 24 will be analyzed via a MMRM analysis. The MMRM analysis will be performed using observed data with no imputation of missing data. The dependent variable will be UA/C change from baseline. As UA/C is a highly right-skewed variable, analyses will be performed on log-transformed data. The model will include the following fixed effects:

- Baseline UA/C in log scale
- Time (ie, analysis visit in weeks)

In addition, patient will be included as a random effect. 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 (CS), heterogeneous first-order autoregressive (AR[1]), Toeplitz, CS, and AR(1).

The least squares (LS) means, and 95% CI 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:

$$(\exp[\text{LS mean change from baseline in natural log } \{UA/C\}] - 1) \times 100$$

Baseline value, absolute change from baseline to Week 24, and percent change from baseline to Week 24 will be summarized descriptively. Observed value, absolute change from baseline, and percent change from baseline at each visit will be summarized similarly and estimates from the MMRM at each visit will also be presented as described above for Week 24.

8.2.2. Secondary Efficacy Analysis

8.2.2.1. Responder Endpoints

The following responder endpoints will be summarized:

- Achievement of UA/C <0.2 g/g at Week 24
- Achievement of 30% reduction from Baseline in UA/C at Week 24
- Achievement of 50% reduction from Baseline in UA/C at Week 24

For each endpoint, the number and percentage of patients responding at Week 24 will be presented. The denominator will be the number of patients with a nonmissing result for the parameter at Week 24. The 95% CI for the percentage of subjects with will be generated from an exact binomial distribution. The analysis will be repeated for each visit for each endpoint.

8.2.2.2. Absolute Change and Percent Change in eGFR and BP

Baseline value, absolute change from baseline at each visit, and percent change from baseline at each visit in eGFR and BP (Systolic and Diastolic) will be summarized descriptively. Additionally, change from Baseline to Week 24 will be analyzed via a MMRM model using observed data only. The dependent variable will be change from baseline. The model will include the following fixed effects:

- Baseline value
- Time (ie, analysis visit in weeks)

In addition, patient will be included as a random effect. The covariance matrix will be chosen similarly to as what is described in Section 8.2.1. The LS means and 95% CI will be extracted from the model and presented for each visit.

8.2.2.3. Absolute Change and Percent Change in UP/C

UP/C will be summarized and analyzed similarly to UA/C as described in Section 8.2.1.

8.2.3. Exploratory Efficacy Endpoints

8.2.3.1. Continuous Endpoints

Quantitative urinalysis parameters (protein excretion, albumin excretion, urea, and creatinine) will be summarized and analyzed similarly to UA/C as described in Section 8.2.1).

8.2.3.2. Responder Endpoints

Achievement of UP/C <0.3 g/g will be summarized similarly to the responder endpoints in Section 8.2.2.1.

8.2.4. Sensitivity Analyses of Efficacy Endpoints

Sensitivity analysis will be conduct based on the PPAS for the primary and secondary efficacy analyses.

Additionally, all analyses based on laboratory data (UA/C, UP/C, eGFR) described above may also be repeated with the inclusion of local laboratory data with the central data, if there is sufficient local laboratory data to warrant such analysis. For these analyses, the value observed closest to the target day will be chosen regardless of if it comes from the local or central laboratory.

8.2.5. Graphical Displays of Efficacy Endpoints

A plot of geometric mean over time with bars for the 95% CI will be generated for quantitative urinalysis parameters (UA/C, UP/C, protein excretion, albumin excretion, urea, and creatine). A plot of mean over time with bars for +/- the SE will be generated for eGFR and BP (Systolic and Diastolic separately). The FAS will be used.

9. SAFETY AND TOLERABILITY

Safety analyses will be based on the FAS. Descriptive statistics will be presented.

9.1. 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, occurring during the treatment period. 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 version 26.0.

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 and total number of entries of study medication (Sparsentan) related TEAEs by MedDRA SOC and PT. Related AEs are those with relationships reported as “Possibly Related” or “Related”. AEs with a missing relationship will be considered related for this summary.
- Patient incidence and total number of entries of SGLT2 inhibitor related TEAEs by MedDRA SOC and PT. Related AEs are those with relationships reported as “Possibly Related” or “Related”. 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 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.

9.1.1. Adverse Events of Interest

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 × upper limit of normal (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 9.1, patient incidence of treatment-emergent AEOIs occurring in the treatment period will be summarized.

9.1.2. 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. A listing of AEs meeting each safety topic of interest will also be generated. All Sponsor-defined terms will be identified prior to database lock and will be included in the CSR.

- Hypotension-associated TEAEs comprised of Sponsor-defined terms.
- Hepatic-associated TEAEs comprised of terms in the Hepatic Disorders Standardised MedDRA Query (SMQ), excluding the following sub-SMQs: alcohol related, congenital, familial, neonatal, and genetic disorders of the liver; liver infections; and pregnancy-related hepatic disorders.
- 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.”

9.2. Extent of Sparsentan Exposure and Compliance

The following extent of exposure parameters will be summarized both continuously using descriptive statistics and categorically using counts and percentages separately for Sparsentan:

- Duration of treatment (weeks)
- Duration of treatment with reduced dose (weeks)
- Duration of treatment with 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 on or prior to the next scheduled visit – Date of first dose of study medication + 1) / 7

Duration of treatment with reduced dose and duration of treatment with target dose will be calculated similarly. For patients who have no dose reductions during the study, the duration of treatment with reduced dose will be set to 0 weeks and the duration on treatment and duration on treatment with reduced dose will be equal.

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 that occurred during the study. For patients with no study medication interruption during the study, the total duration is considered 0 days.

A summary of patients who had dose reductions will be summarized by frequency count and percentages.

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

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

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

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

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

9.3. Extent of SGLT2 Inhibitor Exposure

The following extent of exposure parameters will be summarized both continuously using descriptive statistics and categorically using counts and percentages separately for Sparsentan:

- Type of SGLT2 inhibitor (ie, Dapagliflozin)
- Percentage of MLD at Baseline (Overall and by type of SGLT2 inhibitor)
- Duration of total treatment (weeks)
- Duration of treatment concomitantly with Sparsentan (weeks)
- Duration of treatment with reduced dose (from Baseline) concomitantly with Sparsentan (weeks), if any dose reductions occur
- Total duration of study medication interruptions (days)

The number and percentage of patients on each recorded SGLT2 Inhibitor will be summarized.

Percentage of MLD at Baseline will be calculated as follows:

- Percentage of MLD at Baseline = 100 × (Total daily dose received)/(Total maximum labeled daily dose for the given medication).

Percentage of MLD at Baseline will be summarized continuously and with counts and percentages for the following buckets:

- 0% to <25%
- 25% to <50%
- 50% to <75%
- 75% to100%
- >100%

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

- Duration of treatment = (Date of last dose of study medication or date of completion/early discontinuation if patient is still ongoing on SGLT2 Inhibitor at end of study – Date of first dose of SGLT2 Inhibitor + 1) / 7

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

- Duration of treatment = (Date of last dose of study medication on the same day as a dose of Sparsentan – Date of first dose of study medication on or after the first dose of Sparsentan + 1) / 7

Duration of treatment with reduced dose will be calculated similarly. For patients who have no dose reductions during the study, the duration of treatment with reduced dose will be set to 0 weeks and the duration on treatment concomitantly with Sparsentan and duration on treatment with reduced dose concomitantly with Sparsentan will be equal.

The duration of each incidence of SGLT2 inhibitor interruption will be calculated as follows:

- Duration of SGLT2 inhibitor interruption = (Date of restart of SGLT2 inhibitor – Date of temporary discontinuation)

The total duration of SGLT2 inhibitor interruptions is the sum of duration of SGLT2 inhibitor interruption over each incidence of interruption that occurred during the study. For patients without SGLT2 inhibitor interruption during the study, the total duration is considered 0 days.

A summary of patients who had dose reductions will be summarized by frequency count and percentages.

9.4. 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 the initial dose of study medication. Concomitant procedures are those procedures that were started after the initial dose of study medication.

Pretreatment medications will be listed only.

Prior and new concomitant medications will be summarized separately 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 1 medication per ATC level and preferred name. At each level of patient summarization, a patient is counted once if he/she reported 1 or more medications at that level. Each summary will be ordered by descending order of incidence of ATC level and preferred name within each ATC level.

Prior and concomitant procedures will be summarized for each treatment group by SOC and PT. Each summary will be ordered by descending order of incidence of SOC and PT within each SOC.

9.5. Clinical Laboratory Evaluations

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

9.5.1. 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 value (including scheduled or unscheduled) and last value (including scheduled and unscheduled) will be provided for hematology, serum chemistry, quantitative urinalysis, and lipids. For urinalysis parameters, a shift table depicting shifts to/from positive/negative from baseline to worst and last value will be provided.

9.5.2. Shifts in Common Terminology Criteria for Adverse Events Toxicity Grade

Shifts in Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade of laboratory tests from baseline to worst value (including scheduled or unscheduled) and last value including scheduled and unscheduled will be provided. Results will be attributed to a grade based on CTCAE version 5.

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

9.5.3. Incidence of Liver Function Abnormalities

The incidence of patients (number and percentage of patients) with abnormalities in liver function tests (ALT, AST, alkaline phosphatase [ALP], and total bilirubin) post-baseline during the study will be summarized 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 occurring during the study 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 during the study will be provided.

9.5.4. Incidence of N-Terminal Prohormone of Brain Natriuretic Peptide Elevations

The incidence of patients (number and percentage of patients) with abnormalities N-terminal prohormone of brain natriuretic peptide (NT-proBNP) during the study will be summarized for the following categories:

- Patients with NT-proBNP > ULN post-baseline
- Patients with NT-proBNP > ULN pre- and post-baseline
- Patients with NT-proBNP >47 pmol/L
- Patients with NT-proBNP >142 pmol/L

The denominator will be the number of patients with at least 1 post-baseline result during the study. Patients who do not have a baseline value will be considered to be within the normal range at baseline.

9.6. Vital Signs

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

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

- Systolic BP:
  - ≤100 mmHg
  - A decrease from baseline more than 30 mmHg
  - >180 mmHg
  - An increase from baseline more than 40 mmHg

- Diastolic BP:
  - ≤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

9.7. Physical Examination

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

9.7.1. 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 value (including scheduled and unscheduled), last value (including scheduled and unscheduled) and at each post-baseline scheduled visit will be provided.

10. REFERENCES

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

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