Protocol

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

Date of Document: 31 January 2024

NCT03493685

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

Investigational Medicinal Product:	Sparsentan
Product Code:	RE-021
Protocol Number:	021FSGS16010 (DUPLEX)
IND Number:	115903
EudraCT Number:	2016-00514123
Developmental Phase:	Phase 3
Protocol Version and Date:	Amendment 9: 18 January 2024 (Version history contained in Section 15.4)
Sponsor:	Travere Therapeutics, Inc. 3611 Valley Centre Drive, Suite 300 San Diego, CA 92130 USA

INVESTIGATOR'S AGREEMENT

This protocol was designed and will be conducted, recorded, and reported in accordance with the principles of Good Clinical Practice as stated in the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and any applicable national and regional laws. I have read and agree to abide by the requirements of this protocol.
Investigator Signature: Date:
Investigator Name (print or type):
Address:
Telephone:

STUDY CONTACT INFORMATION

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1. SYNOPSIS

NAME OF COMPANY:
Travere Therapeutics, Inc.
3611 Valley Centre Drive, Suite 300
San Diego, CA 92130
USA

NAME OF FINISHED PRODUCT:
sparsentan tablets

NAME OF ACTIVE INGREDIENT:
sparsentan

TITLE:

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

PROTOCOL NUMBER: 021FSGS16010 (DUPLEX)

STUDY PHASE: Phase 3

INVESTIGATOR STUDY SITES:

Approximately 300 investigational study centers globally will participate in this study.

OBJECTIVES:

Efficacy: To determine the long-term nephroprotective potential of treatment with sparsentan as compared to an angiotensin receptor blocker in patients with primary and genetic focal segmental glomerulosclerosis (FSGS).

Safety: To assess the safety and tolerability of sparsentan by double-blind monitoring of safety endpoints.

Open-label: To assess the long-term efficacy, safety, and tolerability of open-label sparsentan in patients with FSGS.

METHODOLOGY:

This is a 112-week, randomized, multicenter, double-blind, parallel, active-control study (also referred to as DUPLEX) with an open-label extension of up to 156 weeks, for a total study duration of up to 268 weeks. Approximately 300 patients aged 8 to 75 years, inclusive (United States [US] and United Kingdom [UK]), and 18 to 75 years, inclusive (countries other than the US and UK), weighing ≥20 kg, will be enrolled in the study.

Double-blind Period

Patients who meet inclusion criteria during screening who are taking inhibitors of the renin-angiotensin-aldosterone system (RAAS) will undergo a 2-week washout period from these agents prior to Day 1/Randomization.

Following screening (and the washout period for patients taking RAAS inhibitors), all patients will undergo comprehensive baseline evaluations and clinical laboratory tests and will be randomly assigned in a 1:1 ratio to receive either sparsentan or active control (irbesartan) (see Dose/Route/Regimen). Randomization will include stratification by screening estimated glomerular filtration rate (eGFR) and urine protein/creatinine ratio (UP/C) values. The strata will be as follow:

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

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Sparsentan and irbesartan concentrations in plasma will be evaluated. At applicable visits, 1 trough sample will be obtained pre-dose in the clinic.

Unless otherwise specified, endpoints will use pretreatment values obtained prior to randomization as baseline. The follow-up visits to obtain measurements will be conducted at 3-month intervals unless otherwise specified.

Additional antihypertensive agents are allowed during the study to maintain blood pressure ≤130/80 mmHg (patients ≥18 years of age) or ≤ the 75th percentile (patients <18 years of age; Banker 2016), with the exception of those that inhibit the RAAS and endothelin systems (see Section 15.2.1 for concomitant medication considerations).

An unblinded analysis will be performed after 36 weeks following randomization of at least 190 patients (approximately 95 per treatment group) to evaluate the surrogate efficacy endpoint (ie, the proportion of patients achieving a UP/C ≤1.5 g/g [170 mg/mmol] and a >40% reduction in UP/C at Week 36).

Following the 108-week blinded treatment period, treatment with study medication will be discontinued, and patients may be evaluated for eligibility in the open-label extension using values from the Week 108 visit as screening assessments. At this time, the Investigator should resume standard-of-care treatment, including treatment with RAAS inhibitors provided there are no contraindications for their use. If the patient was treated with irbesartan at study entry, an alternative ARB at an equivalent dose is required from Week 108 to Week 112. The Investigator may make additional adjustments in antihypertensive medications as necessary to adequately control the patient's blood pressure.

Patients will return to the site for the final visit of the double-blind period 4 weeks after study medication has been discontinued.

Open-label Extension

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

For patients who agree to participate in the open-label extension and meet eligibility criteria, the Week 112 visit will also serve as the baseline visit for the open-label extension. Standard-of-care treatment (ACEI and/or ARB therapy) will be discontinued before the Week 112 visit. The final dose of an ACEI and/or ARB should be taken on the day before the Week 112 visit. At this visit, patients will sign a new informed consent (if not already completed previously) for the open-label extension and begin taking open-label sparsentan. All Week 112 evaluations must be completed prior to the first dose of open-label sparsentan. Patients taking 2 or 4 capsules of study medication at the end of the double-blind period will initiate treatment in the open-label extension at one-half the corresponding dose of open-label sparsentan for the first 2 weeks, then titrate to the target dose after confirmation of tolerability at Week 114. Patients taking 1 capsule of study medication at the end of the double-blind period will initiate treatment in the open-label extension at 200 mg open-label sparsentan and continue on that dose throughout the open-label extension. Detailed information on the dosing regimen for the open-label extension period is included in the Dose/Route/Regimen section.

Patients will participate in the open-label extension for up to 156 weeks, for a total of 268 weeks in the study (ie, double-blind and open-label). If the product becomes commercially available during the open-label extension period, eligible patients may transition out of the study and onto commercial product before the end of the open-label extension period. After the patient completes the study (Week 268), if sparsentan is not commercially available, patients may potentially receive sparsentan via alternative means depending upon regulations and commercial status in each country.

Supportive Measures for Coronavirus Disease 2019/Unexpected Circumstances

If an on-site visit by the patient is not feasible due to the challenges related to the coronavirus disease 2019 (COVID-19) pandemic or other unexpected circumstances, contingency measures will be implemented to ensure patient safety while participating in the study. These safety measures will continue to be implemented in any situation that interrupts on-site safety oversight and includes visits at home by a trained medical professional

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(eg, licensed nurse), shipping study medication directly to the patient and using courier services for first morning void samples and local laboratories. Details are included in the protocol.

NUMBER OF PATIENTS:

Approximately 300 patients aged 8 to 75 years, inclusive (US and UK) and 18 to 75 years, inclusive (countries other than the US and UK) will be enrolled in the study.

INCLUSION/EXCLUSION CRITERIA:

Eligibility must be confirmed, and signed/dated informed consent obtained, prior to any study-related procedure. When applicable, this includes the patients beginning the 2-week washout from RAAS inhibitors.

For patients who require RAAS inhibitor washout, certain evaluations at Visit 3 (randomization) may no longer fall within the limits set by the inclusion/exclusion criteria. These patients will remain eligible for the study based on their screening results, unless at Visit 3 they have a positive pregnancy test (positive urine pregnancy tests will be confirmed by a serum test) or have experienced the occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes them to substantial risk and/or does not allow them to adhere to the requirements of the protocol.

If in the Investigator's opinion, a laboratory value at screening is deemed unlikely to be representative of the patient's true status, the Investigator may repeat the measurement on that variable through the central laboratory to assess patient eligibility. The Investigator is required to consult with the Medical Monitor for more than 1 repeat measurement to be permitted. In particular, RAAS inhibitors affect protein excretion and eGFR. If, in the Investigator's opinion, withdrawal of RAAS inhibitor may alter these variables sufficiently to meet eligibility criteria, the patient may, if willing, undergo RAAS inhibitor washout and be retested for UP/C and/or eGFR to assess eligibility prior to potential randomization.

Criteria for the Double-blind Period

Inclusion Criteria:

A patient will meet all of the following criteria to be eligible for this study.

1. The patient or parent/legal guardian (as appropriate) is willing and able to provide signed informed consent, and where required, the patient is willing to provide assent, prior to any screening procedures.
2. The patient has biopsy-proven FSGS lesion(s) or documentation of a genetic mutation in a podocyte protein associated with FSGS. The biopsy may have been performed at any time in the past. The patient will be enrolled based on light microscopy diagnosis of FSGS and supportive findings on either electron microscopy (EM) or immunofluorescence (IF) analysis (preferably both). In exceptional cases, the patient may be enrolled based on light microscopy diagnosis of FSGS lesion(s) in the absence of EM and/or IF analysis, provided the history and/or the course of the disease are indicative of primary FSGS and the case has been reviewed by the Medical Monitor and Investigator.
3. Sites within the US and UK: The patient is male or female aged 8 to 75 years, inclusive, weighing ≥20 kg, at screening.
   Sites outside the US and UK: The patient is male or female aged 18 to 75 years, inclusive, weighing ≥20 kg, at screening.
4. The patient has a UP/C ≥1.5 g/g (170 mg/mmol) at screening.
5. The patient has an eGFR ≥30 mL/min/1.73 m^2 at screening.
6. The patient has a mean seated blood pressure ≥100/60 mmHg and ≤160/100 mmHg (patients ≥18 years of age) or between the 5th and 95th percentile for age, sex, and height (patients <18 years of age; Banker 2016).
7. Women of childbearing potential (WOCBP), beginning at menarche, must agree to the use of 1 highly reliable (ie, can achieve a failure rate of <1% per year) method of contraception from 7 days prior to the first dose of study medication until 90 days after the last dose of study medication. Examples of highly reliable contraception methods include stable oral, implanted, transdermal, or injected contraceptive hormones associated with inhibition of ovulation, or an intrauterine device in place for at least 3 months.

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One additional barrier method must also be used during sexual activity, such as a diaphragm or diaphragm with spermicide (preferred) or male partner's use of male condom or male condom with spermicide (preferred) from Day 1/Randomization until 90 days after the last dose of study medication. Women of childbearing potential are defined as those who are fertile, following menarche and until becoming postmenopausal unless permanently sterile; permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as amenorrhea for more than 24 consecutive months without an alternative medical cause; women on hormone replacement therapy must have a documented plasma follicle-stimulating hormone level >40 mIU/mL. All WOCBP must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test, with positive results confirmed by serum, at every study visit from Randomization (Visit 3) and after.
NOTE: Prior to menarche, pregnancy testing and contraceptive use are not required. However, the patient and their parent/guardian must be advised that, immediately upon menarche, the patient will be required to begin pregnancy testing and initiate contraceptive use. This requirement cannot be avoided.

Exclusion Criteria:

A patient who meets any of the following criteria will be excluded from this study.

1. The patient has FSGS secondary to another condition.
2. The patient is ≥18 years of age and has positive findings on serological tests that, in the Investigator's opinion, are diagnostic of another primary or secondary glomerular disease. These may include antinuclear antibody, anti-double stranded deoxyribonucleic acid (DNA) antibodies, complement C3 and C4, anti-neutrophil cytoplasmic antibody, rheumatoid factor, anti-glomerular basement membrane antibodies, any clinically significant abnormalities identified by serum and urine protein electrophoresis or immunofixation, or serum kappa and lambda free light chains. At the Investigator's discretion, these tests may be performed in patients <18 years of age under clinically relevant circumstances.
3. The patient has a history of type 1 diabetes mellitus, uncontrolled type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8%), or non-fasting blood glucose >180 mg/dL (10.0 mmol/L) at screening.
4. The patient has undergone any organ transplantation, with the exception of corneal transplants.
5. The patient requires any of the prohibited concomitant medications (see Section 15.2.1).
6. The patient has been treated with rituximab, cyclophosphamide, or abatacept within ≤3 months prior to screening. If a patient is taking other chronic immunosuppressive medications, the dosage must be stable for ≥1 month prior to screening and during the screening period.
7. The patient has a documented history of heart failure (New York Heart Association Class II-IV) and/or previous hospitalization for heart failure or unexplained dyspnea, orthopnea, paroxysmal nocturnal dyspnea, ascites, and/or peripheral edema.
8. The patient has clinically significant cerebrovascular disease (transient ischemic attack or stroke) and/or coronary artery disease (hospitalization for myocardial infarction or unstable angina, new onset of angina with positive functional tests, coronary angiogram revealing stenosis, or a coronary revascularization procedure) within 6 months prior to screening.
9. The patient has hemodynamically significant valvular disease.
10. The patient has jaundice, hepatitis, or known hepatobiliary disease (excluding asymptomatic cholelithiasis), or alanine aminotransferase and/or aspartate aminotransferase >2 times the upper limit of the normal range at screening.
11. The patient is positive at screening for the human immunodeficiency virus or markers indicating acute or chronic hepatitis B virus (HBV) infection (acute HBV is defined as a positive hepatitis B surface antigen [HBsAg], hepatitis B "e" antigen [HBeAg], HBV DNA in blood or liver, or immunoglobulin M hepatitis B core antibody; chronic HBV is defined as a positive HBsAg and/or HBeAg and/or HBV DNA) or hepatitis C virus (HCV) infection (defined as reactive anti-HCV antibody and HCV RNA).

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12. The patient has a history of malignancy other than adequately treated basal cell or squamous cell skin cancer or cervical carcinoma within the past 2 years.
13. The patient has a screening hematocrit value <27% (0.27 L/L) or hemoglobin value <9 g/dL (90 g/L).
14. The patient has a screening potassium value of >5.5 mEq/L (5.5 mmol/L).
15. The patient is extremely obese (ie, ≥18 years of age with a body mass index [BMI] >40 kg/m^2 or <18 years of age with a BMI in the 99th percentile plus 5 units at screening), in whom, in the Investigator's opinion, there is a causal relationship between obesity and development of the FSGS lesion. For patients with moderate or severe edema, BMI will be calculated based on remission or premorbid weight measured within 3 months prior to screening, if available. If not available, BMI will be calculated based on the estimated dry weight, based on the Investigator's clinical judgment.
16. The patient has a history of alcohol or illicit drug use disorder (as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition), or a reported habitual alcohol intake greater than 21 units/week within 2 years prior to screening.
17. The patient has a history of serious side effect or allergic response to any angiotensin II antagonist or endothelin receptor antagonist, including sparsentan or irbesartan, or has a hypersensitivity to any of the excipients in the study medications.
18. The female patient is pregnant, plans to become pregnant during the course of the study, or is breastfeeding.
19. The patient has participated in a study of another investigational product within 28 days prior to screening or plans to participate in such a study during the course of this study.
20. The patient has had prior exposure to sparsentan.
21. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study, including the ability to swallow the study medication capsules whole.

Patients with a medical condition or abnormal clinically significant laboratory screening value not listed above that may interfere with the evaluation of sparsentan efficacy or safety will be reviewed with the Medical Monitor before consideration of the patient for enrollment. Patients who fail screening may be re-screened up to 2 additional times. Patients who are re-screened will undergo all screening procedures and will be assigned a new patient number. Patients will also repeat the informed consent procedure each time they are re-screened.

Criteria for the Open-label Extension

Inclusion Criteria for the Open-label Extension:

Based on assessments at the Week 108 visit, a patient will meet all of the following criteria to be eligible for the open-label extension.

1. The patient completed participation in the double-blind period, including the Week 112 visit.
2. The patient or parent/legal guardian (as appropriate) is willing and able to provide signed informed consent for participation in the open-label extension.
3. The patient received blinded study medication throughout the duration of the double-blind period (ie, did not permanently discontinue study medication; see Section 6.4.2).

Exclusion Criteria for the Open-label Extension:

Based on assessments at the Week 108 and Week 112 visits, a patient who meets any of the following criteria will be excluded from the open-label extension.

1. The patient has progressed to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT).
2. The patient developed criteria for discontinuation as defined in Section 6.4.2 or Section 6.5 between Week 108 and Week 112.

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3. The patient was unable to initiate, or developed contraindications to, treatment with RAAS inhibitors between Week 108 and Week 112.
4. The patient has an eGFR ≤20 mL/min/1.73 m^2 at Week 108. NOTE: If in the Investigator's opinion, the eGFR value at Week 108 is deemed unlikely to be representative of the patient's true status, the Investigator may repeat the eGFR measurement prior to Week 112 through the central laboratory to assess patient eligibility. Patients with an eGFR <30 mL/min/1.73 m^2 will require close monitoring of eGFR and serum potassium throughout the open-label extension.
5. The female patient is pregnant, plans to become pregnant during the course of the study, or is breastfeeding.

DOSE FORM (TEST ARTICLE):

For the double-blind period, sparsentan will be dispensed as 200 mg tablets over-encapsulated (blinded) with size 00 capsules. For the open-label extension, sparsentan will be dispensed as 200 or 400 mg tablets.

DOSE FORM (REFERENCE TREATMENT):

Irbesartan will be the active control in the double-blind period. Irbesartan will be dispensed as 75 mg tablets over-encapsulated (blinded) with size 00 capsules. Irbesartan will not be used in the open-label extension.

DOSE/ROUTE/REGIMEN (TEST ARTICLE AND REFERENCE TREATMENT):

A dose adjustment will be made for patients whose body weight is ≤50 kg at screening; these patients will receive one-half the otherwise specified doses of study medication (weight will be measured at each visit and the dose increased at the Investigator's discretion if the patient's weight reaches >50 kg).

Double-blind Period

The full daily dose for both sparsentan (active) and irbesartan (control) will preferably be taken prior to the morning meal, with the exception of the day of a study visit. On the day of a study visit, the patient will take their study medication at the clinic. At the visits specified in Section 15.1, study medication will be administered at the clinic after the pre-dose pharmacokinetic (PK) blood sample has been obtained. Allowed doses during the double-blind period are shown in Table 2.

Patients will receive the initial dose (ie, one-half the target dose) based on screening body weight for the first 2 weeks. The Investigator will evaluate dose tolerance in a blinded manner prior to titrating up to the target dose; tolerance is defined as blood pressure measurements >100/60 mmHg (patients ≥18 years of age) or above the 5th percentile for sex and height (patients <18 years of age; Banker 2016) after 2 weeks and no adverse events (AEs) or laboratory findings interfering with the patient's continuation on study medication. Patients who display asymptomatic blood pressure values ≤100/60 mmHg (patients ≥18 years of age) or ≤90/50 mmHg or are below the 5th percentile for sex and height (whichever is lower in patients <18 years of age) or who present with clinical symptoms of orthostatic hypotension but otherwise tolerate the initial dose will continue after the Week 2 visit without titrating up to the target dose (see Section 8.1 and Section 8.3.2).

At the Investigator's discretion, patients weighing >50 kg who do not tolerate the initial dose for any reason (including changes in laboratory parameters assessed at Week 2) may continue at one-half the initial dose. Patients weighing ≤50 kg who do not tolerate the initial dose for any reason (including changes in laboratory parameters assessed at Week 2) will be discontinued from the study.

Open-label Extension

The full daily dose will preferably be taken prior to the morning meal. Allowed doses during the open-label extension are shown in Table 3.

Patients who are taking 2 capsules of study medication (ie, 400 mg sparsentan or 150 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at 200 mg sparsentan for the first 2 weeks of the open-label extension. Likewise, patients who are taking 4 capsules of study medication (ie, 800 mg sparsentan or 300 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at 400 mg sparsentan for the first 2 weeks of the open-label extension. Following 2 weeks

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(ie, Week 114) at one-half the double-blind dose, the Investigator will evaluate dose tolerance, as defined above for the double-blind period, prior to titrating up to the target dose. If the patient is tolerating the initial dose, the patient will titrate to the target dose at this time. Patients who display asymptomatic blood pressure values ≤100/60 mmHg (patients ≥18 years of age) or ≤90/50 mmHg or are below the 5th percentile for sex and height (whichever is lower in patients <18 years of age) 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 114 visit.

Patients who are taking 1 capsule of study medication (ie, 200 mg sparsentan or 75 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at 200 mg sparsentan for the first 2 weeks of the open-label extension. Following 2 weeks at 200 mg sparsentan (ie, Week 114), the Investigator will evaluate dose tolerance, as defined above for the double-blind period. Patients who are tolerating the initial dose will continue on 200 mg sparsentan at this time, including those who display asymptomatic blood pressure values ≤100/60 mmHg (patients ≥18 years of age) or ≤90/50 mmHg or are below the 5th percentile for sex and height (whichever is lower in patients <18 years of age) or who present with clinical symptoms of orthostatic hypotension but otherwise tolerate the initial dose.

For patients who enter the open-label extension with an eGFR value <30 mL/min/1.73 m^2 (ie, at Week 108), any dose titration at Week 114 will be at the Investigator's discretion based on the results of the Week 114 assessments. Patients who do titrate to a higher dose at Week 114 will be contacted by the Investigator at Week 116 to assess tolerance of the higher dose; at the Investigator's discretion, these patients may also come in for an additional visit at this time.

Doses may be modified at any time throughout the open-label extension for safety/tolerability reasons at the Investigator's discretion. In addition, after titration to the target dose, increases above the target doses of 200 or 400 mg sparsentan may be considered for patients who, in the Investigator's opinion (and following consultation with the Medical Monitor), would benefit from an increased dose.

ENDPOINTS:

Primary Efficacy Endpoint:

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

The surrogate efficacy endpoint is the proportion of patients achieving a UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline of the double-blind period (ie, Day 1) in UP/C at Week 36.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints in non-US countries are:

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

The secondary efficacy endpoints in the US are:

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

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Exploratory Endpoints:

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

Safety Endpoints:

Safety endpoints include:

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

Open-label Endpoints:

Endpoints for the open-label extension include, but are not necessarily limited to:

- The absolute and percent change from Week 112 in eGFR at each visit
- The percent change from Week 112 in UP/C at each visit
- Changes from Week 112 in QoL at each visit
- Changes from Week 112 in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters
- Changes from Week 112 in lipid profile (total cholesterol and triglycerides, LDL-C, and HDL-C)
- The incidence of TEAEs during the open-label extension

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STATISTICAL METHODS:

Power and Sample Size:

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

For the surrogate endpoint, at the time of the interim analysis (which is planned for after 36 weeks following randomization of at least 190 patients [approximately 95 per treatment group]), the power to detect a difference in response proportions between treatment groups is more than 90%, assuming the response proportions are 50% for sparsentan and 20% for irbesartan, with a 2-sided α of 0.05.

For the primary endpoint (slope of eGFR) at the final analysis, the study has at least 90% power to differentiate between treatments if the underlying eGFR slope difference is at least 2.5 mL/min/1.73 m^2 per year for the chronic slope over 2 years (non-US) or at least 2.1 mL/min/1.73 m^2 per year for the total slope over 2 years (US). The calculations assume that the separate tests for US and non-US countries are performed at a 2-sided α of 0.05 and that statistically significant difference is demonstrated at the interim analysis of the surrogate endpoint.

Analysis Sets:

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

Per Protocol (PP) Analysis Set: The PP Analysis Set will include all patients in the FAS who meet the study eligibility requirements and have no major protocol deviations that affect the validity of the efficacy measurements. Patients will be analyzed according to their randomized treatment. The PP Analysis Set will be used for a sensitivity analysis of the primary efficacy endpoint. The criteria for inclusion in the PP Analysis Set will be finalized prior to study unblinding and detailed in the Statistical Analysis Plan.

Safety Analysis Set: All patients who are randomized and take at least 1 dose of double-blind study medication will be included in the Safety Analysis Set. Safety analyses will be based on randomized treatment.

Open-Label Extension Full Analysis Set (OLEFAS): All patients who received at least 1 dose of open-label sparsentan in the open-label extension will be included in the OLEFAS. All efficacy and safety analyses during the open-label extension will be based on the OLEFAS.

Demographics and Baseline Characteristics:

Demographic data and baseline characteristics for the FAS, PP, and Safety Analysis Sets will be summarized by treatment group using descriptive statistics. Demographic data include sex, age (years), categorical age (<18 years and ≥18 years), race/ethnicity, weight (kg), height (cm), and calculated BMI. Baseline characteristics also include reproductive status (for females only), HbA1c, baseline eGFR, and current use of: steroids, calcineurin inhibitors, mycophenolate mofetil and other immunosuppressive agents, RAAS inhibitors (ie, angiotensin-converting enzyme inhibitors, ARBs, aldosterone blockers, and aliskiren) prior to the 2-week washout, diuretics, additional antihypertensive treatments, and statins.

Likewise, demographic data and baseline characteristics for the OLEFAS will be summarized overall using descriptive statistics.

Efficacy:

All efficacy analyses during the double-blind period will be performed based on the FAS. The primary endpoint analysis will also be conducted using the PP Analysis Set.

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The eGFR during the screening period will be determined using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation for adults (Levey 2009) and the Modified Schwartz formula (Schwartz 2009a; Schwartz 2009b) for children <18 years of age.

The eGFR for each timepoint (visit) during the double-blind period will be determined using the CKD-EPI equation for adults (Levey 2009) and children ≥16 years of age at screening for the double-blind period, and the Modified Schwartz formula for children <16 years of age at screening for the double-blind period (Schwartz 2009a; Schwartz 2009b). For the double-blind period, UP/C will be determined using first morning void urine samples and will be calculated as the average of 3 first morning void urine samples collected within 5 days prior to each visit at which UP/C is assessed.

The eGFR for each timepoint (visit) during the open-label extension will be determined using the CKD-EPI equation for adults (Levey 2009) and children ≥16 years of age at Week 108, and the Modified Schwartz formula for children <16 years of age at Week 108 (Schwartz 2009a; Schwartz 2009b). For the open-label extension, UP/C will be determined using 1 first morning void sample collected within 5 days prior to each visit at which UP/C is assessed.

As UP/C is a highly-skewed variable, analyses will be performed on log-transformed data; however, for ease of interpretation, results will be presented in the original units.

To control the overall type I error for this study when conducting significance tests for the primary and secondary efficacy endpoints, a hierarchical (gate-keeping) testing procedure will be used.

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

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

1. test the primary efficacy endpoint (eGFR chronic slope over 2 years) at the final analysis at 2-sided $\alpha = 0.05$. If the test is not significant, hypothesis testing stops. If the test is significant,
2. test the 3 secondary efficacy endpoints using a Bonferroni-Holm procedure to control for family-wise error rate at 2-sided $\alpha = 0.05$.

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

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

For the primary endpoint of slope of eGFR evaluated following the initial acute effect of randomized treatment (ie, from Week 6 to Week 108; chronic slope over 2 years), a mixed-effects model with linear spline (knot or change point at Week 6) will be fitted to the available eGFR data. The response variable is the eGFR measured at post-baseline assessments for each patient during the double-blind period. The model will include fixed effects for treatment, both stratification factors for randomization, baseline eGFR (continuous), time (in weeks) from baseline (continuous), and time (in weeks) from the change point (ie, timek = max(time – 6, 0)), time-by-treatment, and timek-by-treatment interactions. The model will also include a random intercept and random slopes (time and timek) for each patient. The mixed model will utilize restricted maximum likelihood estimation with Kenward-Roger method used to compute the denominator degrees of freedom for tests of fixed effects. The model will assume an unstructured covariance matrix. If the model does not converge under the unstructured covariance matrix, the autoregressive-1 covariance structure will be used. The primary efficacy

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hypothesis of interest is whether eGFR slopes over the blinded treatment period (after adjusting for early hemodynamic effects) are different between the 2 treatment groups, ie:

$$H_0: (\beta_{time*treatment} + \beta_{time\ k*treatment}) = 0 \text{ versus } H_1: (\beta_{time*treatment} + \beta_{time\ k*treatment}) \neq 0$$

This hypothesis will be tested using the mixed model by testing whether the time-by-treatment interaction parameters least-squares (LS) mean estimate is equal to zero. Sensitivity analyses are planned to assess the potential impact of major protocol deviations, premature treatment discontinuations, changes in immunosuppressive medications, and the choice of the change point.

For the primary endpoint of slope of eGFR evaluated following initiation of randomized treatment (ie, from Day 1 to Week 108; total slope over 2 years), a mixed-effects model will be fitted to the available eGFR data. The response variable is the eGFR measured at post-baseline assessments for each patient during the double-blind period. The model will include fixed effects for treatment, both stratification factors for randomization, baseline eGFR (continuous), time (in weeks) from baseline (continuous), and time-by-treatment interaction. The model will also include a random intercept and random slope for each patient. The mixed model will utilize restricted maximum likelihood estimation with Kenward-Roger method used to compute the denominator degrees of freedom for tests of fixed effects. The model will assume an unstructured covariance matrix. If the model does not converge under the unstructured covariance matrix, the autoregressive-1 covariance structure will be used. The hypothesis of interest is whether eGFR slopes over the blinded treatment period (after adjusting for early hemodynamic effects) are different between the 2 treatment groups, ie:

H0: $\beta_{time*treatment} = 0$ versus

H1: $\beta_{time*treatment} \neq 0$.

This hypothesis will be tested using the mixed model by testing whether the time-by-treatment interaction parameter LS mean estimate is equal to zero. Sensitivity analyses are planned to assess the potential impact of major protocol deviations, premature treatment discontinuations, changes in immunosuppressive medications, and the choice of the change point.

For the analysis of eGFR absolute change from baseline by visit, a Mixed Model Repeated Measures (MMRM) model will be fitted to the available eGFR data, incorporating all post-baseline visits at which eGFR was measured for each patient during the double-blind period. The model will include treatment, both stratification factors for randomization, baseline eGFR, visit (categorical), and visit-by-treatment interaction as fixed effects. In addition, patient will be included as a random effect. An unstructured within-patient covariance structure will be assumed. If the model does not converge under the unstructured covariance matrix, the autoregressive-1 covariance structure will be used. The LS mean estimate for $\beta_{WKj*treatment}$ (ie, the treatment effect at the visit j of interest) from the MMRM model will be used to perform treatment group comparisons by visit.

The percent change from baseline to 4 weeks post-cessation of randomized treatment at Week 112 in eGFR will be analyzed via analysis of covariance (ANCOVA). The dependent variable will be the natural log(eGFR) of analysis visit Week 112, with treatment and baseline eGFR in log scale included as fixed effects. The analysis will be stratified by the randomization strata. The treatment effect will be the contrast between sparsentan and irbesartan LS means. The LS means, treatment effect estimate, 95% confidence interval (CI), and p-value will be presented. Estimates and CIs will be converted to percentage.

The change from baseline to 4 weeks post-cessation of randomized treatment at Week 112 in eGFR will be analyzed via analysis of covariance (ANCOVA). The dependent variable will be the eGFR at analysis visit Week 112, with treatment and baseline eGFR included as fixed effects. The analysis will be stratified by the randomization strata. The treatment effect will be the contrast between sparsentan and irbesartan LS means. The LS means, treatment effect estimate, 95% confidence interval (CI), and p-value will be presented.

For the analysis of eGFR percent change from baseline by visit, a MMRM approach analogous to the model described for the absolute change from baseline will be used, except that the response variable will be natural

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log(eGFR) and corresponding baseline value natural log(baseline eGFR). Estimates and CIs will be converted to percentages via the following transformation:

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

For the analysis of eGFR percent change from Week 6 by visit, the estimates from the MMRM model used in the analysis of eGFR relative percent change from baseline by visit described above will be utilized. However, for this analysis, the statistical significance of the treatment difference at visit j (eg, Week 108 for the secondary endpoint) will be assessed by testing the following hypothesis:

$$H_0: (\beta_{WKj*treatment} - \beta_{WK6*treatment}) = 0 \text{ versus } H_1: (\beta_{WKj*treatment} - \beta_{WK6*treatment}) \neq 0,$$

where $\beta_{WKj*treatment}$ is the treatment effect at the visit j of interest and $\beta_{WK6*treatment}$ is the treatment effect at Week 6. The LS mean estimate from the MMRM model will be used to perform treatment group comparisons by visit. Estimates and CIs will be converted to percentages via the following transformation:

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

Analyses of the proportion of patients achieving a UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline at each visit (including the surrogate efficacy endpoint at Week 36) will be performed using a generalized linear model with logit link function to model the probability of achieving UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline and to compare sparsentan with irbesartan. The response variable will be a binary indicator of achievement of UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline at each post-baseline visit. Missing response variables will be imputed using the multiple imputation (MI) procedure before analysis. Fixed effects in the model will include baseline UP/C, treatment, time (categorical, in weeks), and treatment-by-time interaction. Analysis will be stratified by a randomization stratification variable (4 levels based on Screening eGFR and UP/C). An unstructured covariance matrix within patient will be assumed. If convergence issues arise, the autoregressive-1 covariance structure will be used. At each post-baseline visit included in the model, the probability of achieving UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline (risk) for each treatment group, treatment effect (risk difference), standard errors of risk and risk difference, 95% CIs of risks and risk difference, and p-values will be extracted from the model. Relative risk ratios and odds ratios, along with standard errors and 95% CIs, will also be presented. This analysis will be performed at the interim analysis (ie, surrogate efficacy endpoint). Sensitivity analyses will be performed using a Cochran-Mantel-Haenszel (CMH) test at Week 36, tipping point analysis, and analysis using observed cases (ie, no MI).

Change from baseline to all post-baseline visits during the double-blind period in natural log(UP/C) will be analyzed using a MMRM model analogous to the one described for percent change from baseline in eGFR. Estimates and CIs will be converted to percentages via the following transformation:

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

The time to achieve the target reduction in UP/C during the double-blind period will be analyzed using Cox proportional hazards model, stratified by randomization stratification variables, with a comparison between treatment groups. Patients who discontinue from treatment during the double-blind period prior to achieving the target reduction will be censored at the time of treatment discontinuation. Patients who never meet target during the double-blind period will be censored at the time of analysis.

The following endpoints will be summarized descriptively for the double-blind period and compared between treatment groups using a CMH test controlling for the randomization stratification variables: the proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or death; the proportion of patients requiring initiation or intensification of immunosuppressive medication during the study; and the proportion of patients with reduction in immunosuppressive medication during the study. Changes from baseline to all post-baseline visits during the double-blind period with respect to QoL scores and blood pressure (systolic and diastolic) values will be analyzed using a MMRM model analogous to the one described for changes from baseline in eGFR.

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Safety:

All safety analyses for the double-blind period will be conducted based on the Safety Analysis Set.

Safety data will include AEs, physical examination results, vital signs, ECG results, and clinical laboratory measurements. Observed data will be listed by patient and summarized using descriptive statistics by treatment group for the double-blind period.

Interim Analysis:

An unblinded interim analysis will be performed after 36 weeks following randomization of at least 190 patients to evaluate the surrogate endpoint.

Open-label Analyses:

Analyses of the endpoints for the open-label extension will be performed using the methods described above as appropriate.

Efficacy and safety endpoints for the open-label extension will be summarized using descriptive statistics and presented overall and by original randomized treatment based on the OLEFAS. Analyses using baselines other than Week 112 (eg, prior to first dose of study medication in the double-blind period) may be explored.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations used throughout the protocol should not be used by the site when documenting adverse events, medical history, etc. on source documents.

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
AE	Adverse event
AEOI	Adverse event of interest
AKI	Acute kidney injury
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AngII	Angiotensin II
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AT_1	Angiotensin II type 1 receptor
BMI	Body mass index
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology (equation)
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DUET	Study RET-D-001, NCT01613118, EudraCT 2014-002358-38: *Efficacy and Safety of Sparsentan (RE-021), a Dual Endothelin Receptor and Angiotensin Receptor Blocker, in Patients with Focal Segmental Glomerulosclerosis (FSGS): A Randomized, Double-blind, Active-control, Dose-escalation Study*
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EM	Electron microscopy
EOS	End of Study
EOT	End of treatment

Abbreviation	Definition
EQ-5D-5L	EuroQol, 5-dimension quality of life instrument, version 5L
EQ-5D-Y	EuroQol, 5-dimension quality of life instrument, version Y
ERA	Endothelin receptor antagonist
ESRD	End-stage renal disease
ET	Early termination
ET_A	Endothelin receptor subtype A
ET_B	Endothelin receptor subtype B
[redacted]	[redacted]
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSGS	Focal segmental glomerulosclerosis
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
HbA1c	Hemoglobin A1c (glycosylated hemoglobin)
HBeAg	Hepatitis B “e” antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IF	Immunofluorescence
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IWRS	Interactive web response system
KDIGO	Kidney Disease Improving-Global Outcomes

Abbreviation	Definition
KDQOL	Kidney Disease Quality of Life (instrument)
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
LS	Least-squares
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	Mixed Model Repeated Measures
NSAID	Non-steroidal anti-inflammatory drug
OLEFAS	Open-label Extension Full Analysis Set
PedsQL	Pediatrics Quality of Life Inventory
PK	Pharmacokinetic(s)
PP	Per Protocol (analysis set)
PRO	Patient-reported outcome
QoL	Quality of life
RAAS	Renin-angiotensin-aldosterone system
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
RRT	Renal replacement therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems
SD	Standard deviation
SOP	Standard operating procedure
SUSAR	Suspected, unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TRPC	Transient receptor potential canonical
UK	United Kingdom
ULN	Upper limit of normal
UP/C	Urine protein/creatinine ratio

Abbreviation	Definition
US	United States
VLDL-C	Very low-density lipoprotein cholesterol
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential

4. INTRODUCTION

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is a renal histological lesion characterized by segmental accumulation of glomerular extracellular matrix resulting in glomerular scarring and capillary obliteration. A variety of heterogeneous clinical conditions may lead to FSGS-type lesions, which could be classified as primary, genetic, or secondary forms. Primary FSGS has no identifiable cause but may result from the actions of putative circulating permeability factors that cause podocyte injury. Genetic causes include mutations in genes encoding proteins required for normal podocyte structure and/or function. In contrast, secondary forms of FSGS are caused by loss of renal parenchyma, metabolic derangements, other antecedent diseases, drugs, or infections (D'Agati 2011).

The presentation of primary and genetic FSGS varies, but can include severe proteinuria, arterial hypertension, edema, and nephrotic syndrome (Coppo 2013; Ponticelli 2013; Sethna 2014), with the potential for progression to end-stage renal disease (ESRD) and the consequent need for dialysis and kidney transplant.

Primary FSGS is a leading and growing cause of nephrotic syndrome (D'Agati 2011), and accounts for 3% to 4% of the prevalence of ESRD (Kitiyakara 2003). In most case series presented in the literature, primary FSGS is associated with a 10-year kidney survival in the range of 40% to 70% (Cameron 1978; Cattran 1998; Korbet 1986; Wehrmann 1990).

Patients with primary FSGS who present with nephrotic-range proteinuria have poor prognosis without treatment and typically progress to ESRD over the course of 3 to 6 years (Korbet 2002; Korbet 2003). Similarly, lack of response to disease-modifying treatments such as steroids has been identified as a negative prognostic sign (Korbet 2002). For patients with genetic FSGS, a rarer form than primary FSGS, kidney survival rates are comparably poor, with the rate of progression to ESRD tending to vary depending on mutation type. Treatment options are limited as genetic FSGS patients are generally resistant to immunosuppressive therapy. Taken together, clinical data show primary and genetic FSGS to be a serious condition associated with significant mortality and morbidity.

Sparsentan is a first-in-class, potent, orally active, dual-acting angiotensin receptor blocker (ARB; angiotensin II type 1 [AT_1]) plus endothelin type A (ET_A) receptor blocker. The selective, dual antagonistic actions of sparsentan have been demonstrated by in vitro binding assays (Kowala 2004).

Role and Pathophysiology of Angiotensin II and Endothelin in FSGS

To date, no studies focusing specifically on the mechanism of action of sparsentan on the kidney have been performed. However, considering known pharmacological actions of dual blockade of AT_1 and ET_A, sparsentan's actions on the renal system can be inferred from literature reports describing separate effects of AT_1 or ET_A receptor inhibition.

Angiotensin II (AngII) and endothelin 1 ([redacted] affect practically all renal compartments and cell types (Kohan 2014; Rüster 2011; Wennmann 2012), being implicated in processes involved in the pathophysiology of chronic kidney disease (CKD). There are overlaps in the actions of both peptides on the renal system that may act in an additive or synergistic manner in the pathogenesis of CKD, thus providing a strong rationale for dual blockade (Komers 2016).

Both AngII (Carmines 1990) and [redacted] are vasoactive peptides that exert renal hemodynamic effects. They promote cell growth, oxidative stress, and increased expression and activity of well-established proinflammatory and profibrotic signaling molecules and mediators (Gerstung 2007; Lenoir 2014; Watson 2010; Saleh 2011a; Saleh 2011b; Saleh 2010; Sasser 2007; Simonson 2011; Zoja 1999; Gagliardini 2009; Boffa 2001). The prosclerotic/fibrogenic and inflammatory actions of [redacted] may occur as part of AngII signaling (Rüster 2011) or as a direct consequence of stimulation of ET_A receptors (Saleh 2010; Simonson 2011).

Relevant to the pathogenesis and treatment of primary FSGS, both AngII and [redacted] affect podocytes, which are an integral part of the glomerular filtration barrier that prevents the passage of proteins into the urinary space. Both peptides play a role in the pathogenesis of proteinuria, being involved in a variety of processes that directly result in podocytic dysfunction and structural alterations. For example, the podocyte-specific overexpression of AT_1 receptors in rats is sufficient to cause proteinuria that eventually results in FSGS-type lesions. At the cellular level, the stimulation of AT_1 leads to activation of ion channels (transient receptor potential canonical [TRPC]5 and TRPC6), increases in cytosolic calcium, and activation of signaling pathways that ultimately induce membrane ruffling and the loss of stress fibers (Greka 2011). The impact on the cytoskeleton is similar to the depletion of synaptopodin, an important podocytic structural protein. Studies with renin-angiotensin-aldosterone-system (RAAS) inhibitors also implicate AngII in the loss of slit diaphragm proteins such as nephrin (Langham 2002).

Similarly, [redacted] is involved in podocyte alterations, apoptosis, and loss of podocytic structural proteins. Nephrin shedding, the loss of synaptopodin, and cytoskeletal rearrangement result in foot process effacement, which is a hallmark of podocytopathies (Barton 2012; Buelli 2014; Lenoir 2014; Saleh 2011b) including FSGS (Buelli 2014; Daehn 2014). Podocytes are not only targets of [redacted] actions, but are also a source of the peptide, resulting in deleterious effects on adjacent glomerular endothelial cells and causing mitochondrial dysfunction and production of reactive oxygen species (Daehn 2014).

In addition, [redacted] acting via ET_A receptors, increases glomerular permeability to albumin both in vitro and in vivo in a blood pressure-independent manner (Saleh 2010; Saleh 2012). These actions contribute to the proteinuric effects of [redacted] Treatment with endothelin receptor antagonists (ERAs; or more recently by genetic deletion of endothelin receptors) ameliorated cytoskeletal changes, restored podocyte structural integrity, and reduced proteinuria in models of podocyte injury and FSGS (Buelli 2014; Daehn 2014; Opocenský 2004). Both experimental and clinical evidence suggests that dual blockade of AngII and [redacted] has more prominent antiproteinuric effects than inhibition of either peptide alone (Komers 2016). However, data demonstrating the superior effect of a dual blockade on the long-term preservation of kidney function are not yet available.

Sparsentan Clinical Development

The purpose of sparsentan clinical development is to combine the potentially synergistic action of AngII receptor blockade with [redacted] receptor antagonism for clinical use in treating FSGS.

Sparsentan has been evaluated in a clinical development program targeted at the treatment of hypertension. That program consisted of 7 Phase 1 studies in 160 healthy volunteers and

2 Phase 2 studies in over 200 hypertensive patients. Dose-proportional pharmacokinetics (PK) and adequate oral exposure have been well defined. In a clinical pharmacodynamic study, sparsentan doses of 250 and 500 mg were shown to block the AngII pressor response in a healthy volunteer challenge test.

A Phase 2a study in hypertensive patients demonstrated clinically meaningful blood pressure reduction. A Phase 2b study that included a head-to-head comparison of sparsentan to irbesartan demonstrated superior efficacy of sparsentan at a dose of 800 mg/day compared to irbesartan at irbesartan's maximal approved dose of 300 mg/day. Progressive dose-dependent blood pressure reduction occurred through the highest sparsentan dose of 800 mg. Phase 1 Clinical Trials in healthy volunteers, and Phase 2 studies in hypertensive patients have shown a favorable safety profile with no drug-related serious adverse events (SAEs), changes in vital signs, or major clinically significant abnormalities in laboratory tests.

Sparsentan is currently being investigated in the ongoing open-label treatment period of the Phase 2 DUET study in patients with primary FSGS (RET-D-001; NCT01613118; EudraCT 2014-002358-38). The study aim is to determine the change in proteinuria after 8 weeks of double-blind treatment in primary FSGS patients receiving sparsentan over a range of dose levels (200 mg, 400 mg, and 800 mg) when compared to treatment with 300 mg irbesartan as active control.

In brief, patients 8 to 75 years of age with biopsy-proven FSGS (or documentation of a genetic mutation in a podocyte protein associated with the disease) were enrolled and assigned to 1 of 5 cohorts, representing 3 escalating sparsentan doses (200 mg, 400 mg, and 800 mg). Within each cohort, patients were randomized to sparsentan or a fixed maximal dose of active control (irbesartan) for an 8-week double-blind period. Patients weighing ≤50 kg received one-half of the randomized dose of either sparsentan or irbesartan. Following the double-blind period, patients were offered open-label sparsentan treatment in the study for an additional 208 weeks.

The primary efficacy objective of the DUET study was to determine the level of proteinuria reduction in patients with primary FSGS; the primary endpoint was the change in proteinuria after 8 weeks of double-blind treatment in patients receiving sparsentan over a range of dose levels (200 mg, 400 mg, and 800 mg) compared with treatment with irbesartan as the active control. Proteinuria was quantified using the urine protein/creatinine ratio (UP/C). The primary safety objective of the DUET study was to assess the safety and tolerability of sparsentan over a range of doses by comparing the safety profile of patients treated with sparsentan with that of patients treated with irbesartan (active control). This study also provided full PK profiles at Day 1 and Week 8, along with trough drug plasma concentrations at all other visits.

The first patient was screened for the DUET study on 13 Mar 2014 and was randomized on 07 Apr 2014. A total of 109 patients have been enrolled, including 23 pediatric FSGS patients (aged 8 to 18 years). Preliminary results are available from an interim analysis of data using a cutoff date of 09 Jun 2016. This analysis includes all safety and efficacy data collected through the double-blind period, as well as all open-label data available as the cutoff date. The preliminary results from this analysis outlined below indicate the greater antiproteinuric potential of sparsentan as compared to the ARB irbesartan.

- The DUET study met its primary efficacy endpoint:
  - The mean percentage reduction in UP/C from baseline in all sparsentan-treated patients (ie, 200 mg, 400 mg, and 800 mg groups combined; n = 64) to the end of the 8-week double-blind treatment phase was 44.8%, compared to a mean percentage reduction in irbesartan-treated patients (n = 32) of 18.5% (p = 0.006).
  - The mean percentage reduction in UP/C from baseline in all patients treated with 400 mg or 800 mg sparsentan (ie, 400 mg and 800 mg groups combined; n = 51) to the end of the 8-week double-blind treatment phase was 47.4%, compared to a mean percentage reduction in irbesartan-treated patients in these 2 dose cohorts (n = 25) of 19.0% (p = 0.011).
  - The comparison of UP/C reduction in the individual sparsentan doses to irbesartan showed clear signals of improvement but did not reach statistical significance.
- For DUET's secondary efficacy endpoint, the proportion of patients experiencing a UP/C ratio ≤1.5 g/g and a >40% reduction from baseline in UP/C at Week 8 was greater among sparsentan-treated patients (28.1%) compared with irbesartan-treated patients (9.4%; p = 0.040).
- Based on the preliminary results of the interim analysis, sparsentan has been well-tolerated thus far in the DUET study, with the majority (96.3%) of treatment-emergent adverse events (TEAEs) being mild or moderate. The most common TEAEs among sparsentan-treated patients were headache, dizziness, hypotension, nausea, diarrhea, vomiting, and peripheral edema/edema.

4.1. Summary of Potential Risks

The potential risks for patients treated with sparsentan are a consequence of its dual antagonist properties of both angiotensin and endothelin receptor blockade. Due to its ARB properties, sparsentan imparts a potential risk of acute kidney injury (AKI) due to reductions in intracapillary glomerular pressure, and a risk of hyperkalemia due to lower glomerular filtration rate (GFR) and aldosterone inhibition. In addition, syncope has been identified as a risk due to sparsentan's antihypertensive properties. These risks are accentuated in patients with reduced kidney function, volume depletion, and those being treated with non-steroidal anti-inflammatory drugs (NSAIDs). Studies have also shown that treatment with ERAs is associated with increased rates of edema and congestive heart failure (CHF) in patients with diabetic nephropathy (Mann 2010).

Selective and nonselective endothelin ET_A/endothelin receptor subtype B (ET_B) receptor antagonists are expected to cause fetal harm (harm to a developing embryo) if given to pregnant women. Similarly, ARBs have been shown to reduce fetal renal function and increase fetal and neonatal morbidity and death during the second and third trimesters of pregnancy. However, a recently completed, thorough, scientific evidence-based review of all available toxicology data evaluating the risk of genotoxic and teratogenic effects of sparsentan in male patients and their female partners indicates that, similar to marketed ERAs and ARBs, the requirement for contraception in male study patients is not warranted.

Because of these potential risks, sparsentan should be used with caution in patients with CKD Stages 3 and 4 and with extreme caution in patients with CKD Stage 5 and patients at risk of AKI. Moreover, sparsentan should be avoided in patients with CHF Stages 2 through 4, and in women who are or may become pregnant or who are breastfeeding.

For details regarding all nonclinical and clinical data on sparsentan, as well as warnings, precautions, and contraindications, the Investigator should refer to the appropriate section of the Investigator's Brochure.

4.2. Summary of Potential Benefits

Treatment-associated reduction in proteinuria in patients with primary FSGS may translate into a long-term nephroprotective effect. Sparsentan's antiproteinuric effect in patients with primary FSGS was observed in the DUET study (see Section 4). The current study will provide additional and essential long-term efficacy data to determine the durability of sparsentan's antiproteinuric effect over time, as well as its ability to slow the progression of primary FSGS, as measured by change in estimated glomerular filtration rate (eGFR) compared to standard-of-care therapies.

4.3. Rationale for the Study

The preliminary results from the interim analysis of data from the DUET study (see Section 4) indicate that sparsentan has a markedly stronger antiproteinuric effect than irbesartan over a period of 8 weeks in patients with primary FSGS. Although most nephrologists accept that even a short-term treatment-associated reduction in proteinuria results in better long-term renal outcomes, this hypothesis must be investigated further in a long-term study focusing on the durability of sparsentan's effect over a longer time period, and also on kidney function as measured by eGFR.

Despite its progressive course, which may result in some patients reaching ESRD within 5 to 10 years, primary FSGS is characterized by relatively slow decline in GFR in most patients. Consequently, utilization of the "hard" endpoints recognized by regulatory agencies for long-term interventional studies in kidney diseases (ie, doubling of serum creatinine, ESRD or renal replacement therapy [RRT], or death) is not practical for investigating appropriate treatments for FSGS. To address this issue, the current study (Protocol 021FSGS16010; also referred to as DUPLEX) will utilize the slope of eGFR decline as the primary endpoint to explore treatment differences between sparsentan and irbesartan. It is assumed that the stronger antiproteinuric effect seen with sparsentan leads to better preservation of kidney function, and consequently to less steep decline in GFR compared with irbesartan.

GFR will be estimated in this study every 3 months to obtain sufficient data for generation of reliable GFR slopes over a period of 2 years. Changes in kidney function will be evaluated in parallel with measurements of antiproteinuric effects of both sparsentan and irbesartan to further support the role of treatment-induced changes in proteinuria as a surrogate for long-term kidney survival.

Because pediatric patients comprise a substantial proportion of patients with FSGS, this study will include patients 8 years of age and older. As with the adult population, the goal of treatment for the pediatric population (aged 8 to 18 years) is reduction of proteinuria and preservation of kidney function; treatment-induced change in proteinuria has been associated with markedly

better long-term kidney survival and reduced need for RRT in both populations. Therefore, the study endpoints chosen are relevant for both pediatric and adult patients.

Current experience with sparsentan treatment in patients with FSGS does not indicate specific safety concerns for pediatric patients. In this study, pediatric patients with a screening body weight >50 kg will be treated with the same dose as adult patients, whereas both adult and pediatric patients with a screening body weight ≤50 kg will receive one-half the target dose of sparsentan or active control.

For details regarding all nonclinical and clinical data on sparsentan, as well as warnings, precautions, and contraindications, the Investigator should refer to the appropriate section of the Investigator's Brochure.

5. STUDY OBJECTIVES

5.1. Efficacy Objective

The efficacy objective of the study is to determine the long-term nephroprotective potential of treatment with sparsentan as compared with an ARB in patients with primary and genetic FSGS.

5.2. Safety Objective

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

5.3. Open-Label Objective

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

6. INVESTIGATIONAL PLAN

6.1. Endpoints

6.1.1. Efficacy Endpoints

6.1.1.1. Primary Efficacy Endpoint

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

The surrogate efficacy endpoint is the proportion of patients achieving a UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline of the double-blind period in UP/C at Week 36.

6.1.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are assessed at the final analysis and are part of a hierarchical (gate-keeping) testing procedure (see Section 12.10.2). Secondary efficacy endpoints in non-US countries include:

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

The secondary efficacy endpoints in the US are:

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

6.1.1.3. Exploratory Endpoints for the Double-Blind Period

- The slopes of eGFR over approximately 1 year of randomized treatment evaluated following the initial acute effect of randomized treatment (ie, from Week 6 to Week 60; chronic slope over 1 year) and after initiation of randomized treatment (ie, from Day 1 to Week 60; total slope over 1 year)
- The absolute and percent change from baseline of the double-blind period in eGFR at each visit
- The percent change from Week 6 in eGFR at each visit
- The proportion of patients achieving a UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline of the double-blind period in UP/C at each visit

- The percent change from baseline of the double-blind period in UP/C at each visit
- The time to achieve the target reduction in UP/C (ie, ≤1.5 g/g [170 mg/mmol] and a >40% reduction)
- The proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or death. (ESRD is defined as initiation of RRT or sustained eGFR <15 mL/min/1.73 m^2 during the study).
- The proportion of patients reaching a confirmed 30% reduction in eGFR, ESRD, or death
- Changes from baseline of the double-blind period in blood pressure at each visit
- The proportion of patients requiring initiation of or intensification in immunosuppressive medication during the study
- The proportion of patients undergoing reduction in immunosuppressive medication during the study
- The time to initiation or intensification of immunosuppressive medication during the study
- Changes from baseline of the double-blind period in quality of life (QoL), measured via patient-reported outcome (PRO) at each visit beginning with Week 12
- Frequency and duration of hospitalizations (for any reason and for reasons related to the kidney)
- Trough plasma PK concentrations during the double-blind period

6.1.2. Safety Endpoints

Safety endpoints include:

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

6.1.3. Open-Label Endpoints

Endpoints for the open-label extension include, but are not necessarily limited to:

- The absolute and percent change from Week 112 in eGFR at each visit
- The percent change from Week 112 in UP/C at each visit
- Changes from Week 112 in QoL at each visit
- Changes from Week 112 in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters

- Changes from Week 112 in lipid profile (total cholesterol and triglycerides, LDL-C, and HDL-C)
- The incidence of TEAEs during the open-label extension

6.2. Study Design

This is a 112-week, randomized, multicenter, double-blind, parallel, active-control study, with an open-label extension of up to 156 weeks, for a total study duration of up to 268 weeks. Approximately 300 patients aged 8 to 75 years, inclusive (US and United Kingdom [UK]) and 18 to 75 years, inclusive (countries other than the US and UK), weighing ≥20 kg, will be enrolled in the study.

6.2.1. Double-Blind Period Design

Patients who meet inclusion criteria during screening who are taking RAAS inhibitors will undergo a 2-week washout period from these agents prior to Day 1/Randomization.

Following screening (and the washout period for patients taking RAAS inhibitors), all patients will undergo comprehensive baseline evaluations and clinical laboratory tests, and will be randomly assigned in a 1:1 ratio to receive either sparsentan (initial dose of 400 mg daily for 2 weeks, titrating up to a target dose of 800 mg daily) or an active control (irbesartan; initial dose of 150 mg daily for 2 weeks, titrating up to a target dose of 300 mg daily) (see Section 8.1). Randomization will include stratification by screening eGFR and UP/C values. The strata will be as follows:

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

Sparsentan and irbesartan concentrations in plasma will be evaluated. At applicable visits (see Section 15.1), 1 trough sample will be obtained pre-dose in the clinic.

Unless otherwise specified, endpoints will use pretreatment values obtained prior to randomization as baseline. The follow-up visits to obtain measurements will be conducted at 3-month intervals unless otherwise specified.

Additional antihypertensive agents are allowed during the double-blind period to maintain blood pressure ≤130/80 mmHg (patients ≥18 years of age) or ≤ the 75th percentile (patients <18 years of age; Banker 2016), with the exception of those agents that inhibit the RAAS and endothelin systems (see Section 15.2.1 for concomitant medication considerations).

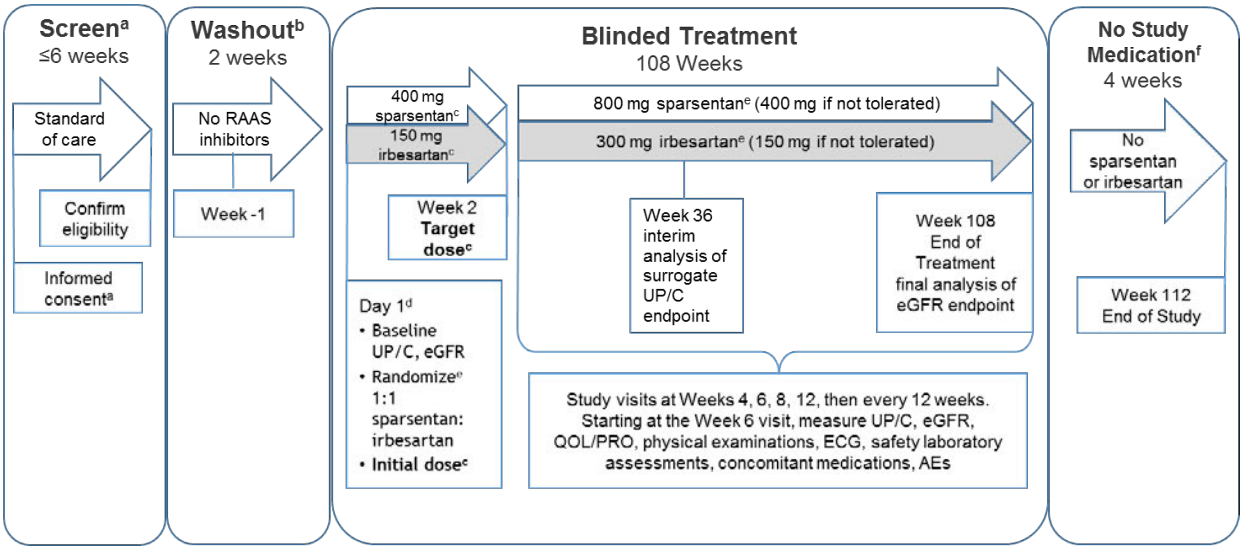
An unblinded analysis will be performed after 36 weeks following randomization of at least 190 patients (approximately 95 per treatment group) to evaluate the surrogate efficacy

endpoint (ie, the proportion of patients achieving a UP/C ≤1.5 g/g [170 mg/mmol] and a >40% reduction in UP/C at Week 36).

Following a 108-week blinded treatment period, treatment with study medication will be discontinued, and patients may be evaluated for eligibility in the open-label extension using values from the Week 108 visit as screening assessments (see Section 6.2.2). At this time, the Investigator should resume standard-of-care treatment, including treatment with RAAS inhibitors provided there are no contraindications for their use. If the patient was treated with irbesartan at study entry, an alternative ARB at an equivalent dose is required from Week 108 to Week 112. The Investigator may make additional adjustments in antihypertensive medications as necessary to adequately control the patient's blood pressure.

Patients will return to the site for the final visit of the double-blind period 4 weeks after study medication has been discontinued (ie, Week 112; see Figure 1).

Figure 1: Study 021FSGS16010 Overview Flow Chart of the Double-Blind Period



[a] Screening may begin after informed consent has been signed. The screening window begins on the day of the patient's first in-clinic study procedure. Patients should be screened within the 6-week screening period; however, under extenuating circumstances the screening period may be extended by a maximum of 2 weeks.

[b] For patients who are undergoing washout from RAAS inhibitors.

[c] Patients whose body weight is ≤50 kg at screening will receive one-half the otherwise specified doses of either sparsentan or irbesartan (active control). Weight will be measured at each visit and the dose increased at the Investigator's discretion if the patient's weight reaches >50 kg.

[d] Day 1 events shown will occur in the order in which they are listed.

[e] Randomization will be stratified by eGFR value (≥30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2 for all patients) and UP/C (≤3.5 g/g and >3.5 g/g [396 mg/mmol; patients ≥18 years of age] or ≤2 g/g and >2 g/g [226 mg/mmol; patients <18 years of age]) at screening.

[f] Following the 108-week blinded treatment period, treatment with study medication will be discontinued and patients may be evaluated for eligibility in the open-label extension. At this time, the Investigator should resume standard-of-care treatment, including treatment with RAAS inhibitors provided there are no contraindications for their use. If the patient was treated with irbesartan at study entry, an alternative ARB at an equivalent dose is required from Week 108 to Week 112. The Investigator may make additional adjustments in antihypertensive medications as necessary to adequately control the patient's blood pressure.

Table 1: Study 021FSGS16010 Double-Blind Study Visits

Visit:	Visit 1[a]	Visit 2 (± 3 days)		Visit 3[d]	Visit 4 (± 3 days)	Visit 5 (± 3 days)	Visit 6 (± 7 days)	Visit 7 (± 7 days)	Visit 8 (± 7 days)
	Screening All Patients	Washout Patients[b]		Blinded Treatment					
Week:	W -6	W -2[b]	W-1[c]	Day 1 (Randomization)	W2	W4	W6	W8	W12

Visit:	Visit 9 (± 7 days)	Visit 10 (± 7 days)	Visit 11 (± 7 days)	Visit 12 (±7 days)	Visit 13 (±7 days)	Visit 14 (±7 days)	Visit 15 (±7 days)	Visit 16[e] (±7 days)	Visit 17 (-7 to +14 days)
	Blinded Treatment								End of Double-Blind Period Visit
Week:	W24	W36	W48	W60	W72	W84	W96	W108	W112

[a] The screening period for all patients is 6 weeks (42 days) prior to Day 1. Under extenuating circumstances, the screening period may be extended by a maximum of 2 weeks.
[b] Patients taking RAAS inhibitors at screening (Visit 1) will complete a 2-week (14-day) washout from these medications prior to Day 1 (Randomization). The washout should begin no later than 4 weeks (28 days) after Visit 1.
[c] Patients undergoing washout will return to the clinic for a follow-up visit to assess safety and blood pressure control approximately 1 week after the start of the washout period.
[d] The Day 1 (Randomization) Visit will occur no later than 6 weeks (42 days) after Visit 1 (8 weeks if the screening period was extended). All eligible patients will be randomized via interactive web response system (IWRS) and the first dose will be administered in the clinic.
[e] Visit 16 is the End of Treatment visit.

6.2.2. Open-Label Extension Design

Patients may be evaluated for eligibility in the open-label extension using values from the Week 108 visit as screening assessments. Patients with an eGFR <30 (but >20) mL/min/1.73 m^2 will be eligible for participation in the open-label extension at the discretion of the Investigator, but will require close monitoring of eGFR and serum potassium (see Section 7.2.2).

For patients who agree to participate in the open-label extension and meet eligibility criteria (see Section 7.2), the Week 112 visit will also serve as the baseline visit for the open-label extension. Standard-of-care treatment (ACEI and/or ARB therapy) will be discontinued before the Week 112 visit. The final dose of an ACEI and/or ARB should be taken on the day before the Week 112 visit. At this visit, patients will sign a new informed consent (if not completed previously) for the open-label extension and begin taking open-label sparsentan. All Week 112 evaluations must be completed prior to the first dose of open-label sparsentan.

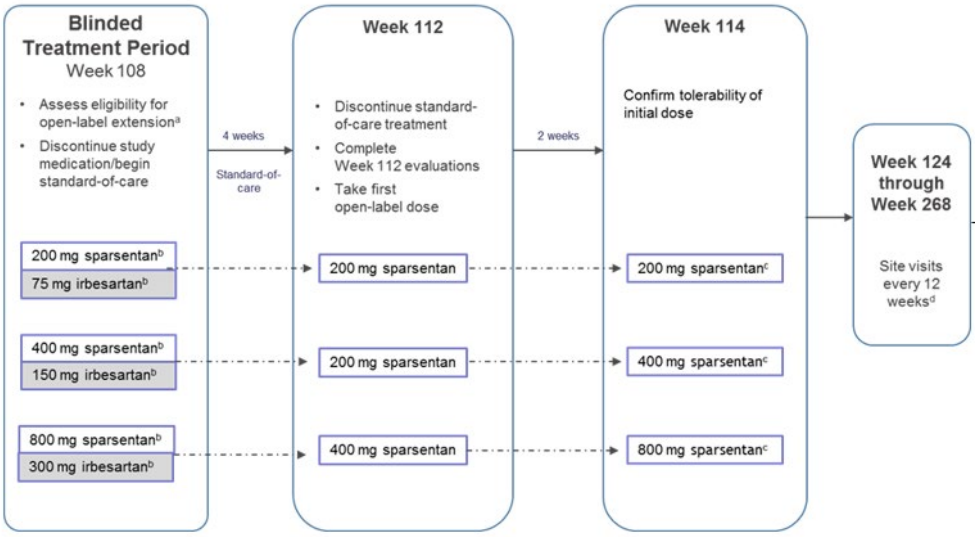
Patients who are taking 2 or 4 capsules of study medication (ie, 400 mg or 800 mg sparsentan or 150 mg or 300 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at one-half the corresponding dose of open-label sparsentan for the first 2 weeks (ie, 200 mg or 400 mg sparsentan, respectively), then titrate to the target dose after confirmation of tolerability at Week 114. Patients who are taking 1 capsule of study medication (ie, 200 mg sparsentan or 75 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at 200 mg open-label sparsentan and continue on that dose

throughout the open-label extension. For details regarding dose titration in the open-label- extension, see Section 8.1.2; for details regarding dose modifications, see Section 8.3.2.

As in the double-blind period, additional antihypertensive agents are allowed during the open-label extension to maintain blood pressure ≤130/80 mmHg (patients ≥18 years of age) or ≤ the 75th percentile (patients <18 years of age; Banker 2016), with the exception of those that inhibit the RAAS and endothelin systems (see Section 15.2.1 for concomitant medication considerations).

Patients will participate in the open-label extension for up to 156 weeks (see Figure 2), for a total of 268 weeks in the study (ie, double-blind and open-label periods). If the product becomes commercially available during the open-label extension period, eligible patients may transition out of the study and onto commercial product before the end of the open-label extension period. After the patient completes the study (Week 268), if sparsentan is not commercially available, patients may potentially receive sparsentan via alternative means depending upon regulations and commercial status in each country.

Figure 2: Study 021FSGS16010 Overview Flow Chart of the Open-Label Extension



[a] See Section 7.2 for eligibility criteria for the open-label extension.
[b] The blinded dose the patient is on at Week 108 is dependent on randomization, weight, and ability to tolerate study medication during the double-blind period.
[c] Dose for the open-label extension will be based on tolerability as determined at Week 114. Any dose titration for patients who enter the open-label extension with an eGFR value <30 mL/min/1.73 m^2 will be at the Investigator's discretion based on the results of the Week 114 assessments. Doses may be modified at any time throughout the open-label extension for safety/tolerability reasons at the Investigator's discretion. In addition, after titration to the target dose, increases above the target doses of 200 mg or 400 mg sparsentan may be considered for patients who, in the Investigator's opinion (and following consultation with the Medical Monitor), would benefit from an increased dose.
[d] Patients who enter the open-label extension with an eGFR value <30 mL/min/1.73 m^2 and titrate at Week 114 will be contacted by the Investigator at Week 116 to assess tolerance of the higher dose; at the Investigator's discretion, these patients may also come in for an additional visit at this time.

6.3. Patient Completion and Overall Study Completion

6.3.1. Patient Completion of the Double-Blind Period

Each patient will participate in the double-blind period of the study for approximately 6 weeks during the screening phase, followed by 108 weeks of double-blind treatment. At the end of the 108-week treatment period, study medication will be discontinued and replaced with standard-of-care therapy treatment, including treatment with RAAS inhibitors provided there are no contraindications for their use. If the patient was treated with irbesartan at study entry, an alternative ARB at an equivalent dose is required from Week 108 to Week 112. The Investigator may make additional adjustments in antihypertensive medications as necessary to adequately control the patient's blood pressure.

Patients will return to the site for the final (Week 112) visit 4 weeks later. Thus, patients will participate in the double-blind period for a total of approximately 118 weeks or about 30 months.

A patient will be considered as having completed the double-blind period, regardless of whether the patient is on or off study medication, if the patient is followed until Week 112. The need for additional intervention for the treatment of FSGS or the occurrence of safety endpoints do not constitute completion of the double-blind period and are not criteria for withdrawal from the study or study medication.

Patients who successfully complete the final Week 112 Visit will complete the assessments listed in the schedule of events (Section 15.1). Patients who received blinded study medication throughout the duration of the double-blind- period (ie, did not permanently discontinue study medication) may be eligible to enroll in the open-label extension (see Section 7.2).

6.3.2. Patient Completion of the Open-Label Extension

Eligible patients may participate in the open-label extension for up to 156 weeks. If the product becomes commercially available during the open-label extension period, eligible patients may transition out of the study and onto commercial product before the end of the open-label extension period. After the patient completes the study (Week 268), if sparsentan is not commercially available, patients may potentially receive sparsentan via alternative means depending upon regulations and commercial status in each country.

6.3.3. Overall Study Completion

The study will be considered complete when the last patient completes their final visit.

6.4. Discontinuation of Study Medication

A patient/patient's parents or guardians is/are free to withdraw assent/consent and/or discontinue the patient's participation in the study at any time, without prejudice to subsequent standard-of-care treatment. As part of the informed consent process, only patients who fully understand and agree to full and long-term participation should be consented to participate. In all cases of impending study medication discontinuation, Investigators should discuss options of continuing in the study with the patient (see Section 6.4.1 and Section 6.4.2). In general, patients should be encouraged to both stay on study medication and remain in the study until study termination.

6.4.1. Temporary Interruption of Study Medication

Patients who temporarily interrupt study medication prior to completion of the study will continue with study visits and assessments according to the Schedule of Study Events (Section 15.1). Unless contraindicated, treatment should be resumed (titrated at the Investigator's discretion according to Section 8.3.2) whenever possible (including between visits), and treatment resumption should be considered at every visit following study medication interruption.

6.4.2. Permanent Discontinuation of Study Medication

During the course of this long-term study, it is anticipated that patients may permanently discontinue study medication (sparsentan or irbesartan) for any of the following reasons:

- Receipt of kidney transplant or initiation of RRT
- Any SAE, AE of interest (AEOI; see Section 10.3), clinically significant laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continuation on study medication is not in the best interest of the patient
- Significant protocol deviation (ie, patient failed to meet entry criteria or did not comply with protocol requirements resulting in an unacceptable risk to the patient's health)
- Investigator discretion
- Patient (or parent/legal guardian) decision to stop study medication
- Patient pregnancy
- Diagnosis of Class II-IV CHF
- Hyperkalemia resistant to treatment (see Appendix B, Section 15.2.2 for hyperkalemia management guidelines)
- Termination of the study by the Sponsor, US Food and Drug Administration (FDA), or other regulatory authorities (see Section 13.4.5)
- Lost to follow-up

Therapy to treat relapse (that is a new or substantial change in immunosuppression) during the study is not a reason for permanent study medication discontinuation.

Patients who permanently discontinue study medication during the double-blind period should be encouraged to continue study visits through Week 112 for continued collection of safety and efficacy data despite stopping study medication, but may withdraw consent at any time (see Section 6.5). Patients who agree to continue regularly scheduled study visits will complete the End of Treatment (EOT) assessments listed in the schedule of events (Section 15.1) as close as possible to the patient's last dose of study medication. The visit data, including the primary reason for discontinuation of study medication, will be recorded on the EOT electronic case report form (eCRF). Subsequent study visit data will be recorded on the visit-specific eCRF, and the patient's final study visit will be recorded on the End of Study (EOS) eCRF.

For patients who permanently discontinue study medication during the double-blind period, the Investigator should resume standard-of-care treatment, including treatment with appropriate medications, as deemed necessary. If the patient was treated with irbesartan at study entry, an alternative ARB or angiotensin-converting enzyme (ACE) inhibitor must be resumed.

Patients permanently discontinuing study medication who are not willing to continue with regular study visits, but who are willing to continue to provide their information for use in the study will be encouraged to remain in the study. The Investigator will contact the Sponsor's designee to determine the best approach based on the patient's situation.

Patients who permanently discontinue study medication during the open-label extension are encouraged to return to the site for a final visit. No other study visits are necessary. If an EOT visit is completed, study medication cannot be resumed.

6.5. Discontinuation of the Patient from the Study

Patients are free to withdraw consent and/or discontinue participation in the study at any time without prejudice to subsequent standard-of-care treatment. A patient's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor. Patients may also be discontinued from the study if the study is terminated (see Section 13.4.5).

Patients may be permanently discontinued from the study for any of the following reasons:

- Death
- Voluntary withdrawal of patient/guardian assent/consent (complete withdrawal of consent requires a patient's/parent's/guardian's refusal of ALL methods of follow-up noted in the informed consent form [ICF])
- Termination of the study by the Sponsor, US FDA, or other regulatory authorities (see Section 13.4.5)
- Lost to follow-up

In general, patients should be encouraged to remain in the study until they complete the double-blind period. A patient who permanently discontinues from the study during the double-blind- period will complete the early termination (ET) assessments listed in the schedule of events (Section 15.1) as close as possible to the patient's last dose of study medication. The visit data, including the primary reason for premature discontinuation from the study, will be recorded on the EOS eCRF.

6.6. Lost to Follow-up

The Investigator must make every effort to contact patients who fail to return for scheduled visits so that they will not be declared "lost to follow-up." Patients will be considered "lost to follow-up" only after reasonable, documented attempts to reach the patient prove unsuccessful. These attempts include, but are not limited to, the following:

1. Contact all telephone numbers for the patient and their listed contacts (to be collected in the source at the patient's entry into the study), as applicable.

2. Contact the patient's primary care physician, referring specialist, or other healthcare professional, as applicable.
3. Send email, text, and postal mail with certified letters to all the patient's addresses and contacts, as applicable.
4. Review available medical records/notes for details of hospitalizations, clinic visits, or other procedures that may indicate the status of the patient, as applicable.
5. Utilize the internet to search for additional contact information, as applicable.
6. Check local, regional, and national public records to locate the patient or search for mortality status as allowed by law, as applicable.

The information and dates of attempted contact must be recorded in the patient's records and the patient's final status recorded in the appropriate eCRF. Once these actions have been exhausted and documented, the Sponsor or Sponsor's designee should be contacted for additional guidance.

7. PATIENT POPULATION AND SELECTION

Eligibility must be confirmed, and signed/dated informed consent obtained, prior to any study-related procedure. Where applicable, this includes the patient beginning the 2-week washout from RAAS inhibitors.

For patients who require RAAS inhibitor washout, certain evaluations at Visit 3 (randomization) may no longer fall within the limits set by the inclusion/exclusion criteria. These patients will remain eligible for the study based on their screening results, unless at Visit 3 they have a positive pregnancy test (positive urine pregnancy tests will be confirmed by a serum test) or have experienced the occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes them to substantial risk and/or does not allow them to adhere to the requirements of the protocol.

If in the Investigator's opinion, a laboratory value at screening is deemed unlikely to be representative of the patient's true status, the Investigator may repeat the measurement on that variable through the central laboratory to assess patient eligibility. The Investigator is required to consult with the Medical Monitor for more than 1 repeat measurement to be permitted. In particular, RAAS inhibitors affect protein excretion and eGFR. If, in the Investigator's opinion, withdrawal of RAAS inhibitor may alter these variables sufficiently to meet eligibility criteria, the patient may, if willing, undergo RAAS inhibitor washout and be retested for UP/C and/or eGFR to assess eligibility prior to potential randomization.

7.1. Criteria for the Study

7.1.1. Inclusion Criteria

A patient will meet all of the following criteria to be eligible for this study.

1. The patient or parent/legal guardian (as appropriate) is willing and able to provide signed informed consent, and where required, the patient is willing to provide assent, prior to any screening procedures.
2. The patient has biopsy-proven FSGS lesion(s) or documentation of a genetic mutation in a podocyte protein associated with FSGS. The biopsy may have been performed at any time in the past. The patient will be enrolled based on light microscopy diagnosis of FSGS and supportive findings on either electron microscopy (EM) or immunofluorescence (IF) analysis (preferably both). In exceptional cases, the patient may be enrolled based on light microscopy diagnosis of FSGS lesion(s) in the absence of EM or IF analysis, provided the history and/or the course of the disease are indicative of primary FSGS and the case has been reviewed by the Medical Monitor and Investigator.
3. Sites within the US and UK: The patient is male or female aged 8 to 75 years, inclusive, weighing ≥20 kg, at screening.
   Sites outside the US and UK: The patient is male or female aged 18 to 75 years, inclusive, weighing ≥20 kg, at screening.
4. The patient has a UP/C ≥1.5 g/g (170 mg/mmol) at screening.
5. The patient has an eGFR ≥30 mL/min/1.73 m^2 at screening.

6. The patient has a mean seated blood pressure ≥100/60 mmHg and ≤160/100 mmHg (patients ≥18 years of age) or between the 5th and 95th percentile for age, sex, and height (patients <18 years of age; Banker 2016).
7. Women of childbearing potential (WOCBP), beginning at menarche, must agree to the use of 1 highly reliable (ie, can achieve a failure rate of <1% per year) method of contraception from 7 days prior to the first dose of study medication until 90 days after the last dose of study medication. Examples of highly reliable contraception methods include stable oral, implanted, transdermal, or injected contraceptive hormones associated with inhibition of ovulation, or an intrauterine device (IUD) in place for at least 3 months. One additional barrier method must also be used during sexual activity, such as a diaphragm or diaphragm with spermicide (preferred), or male partner's use of male condom or male condom with spermicide (preferred), from Day 1/Randomization until 90 days after the last dose of study medication. WOCBP are defined as those who are fertile, following menarche and until becoming postmenopausal unless permanently sterile; permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as amenorrhea for more than 24 consecutive months without an alternative medical cause; women on hormone replacement therapy must have a documented plasma follicle-stimulating hormone level >40 mIU/mL. All WOCBP must have a negative serum pregnancy test at Screening (Visit 1), and a negative urine pregnancy test, with positive results confirmed by serum, at every study visit from Randomization (Visit 3) and after.
   NOTE: Prior to menarche, pregnancy testing and contraceptive use are not required. However, the patient and their parent/guardian must be advised that, immediately upon menarche, the patient will be required to begin pregnancy testing and initiate contraceptive use. This requirement cannot be avoided.

7.1.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study.

1. The patient has FSGS secondary to another condition.
2. The patient is ≥18 years of age and has positive findings on serological tests that, in the Investigator's opinion, are diagnostic of another primary or secondary glomerular disease. These may include: antinuclear antibody, anti-double stranded deoxyribonucleic acid (DNA) antibodies, complement C3 and C4, anti-neutrophil cytoplasmic antibody, rheumatoid factor, anti-glomerular basement membrane antibodies, any clinically significant abnormalities identified by serum and urine protein electrophoresis or immunofixation, or serum kappa and lambda free light chains. At the Investigator's discretion, these tests may be performed in patients <18 years of age under clinically relevant circumstances.
3. The patient has a history of type 1 diabetes mellitus, uncontrolled type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8%), or non-fasting blood glucose >180 mg/dL (10.0 mmol/L) at screening.
4. The patient has undergone any organ transplantation, with the exception of corneal transplants.

5. The patient requires any of the prohibited concomitant medications (see Section 15.2.1).
6. The patient has been treated with rituximab, cyclophosphamide, or abatacept within ≤3 months prior to screening. If a patient is taking other chronic immunosuppressive medications, the dosage must be stable for ≥1 month prior to screening and during the screening period.
7. The patient has a documented history of heart failure (New York Heart Association Class II-IV) and/or previous hospitalization for heart failure or unexplained dyspnea, orthopnea, paroxysmal nocturnal dyspnea, ascites, and/or peripheral edema.
8. The patient has clinically significant cerebrovascular disease (transient ischemic attack or stroke) and/or coronary artery disease (hospitalization for myocardial infarction or unstable angina, new onset of angina with positive functional tests, coronary angiogram revealing stenosis, or a coronary revascularization procedure) within 6 months prior to screening.
9. The patient has hemodynamically significant valvular disease.
10. The patient has jaundice, hepatitis, or known hepatobiliary disease (excluding asymptomatic cholelithiasis), or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2 times the upper limit of the normal range at screening.
11. The patient is positive at screening for the human immunodeficiency virus (HIV) or markers indicating acute or chronic hepatitis B virus (HBV) infection (acute HBV is defined as a positive hepatitis B surface antigen [HBsAg], hepatitis B "e" antigen [HBeAg], HBV DNA in blood or liver, or immunoglobulin M hepatitis B core antibody; chronic HBV is defined as a positive HBsAg and/or HBeAg and/or HBV DNA) or hepatitis C virus (HCV) infection (defined as reactive anti-HCV antibody and HCV RNA).
12. The patient has a history of malignancy other than adequately treated basal cell or squamous cell skin cancer or cervical carcinoma within the past 2 years.
13. The patient has a screening hematocrit value <27% (0.27 L/L) or hemoglobin value <9 g/dL (90 g/L).
14. The patient has a screening potassium value of >5.5 mEq/L (5.5 mmol/L).
15. The patient is extremely obese (ie, ≥18 years of age with a body mass index [BMI] >40 kg/m^2, or <18 years of age with a BMI in the 99th percentile plus 5 units at screening), in whom, in the Investigator's opinion, there is a causal relationship between obesity and development of the FSGS lesion. For patients with moderate or severe edema, BMI will be calculated based on remission or premorbid weight measured within 3 months prior to screening, if available. If not available, BMI will be calculated based on the estimated dry weight, based on the Investigator's clinical judgment.
16. The patient has a history of alcohol or illicit drug use disorder (as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition), or a reported habitual alcohol intake greater than 21 units/week within 2 years prior to screening.

17. The patient has a history of serious side effect or allergic response to any AngII antagonist or ERA, including sparsentan or irbesartan, or has a hypersensitivity to any of the excipients in the study medications.
18. The female patient is pregnant, plans to become pregnant during the course of the study, or is breastfeeding.
19. The patient has participated in a study of another investigational product within 28 days prior to screening or plans to participate in such a study during the course of this study.
20. The patient has had prior exposure to sparsentan.
21. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study, including the ability to swallow the study medication capsules whole.

Patients with a medical condition or abnormal clinically significant laboratory screening value not listed above that may interfere with the evaluation of sparsentan efficacy or safety will be reviewed with the Medical Monitor before consideration of the patient for enrollment. Patients who fail screening may be re-screened up to 2 additional times. Patients who are re-screened will undergo all screening procedures and will be assigned a new patient number. Patients will also repeat the informed consent procedure each time they are re-screened.

7.2. Criteria for the Open-Label Extension

7.2.1. Inclusion Criteria for the Open-Label Extension

Based on assessments at the Week 108 visit, a patient will meet all of the following criteria to be eligible for the open-label extension.

1. The patient completed participation in the double-blind period, including the Week 112 visit.
2. The patient or parent/legal guardian (as appropriate) is willing and able to provide signed informed consent for participation in the open-label extension.
3. The patient received blinded study medication throughout the duration of the double-blind period (ie, did not permanently discontinue study medication; see Section 6.4.2).

7.2.2. Exclusion Criteria for the Open-Label Extension

Based on assessments at the Week 108 and Week 112 visits, a patient who meets any of the following criteria will be excluded from the open-label extension.

1. The patient has progressed to ESRD requiring RRT.
2. The patient developed criteria for discontinuation as defined in Section 6.4.2 or Section 6.5 between Week 108 and Week 112.
3. The patient was unable to initiate, or developed contraindications to, treatment with RAAS inhibitors between Week 108 and Week 112.

4. The patient has an eGFR ≤20 mL/min/1.73 m^2 at Week 108. NOTE: If, in the Investigator's opinion, the eGFR value at Week 108 is deemed unlikely to be representative of the patient's true status, the Investigator may repeat the eGFR measurement prior to Week 112 through the central laboratory to assess patient eligibility. Patients with an eGFR <30 mL/min/1.73 m^2 will require close monitoring of eGFR and serum potassium throughout the open-label extension.
5. The female patient is pregnant, plans to become pregnant during the course of the study, or is breastfeeding.

8. TREATMENTS

8.1. Treatments Administered

For the purposes of this protocol, sparsentan is the investigational product, and irbesartan is the active control. When referring to either investigational product (sparsentan) or active control (irbesartan), the term "study medication" is used.

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 75 mg irbesartan tablets over-encapsulated (blinded) with size 00 capsules. The open-label sparsentan doses to be administered in the open-label extension will be dispensed as 200 mg or 400 mg sparsentan tablets.

A dose adjustment will be made for patients whose body weight is ≤50 kg at screening; these patients will receive one-half the otherwise specified doses of either sparsentan or irbesartan (weight will be measured at each visit and the dose increased at the Investigator's discretion if the patient's weight reaches >50 kg).

8.1.1. Treatments Administered During the Double-Blind Period

Allowed doses during the double-blind period, and the number of capsules to be used for those doses, are shown in Table 2. The full daily dose of study medication will preferably be taken prior to the morning meal, with the exception of the day of a study visit. On the day of a study visit, the patient will take their study medication at the clinic. At the visits specified in Section 15.1, study medication will be administered at the clinic after the pre-dose PK blood sample has been obtained.

Table 2: Sparsentan and Active Control Irbesartan Doses Allowed During the Double-Blind Period

Screening Weight	Initial (or Reduced) Dose		Target Dose		One-Half Initial (or Double Reduced) Dose	
	Number of Capsules[a]	Dose (mg)	Number of Capsules[a]	Dose (mg)	Number of Capsules[a]	Dose (mg)
Randomized to Sparsentan						
>50 kg	2	400	4	800	1	200
20 to ≤50 kg	1	200	2	400	N/A	N/A
Randomized to Irbesartan						
>50 kg	2	150	4	300	1	75
20 to ≤50 kg	1	75	2	150	N/A	N/A

[a] Within each weight category, the number of capsules for each dose category (ie, initial [reduced], target, or one-half initial [double reduced]) are the same for patients randomized to sparsentan and irbesartan, to maintain study blind.

Patients will receive the initial dose (ie, one-half the target dose) based on screening body weight for the first 2 weeks. The Investigator will evaluate dose tolerance in a blinded manner prior to

titrating up to the target dose; tolerance is defined as blood pressure measurements >100/60 mmHg (patients ≥18 years of age) or above the 5th percentile for sex and height (patients <18 years of age; Banker 2016) after 2 weeks and no adverse events (AEs) or laboratory findings interfering with the patient's continuation on study medication. Patients who display asymptomatic blood pressure values ≤100/60 mmHg (patients ≥18 years of age) or ≤ 90/50 mmHg or below the 5th percentile for sex and height (whichever is lower in patients <18 years of age), or who present with clinical symptoms of orthostatic hypotension but otherwise tolerate the initial dose will continue after the Week 2 visit without titrating up to the target dose. At the Investigator's discretion and in consultation with the Medical Monitor, patients weighing >50 kg who do not tolerate the initial dose for any reason (including changes in laboratory parameters assessed at Week 2) may continue at one-half the initial dose. Patients weighing ≤50 kg who do not tolerate the initial dose for any reason (including changes in laboratory parameters assessed at Week 2) will be discontinued from the study.

The Week 2 PK sample will be drawn prior to escalating the patient to the target dose.

Dose modification is permitted as presented in Section 8.3.2.

8.1.2. Treatments Administered During Open-Label Extension

Allowed doses during the open-label extension are shown in Table 3.

Table 3: Sparsentan Doses Allowed During the Open-Label Extension

Number of Capsules Taken During Double-Blind Period	Initial Dose in Open-Label Extension	Target Dose (Week 114)[a]
1	200	200
2	200	400
4	400	800

[a] Tolerability to the initial dose will be assessed after 2 weeks. Patients who tolerate the initial dose will titrate to the target dose after 2 weeks, and patients who do not tolerate the initial dose may continue at the initial dose at the Investigator's discretion. Doses may be modified at any time throughout the open-label extension for safety/tolerability reasons at the Investigator's discretion.

Patients who are taking 2 capsules of study medication (ie, 400 mg sparsentan or 150 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at 200 mg sparsentan for the first 2 weeks of the open-label extension. Likewise, patients who are taking 4 capsules of study medication (ie, 800 mg sparsentan or 300 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at 400 mg sparsentan for the first 2 weeks of the open-label extension. Following 2 weeks at one-half the double-blind dose (ie, Week 114), the Investigator will evaluate dose tolerance (as defined in Section 8.1.1) prior to titrating up to the target dose. If the patient is tolerating the dose, the patient will titrate to the target dose at this time. Patients who display asymptomatic blood pressure values ≤100/60 mmHg (patients ≥18 years of age) or ≤90/50 mmHg or are below the 5th percentile for sex and height (whichever is lower in patients <18 years of age) 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 114 visit. Patients who completed the double-blind period on 4 capsules of study medication (ie, 800 mg sparsentan or 300 mg irbesartan) and initiate treatment in the open-label

extension on 400 mg sparsentan but do not tolerate this dose will be able to reduce their dose down to 200 mg sparsentan. These patients will be able to titrate up to 400 mg sparsentan or 800 mg sparsentan if the Investigator feels the patient can tolerate these doses. Only 1 level of titration up will be allowed at each visit.

Patients who are taking 1 capsule of study medication (ie, 200 mg sparsentan or 75 mg irbesartan) at the end of the double-blind period will initiate treatment in the open-label extension at 200 mg sparsentan for the first 2 weeks of the open-label extension. Following 2 weeks at 200 mg sparsentan (ie, Week 114), the Investigator will evaluate dose tolerance (as defined in Section 8.1.1). Patients who are tolerating the initial dose will continue on 200 mg sparsentan at this time, including those who display asymptomatic blood pressure values ≤100/60 mmHg (patients ≥18 years of age) or ≤90/50 mmHg or are below the 5th percentile for sex and height (whichever is lower in patients <18 years of age) or who present with clinical symptoms of orthostatic hypotension but otherwise tolerate the initial dose.

For patients who enter the open-label extension with an eGFR value <30 mL/min/1.73 m^2 (ie, at Week 108), any dose titration at Week 114 will be at the Investigator's discretion based on the results of the Week 114 assessments. Patients who do titrate to a higher dose at Week 114 will be contacted by the Investigator at Week 116 to assess tolerance of the higher dose; at the Investigator's discretion, these patients may also come in for an additional visit at this time.

Dose modification is permitted during the open-label extension as presented in Section 8.3.2.

8.2. Study Medication

8.2.1. Packaging and Labeling

For the double-blind period, blinded size 00 capsules will be provided in country-specific labeled 150-cc wide-mouth, round, white, high-density polyethylene bottles with polypropylene caps. Each 68-count bottle will have a label that will contain, but will not be limited to, the following: Sponsor's name and address, protocol number, packaging job/lot number, name and strength (mg) of study medication (in a blinded manner), medication identification number, patient information, caution statement, directions for use, and storage conditions.

For the open-label extension, sparsentan 200 mg tablets will be provided in country-specific labeled 150-cc wide-mouth, round, white, high-density polyethylene bottles with polypropylene caps. Each 68-count or 30-count bottle will have a label that will contain, but will not be limited to, the following: Sponsor's name and address, protocol number, packaging job/lot number, name and strength (mg) of study medication, medication identification number, patient information, caution statement, directions for use, and storage conditions.

Sparsentan 400 mg tablets may also be used in the open-label extension.

For the open-label extension, at some point during the study, the supply of sparsentan 200 mg and 400 mg tablets will be provided in country-specific labeled 40-cc wide-mouth, round, white, high-density polyethylene bottles with polypropylene caps. Each 30-count bottle will have a label that will contain, but will not be limited to, the following: Sponsor's name and address, protocol number, packaging job/lot number, name and strength (mg) of study medication, medication identification number, patient information, caution statement, directions for use, and storage conditions.

All study medication used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures (SOPs) of the Sponsor or its designee, Good Manufacturing Practice guidelines, International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and applicable national regulations. All labels on the packaging will be in accordance with local regulations. Additional details can be found in the study reference manuals.

8.2.2. Storage

Over-encapsulated sparsentan and irbesartan tablets and open-label sparsentan tablets will be shipped and stored between 20-25°C (68-77°F); excursions between 15-30°C (59-86°F) are allowed. All study medication must be stored at the site in a secure location with limited access. Further guidance will be provided by the Sponsor in a Pharmacy Manual.

8.2.3. Preparation and Administration of the Study Medication

Patients will be instructed to take the appropriate quantity of capsules/tablets for their assigned oral dose at approximately the same time each day, preferably prior to the morning meal, except on the day of a study visit during the double-blind period. On the day of each study visit in the double-blind period, including the Day 1/Randomization visit, the patient will take their study medication in the clinic. At the visits (both during the double-blind period and open-label period) specified in Section 15.1, study medication will be administered after the pre-dose PK and biorepository (for biomarker assessments) blood samples have been obtained.

Patients will be instructed to swallow the capsules/tablets whole, and not to open, break, chew, crush, or split the capsule/tablet prior to taking. Patients will also be instructed to avoid drinking or eating anything that contains grapefruit, Seville oranges (bitter oranges often used as marmalade), or starfruit (carambola) throughout the study.

If an on-site visit by the patient is not feasible due to challenges related to the coronavirus disease 2019 (COVID-19) pandemic or other unexpected circumstances, study medication may be transported directly to a patient via a traceable courier and/or shipping provider to ensure uninterrupted treatment, if necessary. Before doing this, sites will be instructed to acquire verbal agreement from the patient, verification of correct shipping address, and the patient's availability to receive the shipment. Confirmation of receipt and the shipping process will be documented in the site source documentation. The patient's identity and personal information will continue to be kept confidential and will not be shared with the Sponsor. Refer to the Pharmacy Manual for additional details.

Patients will be instructed that if they miss a dose of study medication prior to the morning meal, they should take the missed dose the same day as soon as it is discovered that they missed the dose. If study medication is missed for the entire day, they will be asked to note the date of the missed dose. Patients should not take 2 doses on any one day.

8.3. Dosing Considerations

8.3.1. Dose Selection Rationale

The most relevant data for sparsentan dose selection are provided by the Phase 2 studies in patients with essential hypertension and by the ongoing DUET trial in patients with FSGS.

In the hypertension studies, a clear dose response related to blood pressure was observed in hypertensive patients who achieved blood pressure control after 12 weeks of treatment with sparsentan (200 mg, 400 mg, and 800 mg). In these Phase 2 studies, the 800 mg/day sparsentan dose was significantly more effective in lowering blood pressure and achieving blood pressure control than the maximal dose of the active control (irbesartan 300 mg/day). Treatment with sparsentan up to 800 mg daily for up to 12 weeks was also found to be generally safe and well tolerated in both healthy adults and patients with stage 1 and 2 hypertension.

Preliminary results from the DUET trial are described in more detail in Section 4. In the DUET study, the highest sparsentan dose (800 mg/day) tended to have the most prominent antiproteinuric effect while maintaining an acceptable safety profile.

The PK profiles seen at the end of the double-blind treatment period in DUET have been utilized to examine the effect of sparsentan exposure on the primary efficacy endpoint (ie, the change in UP/C from baseline to the end of the 8-week double-blind treatment phase) and on the change in mean seated blood pressure. These results showed that UP/C decreased with increased sparsentan exposure, while variability in UP/C increased with decreasing sparsentan exposure. In contrast, change in mean seated blood pressure with change in sparsentan exposure appeared minimal. Thus, with less interpatient variability and fewer patients exhibiting a lack of benefit (based on change in UP/C), along with no meaningful difference in blood pressure effect, a dose of 800 mg/day is preferred for the current study.

At the beginning of the blinded treatment period, patients will initially receive one-half of the targeted dose (defined as the initial dose) of both sparsentan and the active control, irbesartan. In addition, patients entering into the open-label extension (following a 4-week interval in which no study medication is taken) will initially receive one-half of the targeted open-label dose. This approach follows common clinical practice to initiate treatment with RAAS inhibitors at doses lower than the maximum dose to prevent adverse reactions and potentially harmful elevations in serum potassium and reductions in GFR.

8.3.2. Dose Modification, Reduction, or Discontinuation

Patients who display asymptomatic blood pressure values ≤100/60 mmHg (patients ≥18 years of age) or ≤90/50 mmHg or are below the 5th percentile for sex and height (whichever is lower in patients <18 years of age), or who present with clinical symptoms of orthostatic hypotension (see Section 9.6) but otherwise tolerate the initial dose will continue after the Week 2 visit (or the Week 114 visit for the open-label extension) without titrating up to the target dose. Patients who do not titrate up to the target dose at Week 2 (or Week 114) may titrate up to that dose at any time, based on evaluation of the Investigator, in consultation with the Medical Monitor as needed. Reductions from the target dose back to the initial dose are permitted at any time after titrating up to the target dose.

Patients weighing >50 kg at screening who do not tolerate the initial dose for any reason may continue at one-half the initial dose at the Investigator's discretion and in consultation with the Medical Monitor, as needed. Patients weighing ≤50 kg at screening who do not tolerate the initial dose for any reason will be discontinued from the study.

In patients with temporary dose interruptions, treatment should be resumed whenever possible (including between visits), and treatment resumption should be considered at every visit following study medication interruption.

Doses may be modified at any time throughout the open-label extension for safety/tolerability reasons at the Investigator's discretion. In addition, after titration to the target dose for the open-label extension, increases above the target doses of 200 mg or 400 mg sparsentan may be considered for patients who, in the Investigator's opinion (and following consultation with the Medical Monitor), would benefit from an increased dose.

8.4. Prior and Concomitant Medications and Therapeutic Procedures

For enrolled patients, concomitant medications and concomitant therapies will be collected from the 3 months prior to screening through the patient's final study visit. In addition, a lifetime history of medications previously used for treatment of FSGS, including systemic corticosteroids or other systemic immunotherapeutic agents, will be collected. Prohibited concomitant medications and other concomitant medication considerations during study participation are outlined in Section 15.2.1.

8.5. Method of Assigning Patients to Treatment (Randomization)

This study will be conducted in a double-blind, active-controlled manner. Enrolled patients will be randomly assigned in a 1:1 ratio to sparsentan or the active control (irbesartan) based on a predefined randomization code (generated by the Sponsor or designee) via the IWRS at the Day 1/Randomization visit. Randomization will include stratification by screening eGFR and UP/C values. The strata will be as follow:

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

8.6. Blinding and Emergency Unblinding

The patient's treatment allocation will remain blinded to all parties involved with the study throughout its course (including during the open-label extension), with the exception of the Data Monitoring Committee (DMC; see Section 13.2), study medication supply, the SAE reporting contact, and the independent statistical team responsible for the interim analysis (see Section 12.11). Double-blind treatment will not be unblinded for initiation of open-label treatment. The randomization schedule for treatment allocation will be securely maintained and will not be disclosed until after database lock for the entire study.

Doses allowed during the study are shown in Table 2 and Table 3, and dose modifications are discussed in Section 8.3.2.

For emergency unblinding only, randomization codes and corresponding treatment assignments will be made available to the Investigator through the IWRS system. When possible, the Medical Monitor should be consulted if a medical emergency necessitates unblinding (ie, in situations where knowledge of the unblinded treatment is necessary for further medical management of the patient). If it is not reasonable to inform the Medical Monitor in advance of unblinding, the Investigator must promptly document the case in the patient's study record. Subsequently, the Investigator should contact the Medical Monitor to explain any premature unblinding of treatment assignment (eg, accidental unblinding or unblinding due to an SAE). Procedures for unblinding a patient's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind to evaluate an emergent safety issue or for regulatory reporting purposes, the Medical Monitor will document within study correspondence the rationale, circumstances, and the person(s) being informed about the unblinding.

Access to randomization codes and corresponding treatment assignments will be made available through the IWRS system to the appropriate, named individual(s) responsible for unblinding suspected, unexpected serious adverse reactions (SUSARs) for reporting to regulatory authorities.

8.7. Assignment of Site and Patient Numbers

Each study site selected to participate in this study will be assigned a site number by the Sponsor or designee. The site number will be used to categorize patient data and to identify the site and/or Investigator within study documents. This number will be recorded in the eCRF.

At screening, each patient will be registered in the IWRS and assigned a unique identification number which will stay the same throughout the study, including the open-label extension. Patients who are re-screened will be assigned a new patient number.

8.8. Treatment Compliance

The Investigator or designee should assess the patient's compliance with study medication dosing at each visit after Day 1. Study medication compliance is defined as the ratio of the number of actual capsules/tablets taken over the number of capsules/tablets that should have been taken during the dosing period multiplied by 100. Patients will be asked to return all unused study medication and used and unused packaging at each visit. If the Investigator has concerns about a patient's dosing compliance, he/she should reiterate the dosing requirements to the patient, and the discussion should be documented in the source documents.

9. STUDY ASSESSMENTS

9.1. Schedule of Study Events

The schedule of study events is located in Section 15.1.

If an on-site visit by the patient is not feasible due to challenges related to the COVID-19 pandemic or other unexpected circumstances, Investigators/appropriately designated study staff will be allowed to perform study visits as remote study visits (eg, conducted via telephone, video conference). These contacts will be allowed at all protocol-required visits and at any time during the conduct of the study. However, Screening (Week 6), Washout (Week 1), and Day 1 (Randomization) visits must be conducted at the study site. The sites will discuss the patient's current health status, AEs, concomitant medications, and medication compliance during the telephone and video contacts. Patients will be instructed to contact the site personnel with any health concerns. Results of these patient contacts will be fully documented in the patient source documents/health records. Patients will return for an on-site visit as soon as the site and the patient determine that it is appropriate and safe.

Given the importance of ongoing laboratory and clinical tests for safety evaluations and to reduce the burden on the patient to come to the clinical site, the Sponsor is contracting with a home care agency to assist with study visits. Dictated by local public health authority requirements and if an Investigator agrees with the patient to utilize the home care services, a signed consent/assent form for home care visits will be obtained at the next site visit. Due to the challenges related to the COVID-19 pandemic or other unexpected circumstances, a verbal consent/assent may be obtained if allowed by local regulations prior to the home care visit and the signed consent/assent form obtained at the next site visit. A licensed nurse will contact the patient or parent/legal guardian via telephone to schedule the home visits in accordance with the Service Request Form provided by the Investigator. In order to conduct the home visits, the home care nurse, the home care agency, and the home care service provider will have access to the patient's personal data including their individually identifiable protected health information, such as the patient's name, address, or telephone number. This type of information will only be used, as necessary, to schedule and conduct the home visits and will not be provided to the Sponsor, the contract research organization, or any other study vendors. Service providers will complete the services ordered by the Investigator, including collection of laboratory samples, and document the service provided in the source documents. Study procedure instructions for the service provider will be provided in the home care visit training manual. Source documentation will be expedited by courier to the study site.

Home care visits may also be utilized for patient retention during the double-blind and the open-label extension periods in any situation that interrupts safety oversight.

Study sites may implement home blood pressure monitoring to allow for further safety assessment. If requested by the Investigator, the Sponsor will supply blood pressure cuffs to the study site to be provided to the patients for monitoring of blood pressure at home. The Investigator will be responsible for instructing the patient about how to monitor and record blood pressure at home.

9.2. Study Fasting Requirements

Beginning on Day 1, all patients must be instructed to arrive at the study site for their next visit in a fasted state (ie, fasting for at least 8 hours prior to the visit). Water is permitted during the fasting period.

9.3. Screening Assessments

Screening Visit assessments for the double-blind period must be performed within 6 weeks prior to Day 1/Randomization; the screening window begins on the day of the patient's first in-clinic study procedure. Each patient will be registered in the IWRS at screening for the double-blind period and assigned a unique identification number which will stay the same throughout the study (including the open-label extension; see Section 8.7). Patients who fail screening for any reason may be re-screened up to 2 additional times. Patients who are re-screened will repeat all screening procedures and will be re-registered in the IWRS and assigned a new patient number. Patients will also repeat the informed consent procedure at each re-screening.

9.4. Medical History and Demographics

A complete medical history will be obtained from the patient at screening, along with concomitant medications/therapies (including all immunosuppressive therapies the patient has taken in their lifetime) at enrollment. Demographic characteristics will include age, race, ethnicity, and sex. Race is being collected to accurately calculate eGFR (a primary endpoint).

9.5. Physical Examination

Physical examinations will be performed according to the schedule of study events in Section 15.1. Physical examinations will include assessment of the following body systems: abdomen; cardiovascular; ear, nose, and throat; eyes; hair and skin; lymph nodes; mental status; musculoskeletal; neurological; peripheral edema; and respiratory. Peripheral edema will be assessed using the semi-quantitative scale in Appendix B (Section 15.2.3).

9.6. Vital Signs

Vital signs, including blood pressure, heart rate, temperature, respiration rate, weight, and height, will be performed according to the schedule of study events in Section 15.1. Height will only be recorded at screening for patients ≥18 years of age. For patients <18 years of age, height will be measured every 6 months after screening until the patient turns 18. Vital signs will be measured prior to phlebotomies for clinical laboratory evaluations.

At all protocol-specified time points, blood pressure will be measured after the patient has been sitting comfortably in a chair for at least 5 minutes prior to obtaining 3 readings, using the same arm for each reading, and the mean of the last 2 readings will be recorded. At the Day 1/Randomization visit, vital signs will be obtained prior to dosing and at 1, 2, 3, and 4 hours after the first dose of study medication.

Measurements of blood pressure intended to detect possible orthostatic hypotension will also be performed at each visit according to US Centers for Disease Control and Prevention guidelines (US CDC 2017). This should be done after the sitting BP measurements have been taken. Briefly, blood pressure will be measured 3 times: 1 time after the patient has been in a supine

position for 5 minutes, 1 time after the patient has been standing for 1 minute, and 1 time after the patient has been standing for 3 minutes. Heart rate will also be collected each time blood pressure is taken. A decrease in systolic blood pressure of ≥20 mmHg or diastolic blood pressure of ≥10 mmHg, or the presence of lightheadedness or dizziness during the test is considered abnormal and may justify a change in study drug dose at the Investigator's discretion.

9.7. Electrocardiogram

Twelve-lead ECGs should be conducted after the patient has been resting in a supine position for at least 5 minutes. Assessments will be performed according to the schedule of study events in Section 15.1. ECGs will be performed prior to phlebotomies for clinical laboratory evaluations.

Copies of the ECGs may be required to be sent to a central repository for third party review and analysis.

9.8. Clinical Laboratory Assessments

For the double-blind period (with the exception of the Screening Visit [Visit 1]), patients will be instructed to attend each study visit in a fasted state (ie, fasting for at least 8 hours prior to the visit; water is permitted during the fasting period), preferably in the morning, and patients should remain fasted until their blood samples have been collected. For visits that require fasting, the Investigator or designee will document that the patient has fasted in the source documents. If the patient reports having eaten within 8 hours, the Investigator or designee will document accordingly in the source documents and eCRF and remind the patient that fasting is required before all study visits.

For the open-label extension, it is strongly recommended that patients come to the study visit in a fasted state, and patients should remain fasted until their blood samples have been collected. However, if fasting for 8 hours prior to the visit is not possible, the visit should occur as scheduled and it should be documented in the eCRF that the patient was not fasting.

Routine blood and urine samples for laboratory assessments will be collected at the visits specified in the schedule of study events in Section 15.1. The Investigator will receive the results of this testing from the central laboratory and must determine the clinical significance of any results that are outside of the normal range. All randomized patients with clinically significant abnormal test results will be followed regularly until the values return to normal ranges or until further follow-up is deemed medically unnecessary.

Full instructions concerning the number and type of laboratory samples to be collected at each visit, the necessary collection supplies, required sample volumes, sample collection methods, sample processing, sample labeling, and sample shipping will be provided by the central laboratory, and will be appropriately assembled for the specific evaluations required at each visit.

Patients will be provided kits for the home collection of quantitative urinalysis samples. They will also receive full instructions regarding the proper collection of those samples. If necessary, due to challenges related to the COVID-19 pandemic or other unexpected circumstances, a patient or parent/legal guardian may transport the first morning void samples to the site via courier service for processing and shipment to the central laboratory. If a patient cannot come to the site, safety labs may be tested at a local laboratory. It is the responsibility of the Investigator to document this process in the patient's source documents.

The eGFR during screening period will be determined using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation for adults (Levey 2009) and the Modified Schwartz formula (Schwartz 2009a; Schwartz 2009b) for children <18 years of age.

The eGFR for each timepoint (visit) during the double-blind period will be determined using the CKD-EPI equation for adults (Levey 2009) and children ≥16 years of age at screening for the double-blind period, and the Modified Schwartz formula for children <16 years of age at screening for the double-blind period (Schwartz 2009a; Schwartz 2009b). The eGFR for each timepoint (visit) during the open-label extension will be determined using the CKD-EPI equation for adults (Levey 2009) and children ≥16 years of age at Week 108, and the Modified Schwartz formula for children <16 years of age at Week 108 (Schwartz 2009a; Schwartz 2009b).

UP/C will be determined using first morning void urine samples. For the double-blind period, UP/C will be calculated as the average of 3 first morning void urine samples collected within 5 days prior to the visit. If 1 of the samples is missing, the average of the other 2 samples will be used. For the open-label extension, UP/C will be based on a single first morning void sample collected within 5 days prior to the visit.

The list of clinical laboratory analytes to be tested is presented in Section 15.2.4.

9.9. Contraception Requirements and Pregnancy Testing

Women of childbearing potential are defined as females who are fertile, following menarche and until becoming postmenopausal unless permanently sterile; permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as amenorrhea for more than 24 consecutive months without an alternative medical cause; women on hormone replacement therapy must have a documented plasma follicle-stimulating hormone level >40 mIU/mL.

Double-blind:

Women of childbearing potential must not become pregnant, and so beginning at menarche must agree to the use of 1 highly reliable method of contraception from 7 days prior to the first dose of study medication until 90 days after the last dose of study medication. Highly reliable contraception methods are defined as those that can achieve a failure rate of <1% per year; examples of these methods include:

- stable oral, implanted, transdermal, or injected contraceptive hormones associated with inhibition of ovulation, or
- an IUD in place for at least 3 months

Open-label Extension:

Women of childbearing potential must not become pregnant, and so beginning at menarche must agree to the use of 1 highly reliable method of contraception from 7 days prior to the first dose of study medication until 30 days after the last dose of study medication. Highly reliable contraception methods are defined as those that can achieve a failure rate of <1% per year; examples of these methods include:

- stable oral, implanted, transdermal, or injected contraceptive hormones associated with inhibition of ovulation, or

- an IUD in place for a duration defined as effective in product labeling.

One additional barrier method must also be used during sexual activity from Day 1/Randomization until 30 days after the last dose of study medication. Examples of barrier methods include:

- diaphragm
- diaphragm with spermicide (preferred)
- male partner's use of male condom
- male partner's use of condom with spermicide (preferred)

Serum pregnancy tests will be performed on WOCBP at screening. Urine pregnancy tests will be performed at all other study visits, as well as monthly between visits (see next paragraph). A positive urine pregnancy test during the study must be confirmed with a serum pregnancy test.

Urine pregnancy tests will be dispensed to WOCBP to conduct pregnancy testing at home between study visits, beginning at the Week 12 visit, and continuing through the open-label extension. Patients will receive enough tests to conduct pregnancy testing once monthly until the next scheduled study visit. Sites will contact patients monthly to confirm that the pregnancy test has been performed and the results are negative. If the urine pregnancy test is positive, study medication will be immediately discontinued, and a serum pregnancy test will be performed to confirm the result. If the serum pregnancy test is positive, the Sponsor will be notified, and the patient will be followed to pregnancy outcome as outlined in Section 10.8. At every visit and monthly, sites will verify that WOCBP are continuing to use highly reliable contraception methods as defined in this protocol.

Prior to menarche, pregnancy testing and contraceptive use is not required. However, the patient and their parent/guardian must be advised that immediately upon menarche, the patient will be required to begin pregnancy testing and initiate contraceptive use. Upon menarche, study medication should be stopped until highly reliable contraception per protocol specifications has been started and is considered to be effective. These requirements cannot be avoided.

9.10. Patient-reported Outcomes

The following PROs will be used to evaluate the effects of sparsentan (as compared to irbesartan) on improvements in health-related QoL:

- Patients ≥18 years of age:
  - Kidney Disease Quality of Life (KDQOL) instrument
  - EuroQol, 5-dimension QoL instrument, version 5L (EQ-5D-5L)
- Patients <18 years of age:
  - Pediatric Quality of Life Inventory (PedsQL) questionnaire. The PedsQL instrument consists of 2 developmentally appropriate modules; the Child Self-Report for ages 8-12 and Child Self-Report for ages 13-18.
  - EuroQol, 5-dimension QoL instrument, version Y (EQ-5D-Y).

If the questionnaires were NOT completed at baseline of the double-blind period (ie, Day 1), the patient should not complete them for the rest of the double-blind period. Patients participating in the open-label extension who did not complete the questionnaires at Day 1 should complete them at Week 112 (as baseline assessments for the open-label extension) and through the Week 268/End of Study visit. If the questionnaires were not completed at Week 112, the patient should not complete them for the rest of the open-label extension. Once a patient enters the open-label extension portion of the study, questionnaires will continue to be collected through the Week 268/End of Study visit.

9.11. Pharmacokinetic Assessments

Samples enabling assessment of sparsentan and irbesartan in plasma will be taken during the double-blind period according to the schedule of study events in Section 15.1. At applicable visits, 1 sample will be taken pre-dose in the clinic.

9.12. Biorepository Samples

With patient consent (or assent as appropriate), serum, plasma, and urine samples will be collected for assessment of biomarkers that could help better understand the mechanisms of disease and treatment. Additional biomarkers may be identified during or after the study and be considered for assessment in the future.

Samples will be collected at visits specified in the schedule of events during both the double-blind- and open-label periods of the study, as specified in Section 15.1.

Patients may withdraw consent for use of biorepository samples at any time, as described in the ICF. Biorepository samples will not be used for genetic testing. Samples will be shipped and stored according to instructions in the Laboratory Manual. The samples will be destroyed 5 years after the clinical study report is finalized.

9.13. Genotyping

Blood samples for genotyping of FSGS and nephrotic syndrome-associated genes, and apolipoprotein1 polymorphisms will be taken at Day1/Randomization. Test results, if available, may be provided to Investigators after study completion. Samples will be used only for this purpose and will be destroyed once the sample analysis is complete.

9.14. Safety Assessments

The safety and tolerability of sparsentan will be evaluated by AEs and by vital signs, physical examinations, clinical laboratory parameters, and 12-lead ECGs.

10. ADVERSE EVENT REPORTING

10.1. Adverse Event (AE)

An AE is any untoward medical occurrence associated with the use of the study medication (active or placebo, biologic, or device) in a clinical investigation patient, but does not necessarily have a causal relationship with the study medication. An AE can, therefore, be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study medication, whether or not considered related to the study medication.

Adverse events may include:

- Symptoms described by the patient
- Clinically significant changes in the patient's physical examination or other signs observed by the Investigator or medical staff
- Test abnormalities (laboratory tests, ECG, X-rays, etc.) that reflect a change from baseline (Day 1 for the double-blind period or Week 112 for the open-label extension) and/or that may result in changes in administration of study medication or in an alteration in medical care (diagnostic or therapeutic)
- Conditions present at baseline (Day 1 for the double-blind period or Week 112 for the open-label extension) that have either worsened or recurred following resolution

The patient will be evaluated for new AEs and the status of existing AEs at each study visit, including screening or washout periods, or at any time contact is made with the patient outside of a scheduled visit. The Investigator may elicit symptoms using an open-ended question, followed by appropriate questions that clarify the patient's verbatim description of AEs or change in concomitant medications.

10.1.1. COVID-19 Adverse Events

If a patient is diagnosed with COVID-19 by a positive test result and any of the SAE criteria (Section 10.2) are met, report the event as an SAE. If a patient has a positive test result for COVID-19 and is asymptomatic, or is symptomatic but not meeting SAE criteria, it should be reported as an AE.

As with all SAE reporting, the SAE should be reported, per protocol, within 24 hours of becoming aware of the event. If the 24-hour reporting deadline is not met, then a note should be added to the SAE Report Form stating the reason the timeline was not adhered to.

10.2. Serious Adverse Event (SAE)

An SAE is an AE that results in any of the following:

- Death: The patient died as the result of the event.
- Is life-threatening: An AE that places the patient, in the view of the Investigator or the Sponsor, at immediate risk of death from the AE as it occurred; ie, does not include an AE that, had it occurred in a more severe form, might have caused death.

- Requires in-patient hospitalization or prolongation of an existing hospitalization: Note: Planned or elective hospital admissions for treatment/procedures for a condition/disease that existed prior to signing the informed consent will be recorded in the patient's screening documents and will not be captured as SAEs. If, however, the admission or procedure occurs other than planned due to a worsening of the condition, the event will be recorded as an SAE.
- Persistent or significant disability/incapacity: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.
- Congenital anomaly/birth defect: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the study medication.
- Other medically important serious events: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Voluntary admission to the hospital (eg, for elective surgery) will not be considered an SAE.

10.3. Adverse Events of Interest (AEOI)

10.3.1. Abnormal Liver Function Test Results

Abnormal liver function tests that meet the below criteria will be considered AEOIs and must be reported to the Sponsor's Medical Monitor within 24 hours of awareness if one of the following conditions are met:

- The abnormality represents a new elevation in ALT or AST >3 times the upper limit of normal (ULN), with or without an elevation of total serum bilirubin >2 times ULN; or
- The abnormality represents a 2-fold increase in ALT or AST above the baseline value for the double-blind period (ie, Day 1) in patients who had elevated values prior to starting study medication, or a 2-fold increase in ALT or AST above the baseline value for the open-label extension (ie, Week 112) in patients who had elevated values prior to starting open-label sparsentan.

In such instances, the following steps should be taken:

1. Temporarily discontinue study medication.
2. Perform repeat testing of ALT, AST, and total bilirubin, and test liver alkaline phosphatase isoenzyme within 48 to 72 hours to confirm the abnormalities.
3. If the abnormality is confirmed by repeat results:
    a. Complete an AEOI Report Form that documents both the liver function test findings and any associated signs or symptoms and report by email to the SAE contact on the Study Contact Information page of this protocol.
    b. Monitor liver enzymes and serum bilirubin 2 or 3 times weekly. The frequency of re-testing can decrease to once weekly or less if the abnormalities stabilize and the patient is asymptomatic.

c. Perform additional testing to evaluate liver function, as appropriate (eg, international normalized ratio [INR], direct bilirubin).

4. Do not resume study medication until monitoring indicates abnormalities have resolved or stabilized.

Patients are not allowed to resume study medication if they have:

- ALT or AST >8 times ULN
- ALT or AST >5 times ULN for more than 2 weeks
- ALT or AST >3 times ULN and total bilirubin >2 times ULN or INR >1.5
- ALT or AST >3 times ULN with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5% eosinophils)

Additionally, patients who demonstrate elevated liver enzymes a second time after re-introduction of the study medication may continue in the clinical trial; however, they will not receive study medication for the remainder of the trial.

Management of such patients should be closely coordinated with the Sponsor's Medical Monitor. In addition to monitoring liver function tests, the Investigator should perform other relevant clinical and laboratory measurements to identify potential causes of the abnormalities (eg, acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis; biliary tract disease or exposure to hepatotoxic medications or environmental chemical agents).

Cases of increased liver function tests will always be considered serious (ie, medically important) if they meet both the following criteria:

- Study medication is suspected to have caused hepatocellular injury, generally shown by a confirmed elevation of 3-fold or greater above ULN in ALT or AST; and
- The ALT or AST elevations are accompanied by a total bilirubin >2 times the ULN or INR >1.5, without initial findings of cholestasis (elevated serum liver alkaline phosphatase isoenzyme)

10.4. Acute Kidney Injury

The Kidney Disease: Improving-Global Outcomes (KDIGO) guidelines for diagnosing AKI are:

- Increased serum creatinine ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or
- Increased serum creatinine ≥1.5 times baseline (that is known or presumed to have occurred within the prior 7 days); or
- Urine volume <0.5 mL/kg/hour for 6 hours or more (KDIGO 2013).

These KDIGO guidelines typically apply to hospital settings, where baseline values within given timeframes (ie, the preceding 48 hours to 7 days) are available. However, in interventional trials such as the current study, values this recent will not likely be available in most cases. In such instances, at the Investigator's discretion, diagnosis of AKI may be based on the most recently available serum creatinine level preceding the event, provided this creatinine measurement was

conducted at or after the last study visit prior to the event (ie, was within 3 months prior to the event).

The Investigator should always take into consideration whether the event is true acute deterioration of kidney function due to an identified etiology, or whether the event represents natural progression of the underlying kidney disease. In cases of AKI where an etiology is identified, the reported AE term should reflect the etiology for the impairment of renal function (eg, AKI due to hypovolemia).

10.5. Serious Renal Conditions

The following conditions should always be reported as SAEs:

- Progression of CKD leading to chronic dialysis: For patients who undergo transition to chronic maintenance dialysis, the verbatim SAE term should be reported as "progression of CKD leading to chronic dialysis." The term "chronic dialysis" should also be captured on the Concomitant Procedure page of the eCRF.
- Medical conditions requiring transient acute dialysis: For patients who undergo transient acute dialysis, the verbatim SAE term should record the condition for which the dialysis is required. For example, if a patient requires acute dialysis due to hyperkalemia, the verbatim SAE term would be reported as "hyperkalemia requiring transient acute dialysis." The "acute dialysis" should also be captured on the Concomitant Procedure page of the eCRF.
- Kidney transplantation: For patients receiving a kidney transplant, the reason for the transplant should be recorded as the verbatim SAE (eg, "progression of CKD requiring kidney transplant"). The term "kidney transplant" should also be captured on the Concomitant Procedure page of the eCRF.

10.6. Evaluation of Adverse Events/Serious Adverse Events

10.6.1. Causality Assessment

Assessment of the relationship between the AE and exposure to the study medication is important for regulatory reporting and assists in the overall analysis of the safety information. For each AE/SAE the Investigator will determine whether, based on available evidence, there is a reasonable possibility that the study medication caused the event. Causal relationship will be classified according to the following criteria:

- Not Related: There is no suspicion of a causal relationship between exposure and the AE.
- Unlikely Related: There is no evidence for a causal relationship between exposure and the AE; however, such a relationship cannot be ruled out.
- Possibly Related: There is some evidence supporting the possibility of a causal relationship between exposure and the AE.
- Related: There is strong evidence that there is a causal relationship between exposure and the AE.

A causality assessment will be provided for each AE/SAE recorded, even if there is only limited information at the time.

Upon receipt of follow-up information, the Investigator may change their assessment of causality and amend the AE/SAE report accordingly.

10.6.2. Severity

Severity indicates the intensity of the event and should not be confused with seriousness (ie, Section 10.2), which is an event outcome applied for the purpose of event classification and regulatory reporting.

The Investigator will assess the severity of all AEs/SAEs as mild, moderate, or severe, based on the following definitions.

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research patient.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.6.3. Outcome

Outcome describes the status of the AE. The Investigator will provide information regarding the patient outcome of each AE. Definitions for possible results of an AE outcome include:

- Recovered/Resolved: The event has improved, or the patient recuperated.
- Recovering/Resolving: The event is improving.
- Not Recovered/Not Resolved: The event has not improved, or the patient has not recuperated.
- Recovered/Resolved with sequelae: The patient recuperated but retained pathological conditions directly resulting from the disease or injury.
- Fatal: Termination of life as a result of an AE. There should be only 1 AE marked with this outcome.
- Unknown: Not known, not observed, not recorded, or refused.

10.6.4. Action Taken Regarding the Study Medication

The action taken with regard to the study medication in response to the AE will be provided at the time the event is reported. Options for action taken include the following:

- Drug Withdrawn: Medication schedule was modified by permanently terminating a prescribed regimen of medication.

- Dose Reduced: Medication schedule was modified by subtraction, either by changing the frequency, strength or amount.
- Dose Increased: Medication schedule was modified by addition; either by changing the frequency, strength or amount.
- Dose Not Changed: Medication schedule was maintained.
- Drug Interrupted: Medication schedule was modified by temporarily terminating a prescribed regimen of medication.
- Unknown: Not known, not observed, not recorded or refused.
- Not Applicable: Determination of a value is not relevant in the current context, for example, if the AE began and ended prior to treatment or after discontinuation of treatment.

10.6.5. Assessment of Expectedness

The expectedness of an SAE will be determined by the Sponsor in accordance with the sparsentan Reference Safety Information (which is contained in the Investigator's Brochure) or the irbesartan product label, as applicable.

10.7. Reporting Adverse Events and Serious Adverse Events

10.7.1. Reporting Adverse Events

Adverse events (including SAEs) will be captured from the time informed consent is signed to the patient's final visit.

For patients who prematurely discontinue study treatment (see Section 8.3.2) but who are not withdrawn from the study, AEs will continue to be recorded until the patient completes the study (see Section 6.3.1 for definition of patient completion).

If a patient initiates RRT after premature discontinuation of study treatment, only AEs and SAEs considered related or possibly related to study treatment need to be recorded.

Adverse events will be recorded using appropriate medical terminology. When recording, it is preferable to provide a diagnosis. In the absence of a diagnosis, each sign and symptom will be captured as a unique AE. Sufficient information should be sought to assist the Investigator both in determining the diagnosis and in making a causality assessment.

Reporting should not be delayed pending receipt of all required information. If information is unavailable at the time of the initial report, the Investigator is expected to follow-up until the required information has been obtained.

10.7.2. Reporting Serious Adverse Events

The necessity and time requirements for reporting of SAEs to the Sponsor or its designee and/or regulatory agencies are as follows:

- All SAEs will be reported by email to the SAE contact on the Study Contact Information page of this protocol or by fax to the number in the Investigator Site File

within 24 hours of the Investigator's first knowledge of the event, regardless of causal relationship.

- For the double-blind portion of the study (Day 1 through Week 112) and the open-label extension portion of the study (Week 112 and after), a completed SAE Report Form containing a detailed written description of the event along with available supporting documents (eg, discharge summary, autopsy report, diagnostic test results, etc.) will be provided by email to the SAE contact on the Study Contact Information page or by fax to the number in the Investigator Site File. For complete instructions, refer to SAE Report Form completion guidelines.
- Additional information that is not available at the time the initial SAE Report Form was completed will be promptly reviewed and provided by email to the SAE contact on the Study Contact Information page or by fax to the number in the Investigator Site File within 48 hours of receipt. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant patient/hospital records, discharge summaries, laboratory/test results or autopsy reports.
- If at any time after the patient has completed participation in the study (as defined in Section 6.3.1 and Section 6.3.2), the Investigator or study staff becomes aware of an SAE that they suspect is related to the study medication (see Section 10.6.1), the event and any known details will be reported promptly by email to the SAE contact on the Study Contact Information page or by fax to the number in the Investigator Site File, following the reporting instructions in this section.

10.7.3. Follow-up of Adverse Events and Serious Adverse Events

All AEs will be followed until resolution, until the condition stabilizes, or until completion of the patient's participation or study termination, whichever occurs first.

Serious AEs will be followed until resolution, until the condition stabilizes, or until the Investigator and the Sponsor agree that follow-up is no longer necessary.

All AEs/SAEs documented at a previous visit/contact where event outcome is designated as not recovered/not resolved, recovering/resolving or unknown will be reviewed by the Investigator at subsequent visits/contacts. SAEs that are ongoing after completion of the last scheduled visit will continue to be followed to determine the final outcome.

Rules for AE/SAE follow-up apply to all patients, to the extent allowed by the patient's consent. The Investigator will ensure that follow-up includes further investigations consistent with appropriate medical management to understand the nature and/or causality of the AE/SAE. The Sponsor, its designee, or regulatory authorities may also request additional information regarding an SAE at any time.

All follow-up information will be promptly reviewed by the Investigator and provided by email to the SAE contact on the Study Contact Information page of this protocol or by fax to the number in the Investigator Site File within the specified timelines. Additional AEs/SAEs may be identified during the review of follow-up information and will be processed in accordance with requirements defined throughout Section 10.

10.7.4. Reporting to Regulatory Authorities, Investigators and Institutional Review Boards/Independent Ethics Committees

The Sponsor will ensure that processes are in place for provision of SAEs and Expedited SAE reports (SUSARs) to Regulatory Authorities, Investigators, and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) as required, within the specified timelines.

The Sponsor will submit SAE and/or SUSAR reports to regulatory authorities and the Investigator as required. In the US, Investigators will report SAEs and SUSARs to their IRB in accordance with applicable SOPs and/or local reporting requirements. In Europe, the Sponsor or its designee will notify the IEC of any SUSARs. In regions/countries other than the US/Europe, reporting of events to IECs or local authorities will be performed by the Investigator/Sponsor or its designee and will be done in accordance with local procedures/regulations.

Investigators will forward copies of the IRB/IEC notification to the Sponsor or its designee, when applicable.

10.8. Pregnancy Reporting

Although not an AE in itself, exposure to study medication during pregnancy must be reported; therefore, all pregnancies in female patients will be recorded on the AE eCRF. If a patient becomes pregnant during the study, study medication will be immediately discontinued, and pregnancy will be documented as the reason for study medication discontinuation. If a urine pregnancy test is positive, study medication will be immediately discontinued until a serum pregnancy test confirms the result.

If the Investigator suspects that a pregnancy was the result of an interaction between the study medication and the contraceptive method, in addition to the pregnancy, the study medication interaction will also be captured as a separate AE.

The Investigator will report any pregnancy associated with exposure to study medication, from the time of first dose until at least 90 days after final study medication administration (including open-label sparsentan). When a site becomes aware that a patient is pregnant, they are to contact the Medical Monitor immediately (within 24 hours of the site becoming aware of the event), complete an initial Pregnancy Notification Form, and send the form by email to the SAE contact on the Study Contact Information page of this protocol or by fax to the number in the Investigator Site File.

Sites will contact patients monthly to confirm that the required pregnancy test has been performed and the results are negative. Female patients will be instructed to notify the Investigator immediately if they discover they are pregnant.

If the Investigator learns of a report of pregnancy after signing informed consent, the Investigator will complete the Pregnancy forms and submit them to the study contact on the Study Contact Information page of this protocol or by fax to the number in the Investigator Site File.

All pregnancies in female patients will be followed to outcome (ie, delivery, elective termination, spontaneous abortion). Infants should be followed for a minimum of 8 weeks. In certain cases, it may be necessary to follow-up on the long-term outcome of an AE using the pregnancy follow-up form. The Investigator will inform the patient that the Sponsor or its designee is required to gather information regarding the course and outcome of the pregnancy after exposure

to the study medication. All study-related visits/contacts involving a known pregnancy will include pregnancy status assessment until pregnancy outcome is known. The Investigator should further obtain follow-up information no later than 1 month after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information (after obtaining consent from the patient). Upon obtaining pregnancy outcome, the Investigator will complete the pregnancy outcome form and submit it to the study contact on the Study Contact Information page of this protocol or by fax to the number in the Investigator Site File.

All information related to the pregnancy and its outcome will be assessed for the occurrence of an AE or SAE. Spontaneous abortions and stillbirths will always be reported as SAEs. Should an AE or SAE occur in the patient and the patient decides to continue in the study after permanently discontinuing study medication, the event will be processed per routine study guidelines. However, if the patient decides not to continue in the study, all AEs and SAEs will be documented and provided directly to the SAE contact on the Study Contact Information page of this protocol. Likewise, if the pregnancy results in the birth of a child and an AE or SAE occurs in the child, the data will be documented and provided directly to the SAE contact.

11. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

11.1. Recording of Data

The study will use eCRFs for data collection. The data will be entered by trained site personnel only. The Investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that the data can be verified against source data.

AEs, medical history, and concomitant medical procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Similarly, prior and concomitant medications and concomitant therapies will be coded using the World Health Organization Drug Dictionary (WHO-DD).

11.2. Data Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its designee may conduct a quality assurance audit.

11.3. Data Management

Data management will be performed by a qualified vendor under their SOPs. The Sponsor will provide oversight.

12. STATISTICAL METHODS AND PLANNED ANALYSES

12.1. General Considerations

The statistical principles applied in the design and planned analyses of this study are consistent with the ICH Guideline E9 (Statistical Principles for Clinical Trials).

All statistical analyses will be performed using Version 9.2 or later of Statistical Analysis Systems (SAS®).

Data summaries will use descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. Where there are missing values, the number missing will be presented without a percentage. All data collected will be included in by patient data listings.

12.2. Determination of Sample Size

Approximately 300 patients will be randomized and allocated 1:1 to receive sparsentan or irbesartan. This sample size takes into consideration enrollment feasibility in this rare disease setting and was evaluated using simulations. A sample size reassessment procedure is planned when the first 50 randomized patients have completed the Week 60 visit. This procedure will be conducted and overseen by the DMC and will be fully described in the Statistical Analysis Plan (SAP).

12.2.1. Surrogate Endpoint: Proportion of Patients Achieving Target UP/C ≤1.5 g/g (170 mg/mmol) and a >40% Reduction in UP/C at Week 36

Based on the results at Week 8 of the sparsentan Phase 2 DUET study and projected to Week 36, it is assumed that sparsentan will result in approximately 50% of patients achieving the response (p_1), and that irbesartan will result in approximately 20% of patients achieving the response (p_2). For the surrogate endpoint, at the time of the interim analysis (which is planned for after 36 weeks following randomization of at least 190 patients [approximately 95 per treatment group]), the power to detect a difference in response proportions ($p_1 - p_2$) between treatment groups is more than 90%, assuming the response proportions are 50% for sparsentan and 20% for irbesartan, with a 2-sided α of 0.05. The minimum treatment difference that could be declared statistically significant is approximately 13% with approximately 190 patients.

12.2.2. Primary Endpoint: Slope of eGFR

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

Using the available data, the modeling exercise yielded an estimated difference in eGFR slopes between UP/C responders and non-responders of approximately 8.4 mL/min/1.73 m^2 per year based on the eGFR chronic slope. With the assumed treatment difference in response proportions of 30%, the projected treatment difference in eGFR slopes is approximately 2.52 mL/min/1.73 m^2 per year. The model also estimated the residual variability (SD) to be approximately 10.80 mL/min/1.73 m^2 per year. Power calculations follow the approach described in Dupont and Plummer (Dupont 1998).

Based on the eGFR total slope, the modeling exercise yielded a projected treatment difference in eGFR slopes of approximately 2.1 mL/min/1.73 m^2 per year, assuming a treatment difference in response proportions of 30% for the surrogate endpoint. With 300 patients (approximately 150 patients per treatment group) and a 2-sided α of 0.05, the study has at least 90% power to differentiate between treatments. This power calculation is based on the Wald statistic using a standard deviation of the eGFR total slope of 5.50 mL/min/1.73 m^2 per year estimated from blinded interim data from the current study.

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

12.3. Analysis Sets

12.3.1. Full Analysis Set

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

12.3.2. Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set will include all patients in the FAS who meet the study eligibility requirements and have no major protocol deviations that affect the validity of the efficacy measurements. Patients will be analyzed according to their randomized treatment. The PP Analysis Set will be used for a sensitivity analysis of the primary efficacy endpoint. The criteria for inclusion in the PP Analysis Set will be finalized prior to study unblinding and detailed in the SAP.

12.3.3. Safety Analysis Set

All patients who are randomized and take at least 1 dose of double-blind study medication will be included in the Safety Analysis Set. Safety analyses will be based on randomized treatment.

12.3.4. Open-Label Extension Full Analysis Set

All patients who received at least 1 dose of open-label sparsentan in the open-label extension will be included in the OLEFAS. All efficacy and safety analyses during the open-label extension will be based on the OLEFAS.

12.4. Demographics and Baseline Characteristics

Demographic data and baseline characteristics for the FAS, PP, and Safety Analysis Sets will be summarized by treatment group using descriptive statistics. Demographic data include sex, age (years), categorical age (<18 years and ≥18 years), race/ethnicity, weight (kg), height (cm), and calculated BMI. Baseline characteristics also include reproductive status (for females only), HbA1c, baseline eGFR, and current use of: steroids, calcineurin inhibitors, mycophenolate mofetil and other immunosuppressive agents, RAAS inhibitors (ie, ACE inhibitors, ARBs, aldosterone blockers, and aliskiren) prior to the 2-week washout, diuretics, additional antihypertensive treatments, and statins.

Likewise, demographic data and baseline characteristics for the OLEFAS will be summarized overall using descriptive statistics.

12.5. Patient Accountability

For the double-blind period, frequencies and percentages will be displayed for the number of patients who: screened, failed screening, enrolled, were randomized, were treated, completed treatment, completed the study, discontinued treatment early, and withdrew from the study. Data will be presented overall and by treatment group. Similarly, the number and percentage of patients in each analysis set (FAS, PP, and Safety) will be summarized.

For the open-label extension, frequencies and percentages will be displayed for the number of patients who: entered the open-label extension, discontinued open-label treatment, and completed the open-label extension. Data will be presented overall using the OLEFAS.

12.6. Study Treatment Usage and Compliance

For the double-blind period, compliance rates during the treatment period will be derived with the following formula:

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

If a patient is lost to follow-up and did not return all unused capsules/tablets, it will be assumed that the patient did not take any capsules/tablets since the last visit date.

Compliance rates will be presented for the Safety Analysis Set using summary statistics and percentage for the frequency distributions (<40%, 40-<80%, 80-<120%, ≥120%) by treatment group and overall. Duration of treatment in weeks, defined as:

> (date of last dose of study medication - date of first dose of study medication + 1)/7

will also be summarized by treatment group for the Safety Analysis Set.

For the open-label extension, compliance will be calculated using an analogous approach as above but using dosage strength instead of number of capsules/tablets. Compliance will be summarized overall for the OLEFAS.

12.7. Efficacy Analysis

All efficacy analyses during the double-blind period will be performed based on the FAS. The primary endpoint analysis will also be conducted using the PP Analysis Set.

The eGFR during the screening period will be determined using the CKD-EPI equation for adults (Levey 2009) and the Modified Schwartz formula (Schwartz 2009a; Schwartz 2009b) for children <18 years of age.

The eGFR for each timepoint (visit) during the double-blind period will be determined using the CKD-EPI equation for adults (Levey 2009) and children ≥16 years of age at screening for the double-blind period, and the Modified Schwartz formula for children <16 years of age at screening for the double-blind period (Schwartz 2009a; Schwartz 2009b). The eGFR for each timepoint (visit) during the open-label extension will be determined using the CKD-EPI equation for adults (Levey 2009) and children ≥16 years of age at Week 108, and the Modified Schwartz formula for children <16 years of age at Week 108 (Schwartz 2009a; Schwartz 2009b).

For the double-blind period, UP/C will be determined using first morning void urine samples and will be calculated as the average of 3 first morning void urine samples collected within 5 days prior to each visit at which UP/C is assessed. For the open-label extension, UP/C will be determined using 1 first morning void urine sample collected within 5 days prior to each visit at which UP/C is assessed. As UP/C is a highly skewed variable, analyses will be performed on log-transformed data; however, for ease of interpretation, results will be presented in the original units.

12.7.1. Primary Efficacy Analysis

12.7.1.1. Primary Efficacy Endpoint: Slope of eGFR at the Final Analysis

For the primary endpoint of slope of eGFR evaluated following the initial acute effect of randomized treatment (ie, from Week 6 to Week 108; chronic slope over 2 years), a mixed-effects model with linear spline (knot or change point at Week 6) will be fitted to the available eGFR data. The response variable is the eGFR measured at post-baseline assessments for each patient during the double-blind period. The model will include fixed effects for treatment, both stratification factors for randomization, baseline eGFR (continuous), time (in weeks) from baseline (continuous), and time (in weeks) from the change point (ie, timek = max (time – 6, 0)), time-by-treatment, and timek-by-treatment interactions. The model will also include a random intercept and random slopes (time and timek) for each patient. The mixed model will utilize restricted maximum likelihood (REML) estimation with Kenward-Roger method used to compute the denominator degrees of freedom for tests of fixed effects. The model will assume an unstructured covariance matrix. If the model does not converge under the unstructured covariance matrix, the autoregressive-1 covariance structure will be used.

The primary efficacy hypothesis of interest is whether eGFR slopes over the blinded treatment period (after adjusting for early hemodynamic effects) are different between the 2 treatment groups, ie:

$$H_0: (\beta_{time*treatment} + \beta_{timek*treatment}) = 0 \text{ versus:}$$

$$H_1: (\beta_{time*treatment} + \beta_{timek*treatment}) \neq 0.$$

This hypothesis will be tested using the mixed model by testing whether the time-by-treatment interaction parameters least-squares (LS) mean estimate is equal to 0.

For the primary endpoint of slope of eGFR evaluated following initiation of randomized treatment (ie, from Day 1 to Week 108; total slope over 2 years), a mixed-effects model will be fitted to the available eGFR data. The response variable is the eGFR measured at post-baseline assessments for each patient during the double-blind period. The model will include fixed effects for treatment, both stratification factors for randomization, baseline eGFR (continuous), time (in weeks) from baseline (continuous), and time-by-treatment interaction. The model will also include a random intercept and a random slope for each patient. The mixed model will utilize restricted maximum likelihood estimation with Kenward-Roger method used to compute the denominator degrees of freedom for tests of fixed effects. The model will assume an unstructured covariance matrix. If the model does not converge under the unstructured covariance matrix, the autoregressive-1 covariance structure will be used.

The primary efficacy hypothesis of interest is whether eGFR slopes over the blinded treatment period (after adjusting for early hemodynamic effects) are different between the 2 treatment groups, ie:

$$H_0: \beta_{time*treatment} = 0 \text{ versus}$$

$$H_1: \beta_{time*treatment} \neq 0.$$

This hypothesis will be tested using the mixed model by testing whether the time-by-treatment interaction parameter LS mean estimate is equal to zero.

Sensitivity analyses are planned to assess the potential impact of major protocol deviations, premature treatment discontinuations, changes in immunosuppressive medications, and the choice of the change point.

12.7.1.2. Surrogate Efficacy Endpoint: Proportion of Patients Achieving a UP/C ≤1.5 g/g (170 mg/mmol) and a >40% Reduction from Baseline at Week 36

Analyses of the proportion of patients achieving a UP/C ≤1.5 g/g (170 mg/mmol) and a > 40% reduction from baseline at each visit (including the surrogate efficacy endpoint at Week 36) will be performed using a generalized linear model with logit link function to model the probability of achieving UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline and to compare sparsentan with irbesartan. The response variable will be a binary indicator of achievement of UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline at each post-baseline visit. Missing response variables will be imputed using the multiple imputation (MI) procedure before analysis. Fixed effects in the model will include baseline UP/C, treatment, time (categorical, in weeks), and treatment-by-time interaction. Analysis will be stratified by randomization stratification variables (4 levels based on Screening eGFR and UP/C). An unstructured covariance matrix within patient will be assumed. If convergence issues arise, the autoregressive-1 covariance structure will be used.

At each post-baseline visit included in the model, the probability of achieving UP/C ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline (risk) for each treatment group, treatment effect (risk difference), standard errors of risk and risk difference, 95% CIs of risks and risk difference, and p-values will be extracted from the model. Relative risk ratios and odds ratios,

along with standard errors and 95% CIs, will also be presented. This analysis will be performed at the interim analysis (ie, surrogate efficacy endpoint).

Sensitivity analyses will be performed using a Cochran-Mantel-Haenszel (CMH) test at Week 36, tipping point analysis, and analysis using observed cases (ie, no MI).

12.7.2. Secondary Efficacy Analyses

The percent change from Week 6 in eGFR at Week 108 will be analyzed at the final analysis using a Mixed Model Repeated Measures (MMRM) described in Section 12.7.3. Specifically, for this endpoint, the statistical significance of the treatment difference at Week 108 will be assessed by testing:

$$H_0: (\beta_{WK108*treatment} - \beta_{WK6*treatment}) = 0 \text{ vs } H_1: (\beta_{WK108*treatment} - \beta_{WK6*treatment}) \neq 0$$

where $\beta_{WK108*treatment}$ is the treatment effect at Week 108 and $\beta_{WK6*treatment}$ is the treatment effect at Week 6. The LS mean estimate from the MMRM model will be used to perform treatment group comparisons.

The percent change from baseline to 4 weeks post-cessation of randomized treatment at Week 112 in eGFR will be analyzed via analysis of covariance (ANCOVA). The dependent variable will be the natural log(eGFR) of analysis visit Week 112, with treatment and baseline eGFR in log scale included as fixed effects. The analysis will be stratified by the randomization strata. The treatment effect will be the contrast between sparsentan and irbesartan LS means. The LS means, treatment effect estimate, 95% CI, and p-value will be presented. Estimates and CIs will be converted to percentage.

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

12.7.3. Additional Efficacy Analyses

For the analysis of eGFR absolute change from baseline by visit, a MMRM model will be fitted to the available eGFR data, incorporating all post-baseline visits at which eGFR was measured for each patient during the double-blind period. The model will include treatment, both stratification factors for randomization, baseline eGFR, visit (categorical), and visit-by-treatment interaction as fixed effects. In addition, patient will be included as a random effect.

The model will utilize REML estimation with Kenward-Roger method used to compute the denominator degrees of freedom for tests of fixed effects. An unstructured within-patient covariance structure will be assumed. If the model does not converge under the unstructured covariance matrix, the autoregressive-1 covariance structure will be used. The LS mean estimate for $\beta_{WKj*treatment}$ (ie, the treatment effect at the visit j of interest) from the MMRM model will be used to perform treatment group comparisons by visit.

For the analysis of eGFR percent change from baseline by visit, a MMRM approach analogous to the model described for the absolute change from baseline will be used, except that the

response variable will be natural log(eGFR) and corresponding baseline value natural log(baseline eGFR). The LS mean estimate for $\beta_{WKj*treatment}$ (ie, the treatment effect at the visit j of interest) from the MMRM model will be used to perform treatment group comparisons by visit. Estimates and CIs will be converted to percentages via the following transformation:

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

For the analysis of eGFR percent change from Week 6 by visit, the estimates from the MMRM model used in the analysis of eGFR relative percent change from baseline by visit described above will be utilized. However, for this analysis, the statistical significance of the treatment difference at visit j (eg, Week 108 for the secondary endpoint) will be assessed by testing the following hypothesis:

$$H_0: (\beta_{WKj*treatment} - \beta_{WK6*treatment}) = 0, \text{ versus:}$$

$$H_1: (\beta_{WKj*treatment} - \beta_{WK6*treatment}) \neq 0,$$

where $\beta_{WKj*treatment}$ is the treatment effect at the visit j of interest and $\beta_{WK6*treatment}$ is the effect estimate at Week 6. The LS mean estimate from the MMRM model will be used to perform treatment group comparisons by visit. Estimates and CIs will be converted to percentages via the following transformation:

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

Change from baseline to all post-baseline visits during the double-blind period in natural log(UP/C) will be analyzed using a MMRM model analogous to the one described for percent change from baseline in eGFR. The LS mean estimate for $\beta_{WKj*treatment}$ (ie, the treatment effect at the visit j of interest) from the MMRM model will be used to perform treatment group comparisons by visit. Estimates and CIs will be converted to percentages via the following transformation:

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

The time to achieve the target reduction in UP/C during the double-blind period will be analyzed using a Cox proportional hazards model, stratified by randomized stratification variables, with a comparison between treatment groups. Patients who discontinue from treatment during the double-blind period prior to achieving the target reduction will be censored at the time of treatment discontinuation. Patients who never meet the target during the double-blind period will be censored at the time of analysis.

The following endpoints will be summarized descriptively for the double-blind period and compared between treatment groups using a CMH test controlling for the randomization stratification variables:

- the proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or death. (ESRD is defined as initiation of RRT or sustained eGFR <15 mL/min/1.73 m^2 during the study);
- the proportion of patients requiring initiation of or intensification in immunosuppressive medication during the study;
- the proportion of patients with reduction in immunosuppressive medication during the study.

Changes from baseline to all post-baseline visits during the double-blind period with respect to QoL scores and blood pressure (systolic and diastolic) values will be analyzed using a MMRM model analogous to the one described for changes from baseline in eGFR.

The number of hospitalization days during the double-blind period will be analyzed descriptively, and the incidence of patient hospitalizations analyzed using Fisher's exact test. Separate analyses will be presented for hospitalizations due to any reason and due to reasons related to the kidney (list to be determined prior to unblinding).

12.8. Safety Analyses

All safety analyses for the double-blind period will be conducted based on the Safety Analysis Set.

Safety data will include AEs, physical examination results, vital signs, ECG results, and clinical laboratory measurements. Observed data will be listed by patient and summarized using descriptive statistics by treatment group for the double-blind period.

12.8.1. Physical Examination and Vital Signs

The number and percentage of patients with physical examination abnormalities at each visit will be summarized and presented for each body system. A listing of abnormalities will also be provided.

The presence and staging of edema will be summarized by frequency counts and percentages based on semi-quantitative (0, 1+, 2+, 3+, 4+) evaluation of physical examination findings. A shift table indicating changes in edema from baseline to each post-baseline visit will be provided.

Vital signs data will be summarized as changes from baseline and will be classified as low, normal, or high based on reference ranges prespecified in the SAP. Vital sign abnormalities for each treatment will be summarized using shift tables.

12.8.2. Clinical Laboratory Tests

Clinical and laboratory parameters will be measured at baseline and post-baseline visits. Each continuous laboratory variable will be summarized as changes from baseline by treatment group.

Laboratory data will also be classified as low, normal, or high relative to the parameter's reference range. Laboratory abnormalities for each treatment will also be summarized using shift tables.

12.8.3. Adverse Events

Adverse events will be mapped to preferred term and body system using MedDRA. Adverse events that begin after the first administration of study medication, or existing AEs that worsen after the first dose of study medication are considered TEAEs. The number and percentage of patients reporting TEAEs will be summarized for each treatment group by MedDRA system organ class and preferred term, then by severity, and by relationship to study medication. Drug-related TEAEs will be considered those to be at least possibly related to study medication based on the Investigator's assessment. The number and percentage of patients reporting serious AEs or AEOIs, and the number and percentage of patients reporting AEs leading to treatment

discontinuation will also be summarized for each treatment group by MedDRA system organ class and preferred term.

12.8.4. Other Safety Assessments

Electrocardiogram results will be presented descriptively by treatment group and visit and will also be listed.

12.9. Other Analyses

12.9.1. Prior Medications, Concomitant Medications, and Concomitant Medical Procedures

Concomitant medications will be coded using the WHO-DD, and concomitant medical procedures will be coded using MedDRA. The incidence of prior medications, concomitant medications, and concomitant medical procedures will be summarized using frequency and percentage for the double-blind period and separately for the open-label extension.

The use of diuretics required for controlling urine volume, edema, and blood pressure will be summarized separately. Specifically, the number of patients requiring an increase, decrease, or no change in the number of diuretics used from baseline will be analyzed. Prior to analysis, a defined list of medications based on coded terms will be developed to identify appropriate diuretics for this analysis. For the double-blind period, this review and identification of diuretics will be conducted prior to unblinding.

All concomitant medications and medical procedures will be listed for individual patients by treatment group; this listing will include the indication for use, start/stop date, dose/units, frequency, and route of administration.

12.9.2. Pharmacokinetics

Trough plasma study medication levels will be summarized using descriptive statistics.

12.10. Other Statistical Issues

12.10.1. Significance Levels

Unless otherwise specified, all tests will be 2-tailed, using a 0.05 level of significance. All CIs will be 2-sided 95% CIs.

12.10.2. Multiple Comparisons/Multiplicity

To control the overall type I error for this study when conducting significance tests for the primary and secondary efficacy endpoints, a hierarchical (gate-keeping) testing procedure will be used.

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

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

1. test the primary efficacy endpoint (eGFR chronic slope over 2 years) at the final analysis at 2-sided $\alpha = 0.05$. If the test is not significant, hypothesis testing stops. If the test is significant,
2. test the 3 secondary endpoints using a Bonferroni-Holm procedure to control for family-wise error rate at 2-sided $\alpha = 0.05$.

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

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

12.10.3. Missing Data

Patients who discontinue will not be replaced. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. However, if missing data are present, they will be handled as follows:

- Continuous endpoints analyzed via mixed-effects models (including the primary efficacy endpoint): Only available data will be analyzed, using the mixed-effects model with random slope and intercepts and the MMRM approaches described throughout Section 12.7.1. These models implicitly adjust for missing data through a variance covariance structure.
- UP/C response: Missing data at specific visits will be imputed using an MI procedure. Sensitivity analyses will also be performed on observed cases (ie, no imputation) and at Week 36 only imputing missing data as non-responders.

12.11. Interim Analysis

An unblinded interim analysis will be performed after 36 weeks following randomization of at least 190 patients (approximately 95 patients per treatment group) to determine whether the surrogate endpoint (the proportion of patients achieving a UP/C $\leq$1.5 g/g [170 mg/mmol] and a >40% reduction from baseline in UP/C) is statistically significant. The statistical evaluation will be performed on the subset of patients in the FAS who are scheduled to have completed their Week 36 visit, using a generalized linear model with logit link function, at a significance level of $\alpha = 0.05$. The interim analysis will be conducted by an independent statistical team, and the study team will remain blinded to the interim data (see Section 8.6). No unblinded individual patient data will be published. Processes to ensure that the blind is appropriately preserved will be detailed and documented prior to unblinding for the interim analysis.

12.12. Analyses for the Open-Label Extension

Analysis of endpoints for the open-label extension will be performed using the methods described in the sections above as appropriate.

Efficacy and safety endpoints for the open-label extension will be summarized using descriptive statistics and presented overall and by original randomized treatment based on the OLEFAS. Analyses using baselines other than Week 112 (eg, prior to first dose of study medication in the double-blind period) may be explored; details will be provided in the SAP.

13. SPECIAL REQUIREMENTS AND PROCEDURES

This protocol was designed and will be conducted, recorded, and reported in compliance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, 1996; ICH Guidelines for Safety Data Management, 1994; the US Code of Federal Regulations (CFR 21 Parts 50, 56, and 312); and the EU Clinical Trials Directive, 2001/20/EC. The protocol meets legal and regulatory requirements according to the country of conduct.

13.1. Institutional and Ethics Review

This protocol and associated ICF, patient information sheet, any information provided to the patient, the Investigator's Brochure, and any proposed advertising material will be submitted to an appropriate IRB/IEC, applicable regulatory authorities, and host institution(s) for written approval (where applicable). These documents will also be submitted to, and approved by, the above parties for all amendments to the original approved documents (where applicable) prior to implementation. Documentation of any applicable approval(s) and the approved ICF and assent form (if applicable) will be received by the Sponsor or its designee prior to enrollment of patients and release of study medication.

13.2. Data Monitoring Committee

During the double-blind period, the study will employ an independent DMC that may include nephrology, internal medicine, statistician(s), and/or pharmacovigilance physicians. The DMC members will not be involved in the study as Investigators or consultants. The DMC will have study conduct oversight as defined by the DMC charter. All members will have considerable experience with clinical study conduct and DMCs. Any candidate found to have a financial, intellectual, or personal conflict of interest, or whose name is listed on the FDA debarment list, will not be offered membership. Conflicts of interest will be assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The DMC will meet approximately biannually at scheduled meetings but may agree to adjust meeting frequency based upon actual and projected data availability. In addition, ad hoc meetings may be convened, as appropriate, to review safety data. Based on review of available data, the DMC will advise the Sponsor on the validity and scientific merit of continuing the study. Adjustments to or stopping of the protocol defined doses may be considered based on DMC evaluation of safety and tolerability data.

Written minutes of both open and closed DMC sessions will be prepared. The minutes of closed sessions will be made available to the appointed Sponsor representatives only after the database is locked and all data are unblinded.

The DMC may request unblinded individual patient data as appropriate. Data reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA-coded AEs, and AEs leading to early withdrawal of study medication. At each meeting, detailed narratives of interval SAEs (including events resulting in death) are reviewed by the DMC in addition to a cumulative list of all SAEs.

All Investigators and responsible IRBs/IECs will be informed of any decisions made by the Sponsor based on recommendations from the DMC relating to patient safety that alter the

conduct of this study. The Investigators will inform patients of such actions, and the protocol and ICF will be revised, as appropriate.

13.3. Changes to the Conduct of the Study or Protocol

Any changes to the study protocol, such as changes in the study design, objectives or endpoints, inclusion and exclusion criteria, and/or procedures (except to eliminate an immediate hazard) will be implemented only after approval by the Sponsor or its designee. All protocol changes will be documented in protocol amendment(s). Protocol amendment(s) (excluding urgent safety amendments) will be signed by the Investigator and approved by the IRB/IEC and regulatory agencies (where required) prior to implementation. Any changes in study conduct that result from a pending amendment will be considered protocol deviations and should be reported to the IRB/IEC. Documentation of IRB/IEC approval will be returned to the Sponsor or its designee.

13.4. Investigator's Responsibilities

The Investigator agrees to:

- Conduct the study in accordance with the protocol and make changes only after receiving written approval from the Sponsor or its designee, except to protect the safety, rights, or welfare of patients.
- Personally conduct or supervise the study.
- Ensure that requirements related to obtaining informed consent and IRB/IEC review and approval comply with ICH E6, CFR 21 Parts 50 and 56, and local laws.
- Report to the Sponsor or its designee any AEs that occur during the study in accordance with ICH E6, CFR 21 Part 312.64 and local laws.
- Read and understand the Investigator's Brochure, including potential risks and side effects of the investigational product (study medication).
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.
- Maintain adequate records in accordance with ICH E6, 21 CFR Part 312.62, and local laws, and have records available for inspection by the Sponsor, FDA, or other authorized agency.
- Ensure that the IRB/IEC complies with requirements of ICH E6, 21 CFR Part 56, and local laws and will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB/IEC and the Sponsor or its designee all changes in research activity and unanticipated problems involving risks to patients or others (including amendments and expedited safety reports).
- Comply with all other requirements regarding obligations of Investigators and all other pertinent requirements listed in ICH E6, 21 CFR Part 312 and local laws.
- Provide progress reports and notifications of SAEs to the IRB/IEC according to local regulations and guidelines.

13.4.1. Patient Informed Consent

Investigators agree to adhere to GCP, which includes ethical principles that have their origin in the Declaration of Helsinki, when developing the patient ICF and Assent Form (where applicable) and when obtaining consent/assent from the patient, parent, or legal guardian. Written informed consent is required prior to enrollment in the study. It is the responsibility of the Investigator to document the consent process within the source documents and obtain consent/assent using an IRB/IEC-approved consent/assent form.

The Investigator will ensure that each patient/parent/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risks, and benefits of the study as well as potential treatment alternatives. Patients/parents/legal guardians will be notified that they are free to discontinue participation in the study at any time and will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed ICF will be provided to the patient. A separate ICF will be obtained for patients who participate in the open-label extension.

If necessary, due to challenges related to the COVID-19 pandemic or other unexpected circumstances, each patient or parent/legal guardian may provide informed consent/assent remotely (ie, via telephone, email, etc.), as dictated by local public health authority requirements. It is the responsibility of the Investigator to document this consent/assent process within the source documents. Each patient or parent/legal guardian must also provide a manually signed copy of the ICF as soon as reasonably possible, either by mail or at the next site visit.

13.4.2. Case Report Forms

Copies of pertinent records in connection with the study, including all source documents, will be made available to the Sponsor or its designee upon request with due precaution toward protecting the privacy of the patient.

Data will be entered by the site onto the eCRFs in the Electronic Data Capture system or downloaded from a device, in the case of PROs. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the eCRFs will be corrected by the site. Changes made to the data after initial entry into the eCRF will be captured via an electronic audit trail and will include the reason for change. Incomplete entries or entries needing additional explanation will be queried to the site for clarification.

13.4.3. Record Retention

The Investigator is responsible for oversight and maintenance of the study records and patient source documents. These records will be readily available for audit or inspection.

The Investigator will retain study records for at least 2 years after the last marketing approval has been granted and there are no pending marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical program. However, these documents should be retained for a longer period, if required by other applicable requirements (eg, applicable local regulatory requirement) or by an agreement with the Sponsor or its designee. The Investigator will contact the Sponsor or its designee prior to any record destruction.

Patient records or other source data will be kept for the maximum period of time mandated by the hospital, institution, or private practice, but not less than 15 years.

If off-site archiving is used, all records will be retrieved and made available for review at the time of an audit or regulatory authority inspection.

13.4.4. Monitoring

A representative of the Sponsor or its designee will visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with the protocol, GCP, and local regulations. Noncompliance with the protocol, GCP, and local regulations will be documented and corrective actions implemented, if necessary. It is the responsibility of the Investigator to be present or available for consultation during monitoring visits. During these routine visits, all data pertaining to a patient's participation in this clinical investigation will be made available to the Study Monitor. The Investigator will comply with applicable privacy and security laws for use and disclosure of information. Study Monitors will perform source document verification according to the clinical monitoring plan to ensure consistency between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP.

If necessary, due to challenges related to the COVID-19 pandemic or other unexpected circumstances, monitoring activities may be performed remotely as dictated by local public health authority requirements. An emergency remote data verification (rDV) process is being implemented in countries where this is allowed, according to local laws and regulations. Alternative ways of monitoring the data, where allowed, will be implemented. It is intended that this process will facilitate adequate ongoing oversight of the conduct of clinical studies in order to identify and eliminate any immediate risk to study patients while on-site monitoring activities cannot be performed due to COVID-19 restrictions or other unexpected circumstances.

At any time prior to, during, or after completion of the clinical study, an audit may be performed on a study site by the Sponsor or its designee, an IRB/IEC, or a representative of a national regulatory agency. Investigators will notify the Sponsor or its designee upon notification of inspection by a representative of a national regulatory agency. A Sponsor or designee representative will be available to assist in the preparation for study site inspections. All pertinent study data will be made available for verification, audit, or inspection purposes.

13.4.5. Study or Site Termination

If the Sponsor or its designee, the Investigator, or regulatory authorities discover any conditions during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation between the Sponsor, its designee, and the Investigator. The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason which may include the following:

- The incidence and severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

- Investigator(s) do(es) not adhere to the protocol or applicable regulatory guidelines in conducting this study.
- Knowingly false information from the study site is submitted to the Sponsor, its designee, or regulatory authorities.
- The site does not randomize any patients into the double-blind period of the study, the site has no patients who participate in the open-label extension, or patients participating in the open-label extension discontinue from the study.

In the event that the study is terminated early, the Sponsor or its designee will provide specific guidance to investigational sites regarding the End of Study procedures.

13.4.6. Study Medication Control

The Investigator will acknowledge that study medication supplies are investigational, and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Sub-Investigator(s) listed on Form FDA 1572 (or regional equivalent). Study medication must be stored in a safe and secure place with limited access and according to Sponsor instructions.

The Investigator must maintain adequate records documenting the receipt and disposition of all study medication supplies. The Sponsor or its designee will supply forms on which to record the date study medication was received and a dispensing record in which to record each patient's use. It is the Investigator's responsibility to ensure that patients return their unused study medication.

13.4.6.1. Receipt of Study Medication

A proof of receipt, which details the quantity and description of the study medication, will accompany the shipment from the Sponsor or its designee to the Investigator. The Investigator will provide the Sponsor or its designee with a signed and dated copy of this receipt (or an electronic equivalent) within 48 hours after receipt of study medication, while retaining the original within the site pharmacy files. The Investigator is responsible for ensuring that the study medication is maintained in a controlled location, with limited access, and under adequate storage conditions.

13.4.6.2. Disposition of Unused Study Medication

All unused study medication will be maintained under adequate storage conditions in a limited access area. If any unused material is remaining upon completion of the study, the material will be returned to the Sponsor or its designee or destroyed only after the following has been completed:

- Accountability has been performed by a representative of the Sponsor or its designee.
- Appropriate study medication return/destruction documentation has been completed by the clinical site pharmacist or their designee.

13.4.6.3. Product Handling and Complaints Reporting

If any issues arise during the course of the study-related to the quality of the study medication, the clinical site pharmacist or pharmacy designee will contact the product handling/complaints group listed on the Study Contact Information page of this protocol.

13.4.7. Insurance

The Sponsor will maintain a liability insurance policy covering all clinical studies under its sponsorship, and that policy will comply with local laws and requirements. The Sponsor or its designee will provide a certificate of insurance to any IRB/IEC, National Competent Authority, or regional health authority that may require such a document. Note that this Sponsor insurance coverage does not relieve the Investigator, the institution, and their collaborators from each maintaining their own liability insurance policy for their clinical research activity.

13.4.8. Data Confidentiality

All patient information obtained during the conduct of the study will be regarded as confidential. Study Monitors, auditors, and inspectors who require access to a patient's medical notes for source document verification will maintain patient confidentiality at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the ICF. No study data will be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the Sponsor. All data shall be secured against unauthorized access.

13.4.9. Clinical Study Report

The Sponsor or its designee is responsible for preparing a clinical study report. Study results will be provided to the Investigator.

14. REFERENCES

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15. APPENDICES

15.1. Appendix A: Schedule(s) of Study Events

Informed consent will be obtained prior to any protocol-required procedure.

Table 4: Double-Blind Period: Schedule of Events from Screening Through Week 12

	Screening All Patients[b]	Washout Patients[c]	Randomization	Blinded Treatment Period				
Week	**Week -6**	**Week -1**	**Day 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**
Visit[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Visit Window		**± 3 days**		**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**
Patient Registration (informed consent/assent)	X							
Inclusion/Exclusion	X		X[d]					
Complete Medical History	X							
Demographics	X							
Physical Examination[e]	X	X	X	X	X	X	X	X
Vital Signs[f]	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments (chemistry, hematology)[g]	X	X	X	X	X	X	X	X
NT-proBNP[h]			X		X			X
Aldosterone, Plasma Renin Activity, Endothelin			X				X	X
Biorepository Samples (blood and urine, if consented)			X					X
HbA1c, Prothrombin Time, INR	X							
HIV, Hepatitis B & C Screening[i]	X							
Serology Screening (autoimmune)[j]	X							
Urine Drug and Alcohol Screen	X							
12-lead Electrocardiogram	X		X			X	X	X
Genotyping Sample			X					

	Screening All Patients[b]	Washout Patients[c]	Randomization	Blinded Treatment Period				
Week	**Week -6**	**Week -1**	**Day 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**
Visit[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Visit Window		**± 3 days**		**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**
Quantitative Urinalysis (3 first morning voids)[k]	X		X			X		X
Routine Urinalysis	X		X			X	X	X
PK Plasma Levels[l]				X		X		X
QoL Questionnaire[m]			X					X
Serum pregnancy test	X							
Urine Pregnancy Test[n]	X		X	X	X	X	X	X
Dispense Urine Pregnancy Tests[m]								X
Medication Dispensing[o]			X	X		X	X	X
Medication Accountability				X		X	X	X
Randomization			X					
Adverse Event Assessment	----------Continuous Monitoring ----------							
Concomitant Medications/Therapies	----------3 Months Prior to Screening Followed by Continuous Monitoring ----------							

ALP = alkaline phosphatase; ALT = alanine transaminase; ARB = angiotensin receptor blocker; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DNA = deoxyribonucleic acid; EDTA = ethylenediaminetetraacetic acid; (e)GFR = (estimated) glomerular filtration rate; EQ-5D = EuroQol, 5-dimension QoL instrument; HbA1c = hemoglobin A1c; HBeAg = hepatitis B "e" antigen; HBsAg = hepatitis B surface antigen; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; INR = international normalized ratio; IWRS = Integrated Web Response System; KDQOL = Kidney Disease Quality of Life instrument; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PedsQL = Pediatrics Quality of Life Inventory; PK = pharmacokinetics; QoL = Quality of life; RAAS = renin-angiotensin-aldosterone-system; UP/C = urine protein/creatinine ratio; VLDL = very low-density lipoprotein; WBC = white blood cell; WOCBP = women of childbearing potential

a If an on-site visit is not feasible due to challenges related to the COVID-19 pandemic or other unexpected circumstances, Investigators/appropriately designated study staff will be allowed to perform study visits as remote study visits (eg, conducted via telephone, video conference). These contacts will be allowed at all protocol-required visits and at any time during the conduct of the study. However, Screening, Washout, and Day 1 visits must be conducted at the study site.

b Screening for all patients is 6 weeks (42 days) prior to Day 1/Randomization; the screening window begins on the day of the patient's first in-clinic study procedure. Under extenuating circumstances the screening period may be extended by a maximum of 2 weeks. Screening may include more than 1 site visit to

accommodate all assessments. Patients who are taking an RAAS inhibitor will be informed that they will be contacted once screening results confirm eligibility so these medications can be discontinued and the washout period can begin (see footnote b). Patients who fail screening may be re-screened up to 2 additional times. Patients who are re-screened will undergo all screening procedures and will be assigned a new patient number. Patients will also repeat the informed consent procedure at this time.

c Patients taking RAAS inhibitors at screening (Visit 1) will complete a 2-week (14-day) washout from these medications prior to Day 1/Randomization. The washout period should begin no later than 4 weeks (28 days) after Visit 1. Appropriate blood pressure control must be achieved during the washout period using antihypertensive agents, with the exception of those that inhibit the RAAS and endothelin systems. Patients undergoing washout will return to the clinic for a follow-up visit to assess safety and blood pressure control approximately 1 week after the start of the washout period.

d A review and confirmation of inclusion and exclusion will be completed at Visit 3. Patients who require RAAS inhibitor washout will remain eligible for the study based on their screening results, unless at Visit 3 they have a positive pregnancy test (positive urine pregnancy tests will be confirmed by a serum test) or have experienced the occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes them to substantial risk and/or does not allow them to adhere to the requirements of the protocol. Patients who turn 18 years of age after the Screening visit do not need to undergo the screening autoimmune panel.

e Physical examinations will include assessment of the following body systems: abdomen; cardiovascular; ear, nose, and throat; eyes; hair and skin; lymph nodes; mental status; musculoskeletal; neurological; peripheral edema; and respiratory. Peripheral edema will be assessed using the semi-quantitative scale shown in Appendix B (Section 15.2.3).

f Vital signs will always be measured prior to having blood drawn for laboratory evaluations. Blood pressure will be measured after patients have been sitting comfortably in a chair for at least 5 minutes prior to obtaining 3 readings using the same arm for each reading; the mean of the last 2 readings will then be recorded. At the Day 1/Randomization visit, vital signs will be obtained prior to dosing and at 1, 2, 3, and 4 hours after the first dose of study medication. Measurements of blood pressure intended to detect possible orthostatic hypotension will also be performed at each visit (see Section 9.6). For these measurements, blood pressure will be measured 3 times: 1 time after the patient has been in a supine position for 5 minutes, 1 time after the patient has been standing for 1 minute, and 1 time after the patient has been standing for 3 minutes. Weight, heart rate, temperature, respiration rate, and height (only at screening for patients ≥18 years of age) will also be recorded. For patients <18 years of age, height will be measured every 6 months after screening until the patient turns 18.

g Includes clinical chemistry (sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, phosphate, glucose, cystatin, uric acid, BUN, creatinine [including calculation of eGFR], bilirubin [total, direct, and indirect], ALT, AST, ALP, gamma glutamyl transferase, creatine kinase, amylase, lipase, and bile acids [bile acids only on Day 1 and Weeks 4 and 12]); lipid panel (total cholesterol, LDL [direct], HDL [direct], triglycerides [direct], and VLDL [indirect]); and hematology (red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, WBC, and WBC differential [neutrophils, eosinophils, basophils, lymphocytes, and monocytes; % and absolute]). All chemistry, hematology, and lipid analytes are shown in Section 15.2.4.

h NT-proBNP in patients ≥18 years of age only.

i Includes HBsAg, HBeAg, hepatitis B DNA (performed if HBsAg and HBeAg are positive), immunoglobulin M hepatitis B core antibody, anti-hepatitis C antibody, hepatitis C ribonucleic acid (performed if anti- hepatitis C antibody is positive), and HIV antibody. Abnormal hepatitis C results will require an additional sample drawn for confirmation.

j For patients ≥18 years of age; however, at the Investigator's discretion these tests may be performed in patients <18 years of age under clinically relevant circumstances. Includes serum antinuclear antibody, anti-double stranded DNA, anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane, kappa and lambda light chains, clinically significant abnormalities identified by serum and urine protein electrophoresis, complement components C3 and C4, and rheumatoid factor.

k Urine total protein, albumin, creatinine, urea, and sodium. The patient will collect the first morning void on 3 mornings within 5 days prior to the visit and bring them to the site visit.

l A blood sample for plasma PK will be drawn within 1 hour prior to study medication administration. In particular, on visit days at which dose adjustments are made, the PK sample will be drawn prior to the dose adjustment.

m Patients ≥18 years of age will complete the KDQOL instrument, and patients <18 years of age will complete the PedsQL QoL questionnaire. All patients will also complete the EQ-5D. If the questionnaires were NOT completed at baseline for the double-blind period (Day 1), the patient should not complete them for the rest of the double-blind period. Patients participating in the open-label extension who did not complete the questionnaires at Day 1 should complete them at Week 112 as baseline assessments for the open-label extension.

n Urine pregnancy tests will be dispensed to WOCBP to conduct pregnancy testing at home between study visits. Site will provide the patient enough tests to conduct pregnancy testing once per month until the next scheduled study visit and will contact these patients monthly to confirm that the pregnancy test has been performed and the results are negative. A positive urine pregnancy test at any visit, including Screening, will be confirmed by a serum test.

o Dispense study medication. Note: at Visit 3, patients will be randomized via IWRS and the first dose will be administered in the clinic. Patients will be instructed to take their study medication at the clinic on the day of office visits. All other days, study medication should be taken at approximately the same time each day, preferably prior to the morning meal. Patients will be instructed to swallow the capsules whole, and not to open, break, chew, crush, or split the capsule prior to taking. Patients will also be instructed to avoid drinking or eating anything that contains grapefruit, Seville oranges (bitter oranges often used as marmalade), or starfruit (carambola) throughout the study. The patient will be instructed to bring all study medication and their original containers to the next clinic visit.

Table 5: Double-Blind Period: Schedule of Events from Week 24 Through End of the Double-Blind Period

	Blinded Treatment Period								End of Blinded Treatment[k]
Week	**Week 24**	**Week 36**	**Week 48**	**Week 60**	**Week 72**	**Week 84**	**Week 96**	**Week 108[j]/ EOT/ET**	**Week 112**
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Visit Window	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**-7 to +14 days**
Physical Examination[a]	X	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments (chemistry, hematology)[c]	X	X	X	X	X	X	X	X	X
Aldosterone, NT-proBNP,[d] Plasma Renin Activity, Endothelin		X		X		X		X	X
Biorepository Samples (blood and urine, if consented)		X		X		X		X	X
12-lead Electrocardiogram	X	X	X	X	X	X	X	X	
Quantitative Urinalysis (3 first morning voids)[e]	X	X	X	X	X	X	X	X	X
Routine Urinalysis	X	X	X	X	X	X	X	X	
PK Plasma Levels[f]	X	X	X						
QoL Questionnaire[g]	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[h]	X	X	X	X	X	X	X	X	X
Dispense Urine Pregnancy Tests[h]	X	X	X	X	X	X	X	X	X[l]
Medication Dispensing for Double-Blind Period	X	X	X	X	X	X	X		
Informed Consent for OLE									X[l]
Medication Dispensing for OLE[i]									X[l]
Medication Accountability	X	X	X	X	X	X	X	X	
Adverse Event Assessment	----------Continuous Monitoring ----------								
Concomitant Medications/Therapies	----------3 Months Prior to Screening Followed by Continuous Monitoring ----------								

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; EOT = end of treatment; EQ-5D = EuroQol, 5-dimension QoL instrument; ET = early termination; HDL = high-density lipoprotein; KDQOL = Kidney Disease Quality of Life instrument; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; OLE = open-label extension; PedsQL = Pediatrics Quality of Life Inventory; PK = pharmacokinetics; QoL = quality of life; RAAS = renin-aldosterone-angiotensin; WBC = white blood cell; WOCBP=women of childbearing potential

[a] Physical examinations will include assessment of the following body systems: abdomen; cardiovascular; ear, nose, and throat; eyes; hair and skin; lymph nodes; mental status; musculoskeletal; neurological; peripheral edema; and respiratory. Peripheral edema will be assessed using the semi-quantitative scale shown in Appendix B (Section 15.2.3).

[b] Vital signs will always be measured prior to having blood drawn for laboratory evaluations. Blood pressure will be measured after patients have been sitting comfortably in a chair for at least 5 minutes prior to obtaining 3 readings using the same arm for each reading; the mean of the last 2 readings will then be recorded. Measurements of blood pressure intended to detect possible orthostatic hypotension will also be performed at each visit (see Section 9.6). For these measurements, blood pressure will be measured 3 times: 1 time after the patient has been in a supine position for 5 minutes, 1 time after the patient has been standing for 1 minute, and 1 time after the patient has been standing for 3 minutes. Weight, heart rate, temperature, and respiration rate will also be recorded. For patients <18 years of age, height will be measured every 6 months.

[c] Includes clinical chemistry (sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, phosphate, glucose, cystatin, uric acid, BUN, creatinine [including calculation of eGFR], bilirubin [total, direct, and indirect], ALT, AST, ALP, gamma glutamyl transferase, creatine kinase, amylase, and lipase); lipid panel (total cholesterol, LDL [direct], HDL [direct], triglycerides [direct], and VLDL [indirect]); hematology (red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, WBC, and WBC differential [neutrophils, eosinophils, basophils, lymphocytes, and monocytes, % and absolute]). All chemistry, hematology, and lipid analytes are shown in Section 15.2.4.

[d] NT-proBNP in patients ≥18 years of age only.

[e] Urine total protein, albumin, creatinine, and sodium. The patient will collect the first morning void on 3 mornings within 5 days prior to the visit and bring them to the site visit.

[f] A blood sample for plasma PK will be drawn within 1 hour prior to study medication administration. In particular, on visit days at which dose adjustments are made, the PK sample will be drawn prior to the dose adjustment.

[g] Patients ≥18 years of age will complete the KDQOL instrument, and patients <18 years of age will complete the PedsQL QoL questionnaire. All patients will also complete the EQ-5D. If the questionnaires were NOT completed at baseline for the double-blind period (Day 1), the patient should not complete them for the rest of the double-blind period. Patients participating in the open-label extension who did not complete the questionnaires at Day 1 should complete them at Week 112 as baseline assessments for the open-label extension.

[h] Urine pregnancy tests will be dispensed to WOCBP to conduct pregnancy testing at home between study visits. Site will provide the patient enough tests to conduct pregnancy testing once per month until the next scheduled study visit and will contact these patients monthly to confirm that the pregnancy test has been performed and the results are negative. A positive urine pregnancy test will be confirmed by a serum test. At every visit and monthly, sites will verify that WOCBP are continuing to use highly reliable contraception methods.

[i] Dispense study medication. Patients will be instructed to take their study medication at the clinic on the day of office visits. All other days, study medication should be taken at approximately the same time each day, preferably prior to the morning meal. Patients will be instructed to swallow the capsules whole, and not to open, break, chew, crush, or split the capsule prior to taking. Patients will also be instructed to avoid drinking or eating anything that contains grapefruit, Seville oranges (bitter oranges often used as marmalade), or starfruit (carambola) throughout the study. The patient will be instructed to bring all study medication and their original containers to the next clinic visit.

[j] Following the 108-week blinded treatment period, treatment with study medication will be discontinued. Assessments at this visit will be used to determine eligibility to continue in the open-label extension. At this time, the Investigator should resume standard-of-care treatment, including treatment with RAAS inhibitors provided there are no contraindications for their use. If the patient was treated with irbesartan at study entry, an alternative ARB at an equivalent dose is required from Week 108 to Week 112. The Investigator may make additional adjustments in antihypertensive medications as necessary to adequately control the patient's blood pressure. Standard-of-care treatment (ACEI and/or ARB therapy) will be discontinued before the Week 112 visit. The final dose of an ACEI and/or ARB should be taken on the day before the Week 112 visit. If an EOT visit is completed, study medication cannot be resumed.

[k] Assessments at this visit will be used as baseline for patients entering the open-label extension. All Week 112 evaluations must be completed prior to the first dose of open-label sparsentan.

[l] Patients entering the open-label extension only. Patients who may be eligible for the OLE should be given the OLE informed consent document at Week 108 if at all possible.

Table 6: Open-Label Extension: Schedule of Events from Week 114 through Week 184

Week	Open-Label Treatment						
	Week 114	Week 124	Week 136	Week 148	Week 160	Week 172	Week 184
Visit[a]	18	19	20	21	22	23	24
Visit Window	± 2 weeks	± 4 weeks	± 4 weeks	± 4 weeks	± 4 weeks	± 4 weeks	± 4 weeks
Physical Examination[b]	X	X	X	X	X	X	X
Vital Signs[c]	X	X	X	X	X	X	X
Clinical Laboratory Assessments (chemistry, hematology)[d]	X[e]	X	X	X	X	X	X
NT-proBNP[f]		X	X	X	X	X	X
Quantitative Urinalysis (1 first morning void)[g]		X	X	X	X	X	X
Routine Urinalysis		X	X	X	X	X	X
QoL Questionnaire[h]		X	X	X	X	X	X
Urine Pregnancy Test[i]		X	X	X	X	X	X
Dispense Urine Pregnancy Tests[i]		X	X	X	X	X	X
Biorepository Samples (blood and urine, if consented)		X	X	X	X	X	X
Medication Dispensing[j]	X	X	X	X	X	X	X
Medication Accountability		X	X	X	X	X	X
Adverse Event Assessment	----------Continuous Monitoring ----------						
Concomitant Medications/Therapies	----------3 Months Prior to Screening Followed by Continuous Monitoring ----------						

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol, 5-dimension QoL instrument; HDL = high-density lipoprotein; KDQOL = Kidney Disease Quality of Life instrument; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PedsQL = Pediatrics Quality of Life Inventory; QoL = quality of life; RAAS = renin-aldosterone-angiotensin; WBC = white blood cell; WOCBP = women of childbearing potential

[a] Informed consent for participation in the open-label period (either at Study Visit Week 108 or Study Visit Week 112) must be obtained prior to any assessment or study medication administration.

[b] Physical examinations will include assessment of the following body systems: abdomen; cardiovascular; ear, nose, and throat; eyes; hair and skin; lymph nodes; mental status; musculoskeletal; neurological; peripheral edema; and respiratory. Peripheral edema will be assessed using the semi-quantitative scale shown in Appendix B (Section 15.2.3).

[c] Vital signs will always be measured prior to having blood drawn for laboratory evaluations. Blood pressure will be measured after patients have been sitting comfortably in a chair for at least 5 minutes prior to obtaining 3 readings using the same arm for each reading; the mean of the last 2 readings will then be recorded. Measurements of blood pressure intended to detect possible orthostatic hypotension will also be performed at each visit (see Section 9.6). For these measurements, blood pressure will be measured 3 times: 1 time after the patient has been in a supine position for 5 minutes, 1 time after the patient has been

standing for 1 minute, and 1 time after the patient has been standing for 3 minutes. Weight, heart rate, temperature, and respiration rate will also be recorded. For patients <18 years of age, height will be measured every 6 months until the patient turns 18.

[d] Except for Week 114 (see footnote e), Includes clinical chemistry (sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, phosphate, glucose, cystatin, uric acid, BUN, creatinine [including calculation of eGFR], bilirubin [total, direct, and indirect], ALT, AST, ALP, gamma glutamyl transferase, creatine kinase, and amylase); lipid panel (total cholesterol, LDL [direct], HDL [direct], and triglycerides [direct]); hematology (red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, WBC and WBC differential [neutrophils, eosinophils, basophils, lymphocytes, and monocytes, % and absolute]). All chemistry, hematology, and lipid analytes are shown in Section 15.2.4.

[e] Includes only serum creatinine and serum potassium.

[f] NT-proBNP in patients ≥18 years of age only.

[g] Urine total protein, creatinine, and microalbumin. The patient will collect the first morning void within 5 days prior to the visit and bring the sample to the site visit.

[h] Patients ≥18 years of age will complete the KDQOL instrument, and patients <18 years of age will complete the PedsQL QoL questionnaire. All patients will also complete the EQ-5D. If the questionnaires were NOT completed at Week 112 (ie, Visit 17), the patient should not complete them for the rest of the open-label extension.

[i] Urine pregnancy tests will be dispensed to WOCBP to conduct pregnancy testing at home between study visits. Site will provide the patient enough tests to conduct pregnancy testing once per month until the next scheduled study visit and will contact these patients monthly to confirm that the pregnancy test has been performed and the results are negative. A positive urine pregnancy test will be confirmed by a serum test. At every visit and monthly, sites will verify that WOCBP are continuing to use highly reliable contraception methods.

[j] Dispense investigational product. Patients will be instructed to take their investigational product at the clinic on the day of office visits. All other days, investigational product should be taken at approximately the same time each day, preferably prior to the morning meal. Patients will be instructed to swallow the tablets whole, and not to open, break, chew, crush, or split the tablet prior to taking. Patients will also be instructed to avoid drinking or eating anything that contains grapefruit, Seville oranges (bitter oranges often used as marmalade), or starfruit (carambola) throughout the study. The patient will be instructed to bring all investigational product and their original containers to the next clinic visit.

Table 7: Open-Label Extension: Schedule of Events from Week 196 through End of Study

Week	Open-Label Treatment						
	Week 196	Week 208	Week 220	Week 232	Week 244	Week 256	Week 268 End of Study
Visit	**25**	**26**	**27**	**28**	**29**	**30**	**31**
Visit Window	**± 4 weeks**	**± 4 weeks**	**± 4 weeks**	**± 4 weeks**	**± 4 weeks**	**± 4 weeks**	**± 4 weeks**
Physical Examination[a]	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X
Clinical Laboratory Assessments (chemistry, hematology)[c]	X	X	X	X	X	X	X
NT-proBNP[d]	X	X	X	X	X	X	X
Quantitative Urinalysis (1 first morning void)[e]	X	X	X	X	X	X	X
Routine Urinalysis	X	X	X	X	X	X	X
QoL Questionnaire[f]	X	X	X	X	X	X	X
Urine Pregnancy Test[g]	X	X	X	X	X	X	X
Dispense Urine Pregnancy Tests[g]	X	X	X	X	X	X	
Biorepository Samples (blood and urine, if consented)	X	X	X	X	X	X	X
Medication Dispensing[h]	X	X	X	X	X	X	
Medication Accountability	X	X	X	X	X	X	X
Adverse Event Assessment	----------Continuous Monitoring ----------						
Concomitant Medications/Therapies	----------3 Months Prior to Screening Followed by Continuous Monitoring ----------						

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol, 5-dimension QoL instrument; HDL = high-density lipoprotein; KDQOL = Kidney Disease Quality of Life instrument; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PedsQL = Pediatrics Quality of Life Inventory; QoL=quality of life; RAAS = renin-aldosterone-angiotensin; WBC = white blood cell; WOCBP=women of childbearing potential

[a] Physical examinations will include assessment of the following body systems: abdomen; cardiovascular; ear, nose, and throat; eyes; hair and skin; lymph nodes; mental status; musculoskeletal; neurological; peripheral edema; and respiratory. Peripheral edema will be assessed using the semi-quantitative scale shown in Appendix B (Section 15.2.3).

[b] Vital signs will always be measured prior to having blood drawn for laboratory evaluations. Blood pressure will be measured after patients have been sitting comfortably in a chair for at least 5 minutes prior to obtaining 3 readings using the same arm for each reading; the mean of the last 2 readings will then be recorded. Measurements of blood pressure intended to detect possible orthostatic hypotension will also be performed at each visit (see Section 9.6). For these measurements, blood pressure will be measured 3 times: 1 time after the patient has been in a supine position for 5 minutes, 1 time after the patient has been standing for 1 minute, and 1 time after the patient has been standing for 3 minutes. Weight, heart rate, temperature, and respiration rate will also be recorded. For patients <18 years of age, height will be measured every 6 months.

[c] Includes clinical chemistry (sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, phosphate, glucose, cystatin, uric acid, BUN, creatinine [including calculation of eGFR], bilirubin [total, direct, and indirect], ALT, AST, ALP, gamma glutamyl transferase, creatine kinase, and amylase); lipid panel (total cholesterol, LDL [direct], HDL [direct], and triglycerides [direct]); hematology (red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, WBC and WBC differential [neutrophils, eosinophils, basophils, lymphocytes, and monocytes, % and absolute]). All chemistry, hematology, and lipid analytes are shown in Section 15.2.4.

[d] NT-proBNP in patients ≥18 years of age only.

[e] Urine total protein, creatinine, and microalbumin. The patient will collect the first morning void within 5 days prior to the visit and bring the sample to the site visit.

[f] Patients ≥18 years of age will complete the KDQOL instrument, and patients <18 years of age will complete the PedsQL QoL questionnaire. All patients will also complete the EQ-5D. If the questionnaires were NOT completed at Week 112 (ie, Visit 17), the patient should not complete them for the rest of the open-label extension.

[g] Urine pregnancy tests will be dispensed to WOCBP to conduct pregnancy testing at home between study visits. Site will provide the patient enough tests to conduct pregnancy testing once per month until the next scheduled study visit and will contact these patients monthly to confirm that the pregnancy test has been performed and the results are negative. A positive urine pregnancy test will be confirmed by a serum test. At every visit and monthly, sites will verify that WOCBP are continuing to use highly reliable contraception methods.

[h] Dispense investigational product. Patients will be instructed to take their investigational product at the clinic on the day of office visits. All other days, investigational product should be taken at approximately the same time each day, preferably prior to the morning meal. Patients will be instructed to swallow the tablets whole, and not to open, break, chew, crush, or split the tablet prior to taking. Patients will also be instructed to avoid drinking or eating anything that contains grapefruit, Seville oranges (bitter oranges often used as marmalade), or starfruit (carambola) throughout the study. The patient will be instructed to bring all investigational product and their original containers to the next clinic visit.

15.2. Appendix B: Supplemental Study Information

15.2.1. Concomitant Medication Considerations

A. While Taking Study Medication (ie, Day 1 Through Week 108)

1. Prohibited Medications While Taking Study Medication (ie, Day 1 Through Week 108)

Inhibitors of RAAS and the endothelin system:

- Patients who are taking any dose of these agents will undergo a 2-week washout period prior to randomization.
- Examples of RAAS inhibitors include (not all inclusive): ACE inhibitors, aldosterone blockers, ARBs, spironolactone, eplerenone, and aliskiren.
- Examples of the endothelin system include: bosentan, macitentan, and ambrisentan.

- Potassium-sparing diuretics (eg, amiloride, triamterene).
- Selected anti-diabetic drugs (thiazolidinediones and sodium-glucose cotransporter-2 inhibitors) should be avoided completely. Other anti-diabetic drugs (eg, metformin, glyburide) should be used in accordance with their guidelines for use in patients with impaired kidney function.
- Digoxin, amiodarone, or any other antiarrhythmic medications that may put the patient at higher risk due to the underlying disease.
- Amphetamines, amphetamine derivative agents, and prescribed weight loss medications including orlistat (eg, Alli®, Xenical®).
- St. John's Wort or other hypericum-derived products.
- Strong CYP3A inhibitors. For a detailed list of these medications, see the P450 Drug Interaction Table at: http://medicine.iupui.edu/clinpharm/ddis/main-table.
  NOTE: The Sponsor recognizes that in some cases concomitant use of these medications may be medically necessary (for example, azole antifungals for severe mycotic infections) and alternatives are either unavailable or inappropriate from a medical and safety perspective. In these cases, limited systemic exposure may be warranted; however, systemic use of strong CYP3A4 inhibitors should be avoided. In addition, a reduction in dose or temporary cessation of study medication and more intensive patient monitoring is recommended.
- The following medications are prohibited <u>for 7 days prior to study visits</u> and should be used with caution at other times during the study. Investigators must review each patient case individually and use clinical judgment.
  - Sulfamethoxazole/trimethoprim (eg, Bactrim™, Septra®), cimetidine, pyrimethamine, cetirizine, cobicistat, probenecid, vandetinib, dolutegravir, ranolazine, dronedarone, ritonavir, and telaprevir cannot be used within at least 7 days prior to any visit at which eGFR is assessed.

  - Fibrates.

See Bullet B for prohibited medications following discontinuation of study medication.

2. Medications to Be Used with Caution While Taking Study Medication (ie, Day 1 Through Week 108)

For any of the medications in this category, the dosage of study medication may need to be adjusted.

- Strong P-gp inhibitors:
  - In a clinical drug-drug interaction study, administration of cyclosporine increased sparsentan overall exposure by approximately 1.7-fold. Adjustment of study medication dosage may be needed during concomitant administration of a strong P-gp inhibitor.
  - The Investigator should actively look for potential AEs such as hypotension, hyperkalemia, or decline in eGFR, during the concomitant use of a strong P-gp inhibitor. See sparsentan dose reduction guidance in (Section 8.3.2).
  - Examples relevant to the study population include (not all inclusive): cyclosporine A, verapamil, quinidine.
- CYP2B6 substrates:
  - In a clinical drug-drug interaction study, administration of sparsentan for several days decreased exposure of bupropion, a CYP2B6 substrate, to approximately 66% to 68%.
  - Dosage adjustment of CYP2B6 substrate medications may be required during study medication treatment.
  - Examples relevant to the study population include (not all inclusive): bupropion, cyclophosphamide, ketamine, meperidine, methadone.
- Statins:
  - As CKD and proteinuria are associated with high cardiovascular risk, the use of statins may be warranted to reduce this risk.
  - Treatment should be initiated at the discretion of the Investigator (after consulting with the Medical Monitor, if needed), based on current guidelines for cardiovascular risk reduction. The lowest possible effective dose should be used.
- Non-steroidal anti-inflammatory drugs (NSAIDs):
  - NSAID use is discouraged during the study. Short-term (<1 week) or intermittent NSAID use is allowed, provided no doses are taken within 48 hours immediately preceding a study visit.
  - Aspirin at doses >325 mg/day is not allowed during the study.
- Steroids, calcineurin inhibitors, mycophenolate mofetil, and azathioprine doses must be stable for at least 30 days prior to screening and during the screening period.

Stable doses are defined as unchanged for the prior 30 days, with the exception of routine minor changes in calcineurin inhibitors. NOTE: It is recommended that systemic corticosteroid and/or immunosuppressive therapy for the treatment of FSGS be avoided for the duration of participation in the study. If, in the Investigator's opinion, systemic corticosteroid and/or immunosuppressive therapy is warranted, such intervention may be provided in addition to study medication at the discretion of the Investigator. Consultation with the Medical Monitor is recommended before starting interventional therapy, when possible. The medications in the categories above should be avoided or used with caution while taking study medication.

- Lithium:
  - Caution is required when combining lithium with inhibitors of RAAS, as it may enhance the actions of ACE inhibitors or ARBs.
- Warfarin:
  - Although no specific drug-drug interaction clinical studies have been performed, a theoretical potential exists for a drug-drug interaction between sparsentan and warfarin via protein binding displacement.
  - INR monitoring is recommended if warfarin is used concomitantly with study medication.

3. Additional Information

Additional medications potentially interacting with sparsentan (CYP3A inhibitors, P-gp inhibitors, CYP 2B6 substrates) can be found at:
http://medicine.iupui.edu/clinpharm/ddis/main-table/

B. Prohibited Medications Following Discontinuation of Study Medication

1. Non-treatment Period from Week 108 Through Week 112

- Irbesartan.
- Selected anti-diabetic drugs (thiazolidinediones and sodium-glucose cotransporter-2 inhibitors) should be avoided completely. Other anti-diabetic drugs (eg, metformin, glyburide) should be used in accordance with their guidelines for use in patients with impaired kidney function.
- Digoxin, amiodarone, or any other antiarrhythmic medications that may put the patient at higher risk due to the underlying disease.
- Amphetamines and amphetamine derivative agents.
- The following medications are prohibited <u>for 7 days prior to study visits</u> and should be used with caution at other times during the study. Investigators must review each patient case individually and use clinical judgment.
  - Sulfamethoxazole/trimethoprim (eg, Bactrim™, Septra®), cimetidine, pyrimethamine, cetirizine, cobicistat, probenecid, vandetinib, dolutegravir, ranolazine, dronedarone, ritonavir, and telaprevir cannot be used within at least 7 days prior to any visit at which eGFR is assessed.

- Fibrates.

C. Patients Who Have Permanently Discontinued Study Medication Prior to Week 108

- Irbesartan.
- The following medications are prohibited for 7 days prior to study visits and should be used with caution at other times during the study. Investigators must review each patient case individually and use clinical judgment.
  - Sulfamethoxazole/trimethoprim (eg, Bactrim™, Septra®), cimetidine, pyrimethamine, cetirizine, cobicistat, probenecid, vandetinib, dolutegravir, ranolazine, dronedarone, ritonavir, and telaprevir cannot be used within at least 7 days prior to any visit at which eGFR is assessed.
  - Fibrates.

D. While Taking Study Medication During the Open-label Extension Period (Starting at Week 112)

1. Prohibited Medications While Taking Study Medication (ie, During the Open-label Extension Period Starting at Week 112)

- Inhibitors of the RAAS
  - Examples include (not all inclusive) the following: ACEIs, aldosterone blockers, ARBs, and aliskiren
- Inhibitors of the endothelin system (bosentan, macitentan, and ambrisentan)
- Potassium-sparing diuretics (eg, amiloride and triamterene)
- Thiazolidinediones should be avoided completely. Other anti-diabetic drugs (eg, metformin and glyburide) should be used in accordance with their guidelines for use in patients with impaired kidney function.
- Digoxin, amiodarone, or any other antiarrhythmic medications that may put the patient at higher risk due to the underlying disease
- St. John's Wort or other hypericum-derived products
- Strong CYP3A inhibitors. For a detailed list of these medications, see the P450 Drug Interaction Table at: http://medicine.iupui.edu/clinpharm/ddis/main-table.
  NOTE: The Sponsor recognizes that, in some cases, concomitant use of these medications may be medically necessary (eg, azole antifungals for severe mycotic infections), and alternatives are either unavailable or inappropriate from a medical and safety perspective. In these cases, limited systemic exposure may be warranted; however, systemic use of strong CYP3A4 inhibitors should be avoided. In addition, a reduction in dose or temporary cessation of study medication and more intensive patient monitoring is recommended.

2. Medications to Be Used with Caution While Taking Study Medication During the Open-label Extension Period (Starting at Week 112)

It is recommended that systemic corticosteroid and/or immunosuppressive therapy for the treatment of FSGS be avoided for the duration of participation in the study. If, in the Investigator's opinion, systemic corticosteroid and/or immunosuppressive therapy is warranted, such intervention may be provided in addition to study medication at the discretion of the Investigator. Consultation with the Medical Monitor is recommended before starting interventional therapy, when possible.

The medications in the categories below should be avoided or used with caution while taking study medication.

- Mineralocorticoid receptor antagonists (spironolactone and eplerenone) could be used at the discretion of the Investigator with appropriate serum potassium monitoring.
- Sodium-glucose cotransporter-2 inhibitors are allowed in the study at the discretion of the Investigator with appropriate monitoring of blood pressure and serum creatinine/eGFR. NOTE: When prescribing these medications, the Investigator should be aware of the fact that this class has not been tested and approved in pediatric patients and that the combination with immunosuppressive drugs is not recommended.
- Strong P-gp inhibitors
  - In a clinical drug-drug interaction study, administration of cyclosporine increased sparsentan overall exposure by approximately 1.7-fold. Adjustment of study medication dosage may be needed during concomitant administration of a strong P-gp inhibitor.
  - The Investigator should actively look for potential AEs, such as hypotension, hyperkalemia, or decline in eGFR during the concomitant use of a strong P-gp inhibitor. See sparsentan dose reduction guidance in Section 8.3.2.
  - Examples relevant to the study population include (not all inclusive) the following: cyclosporine A, verapamil, and quinidine.
- CYP2B6 substrates
  - In a clinical drug-drug interaction study, administration of sparsentan for several days decreased the exposure of bupropion, a CYP2B6 substrate, to approximately 66% to 68%.
  - Effectiveness of drugs that are CYP2B6 substrates may be reduced, and monitoring of the effectiveness of CYP2B6 substrate medications, if possible, is recommended during treatment with study medication.
  - Examples relevant to the study population include (not all inclusive) the following: bupropion, cyclophosphamide, ketamine, meperidine, and methadone.

- NSAIDs
  - NSAID use is discouraged during the study. Short-term (<1 week) or intermittent NSAID, including aspirin use, is allowed. Chronic low-dose aspirin at doses ≤100 mg/day for cardiovascular protection is allowed during the study.
- Lithium
  - Caution is required when combining lithium with inhibitors of RAAS as it may enhance the actions of ACEIs or ARBs.
- Warfarin
  - Although no specific drug-drug interaction clinical studies have been performed, a theoretical potential exists for a drug-drug interaction between sparsentan and warfarin via protein binding displacement.
  - INR monitoring is recommended if warfarin is used concomitantly with study medication.

3. Additional Information

Additional medications potentially interacting with sparsentan (CYP3A inhibitors, P-gp inhibitors, and CYP2B6 substrates) can be found at:
http://medicine.iupui.edu/clinpharm/ddis/main-table/.

15.2.2. Recommendations for Management of Hyperkalemia

Serum potassium checks should be completed at each visit for clinical evidence of electrolyte imbalance. If a patient has a serum potassium value >5.5 mmol/L (5.5 mEq/L) at any time during the study, the following steps are recommended:

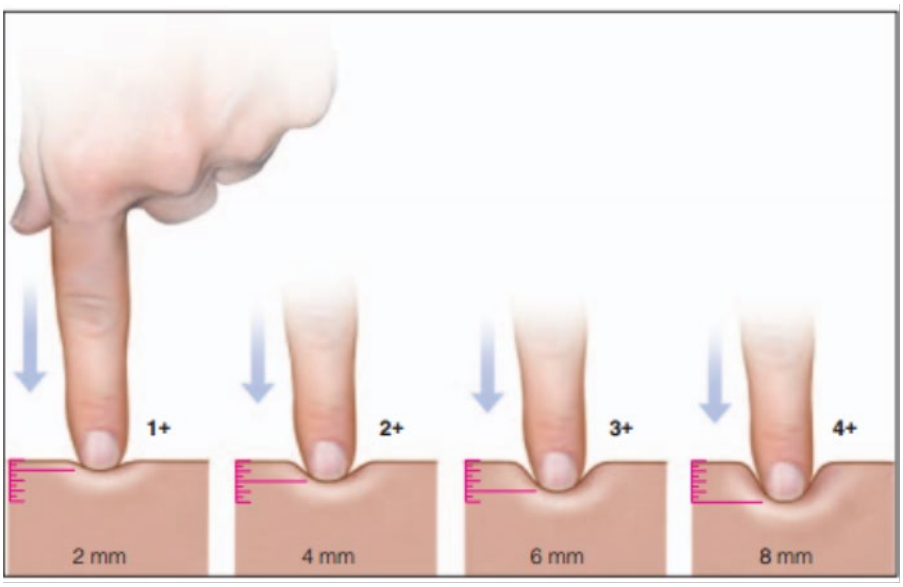
1. If the serum potassium value is ≥6.5 mmol/L, emergency management should be implemented based on the site policies and Investigator's decision.
2. If the serum potassium value is >5.5 and <6.5 mmol/L (6.5 mEq/L), rule out measurement errors or likely reasons for the increase (eg, sample hemolysis, metabolic acidosis, discontinuation of diuretic intake by the patient/lack of compliance, diet transgression).
    a. If the causes listed above are ruled out and the patient is not receiving a diuretic, it is recommended to start a diuretic (if the patient's volume status and blood pressure permit). The choice of a thiazide or a loop diuretic is at the discretion of the Investigator. Assess the patient's tolerability and measure their blood pressure, eGFR, sodium, and potassium within 1 week after starting the diuretic.
    b. If the causes listed above are ruled out and the patient is already receiving a diuretic, increase the dose of the diuretic by 50% (if the patient's volume status and blood pressure permit). Assess the patient's tolerability and measure their blood pressure, eGFR, sodium, and potassium within 1 week after increasing the dose. Consider correction of metabolic acidosis, if relevant.
3. In both scenarios 2a and 2b, adjust the dose of diuretic accordingly after 1 week. If the patient's serum potassium value is still >5.5 mmol/L, reinforce diet counseling/restrictions, rule out other potential causes of hyperkalemia, and consider increasing the diuretic dose. If, after an additional week, the serum potassium value is still >5.5 mmol/L, reduce the dose of study medication by 50%. For long-term prevention of hyperkalemia, consider treatment with patiromer or sodium zirconium cyclosilicate.
4. If hyperkalemia persists or recurs, study medication must be discontinued permanently.

15.2.3. Peripheral Edema Assessment Guidance

Assess for peripheral edema by pressing the area firmly with the thumb or index finger for 5 seconds and then release. Determine depth of indentation to determine severity using the following grades/definitions:

Grade	Definition
1+	2 mm depression, slight pitting, disappears immediately (Trace)
2+	2- to 4-mm somewhat deeper pitting, disappears in 10 – 15 seconds (Mild)
3+	4- to 6-mm noticeably deep pit, lasts 1 to 2 minutes (Moderate)
4+	6- to 8-mm: very deep pit, lasts 2 to 5 minutes (Severe)

Adapted from the Guelph General Hospital Congestive Heart Failure Pathway



15.2.4. Clinical Laboratory Assessments Performed During the Study

Table 8: Clinical Laboratory Assessments During the Double-Blind Period

Clinical Chemistry
Sodium
Potassium
Chloride
Bicarbonate
Total protein
Albumin
Calcium
Phosphate

Screening Tests
Hepatitis B surface antigen
Hepatitis B "e" antigen
Hepatitis B DNA
Immunoglobulin M hepatitis B core antibody
Anti-hepatitis C antibody
Hepatitis C RNA
HIV antibody
HbA1c
Drug/Alcohol screen

Screening Autoimmune Panel
Antinuclear antibody
Anti-neutrophil cytoplasmic antibodies
Anti-glomerular basement membrane antibody
Kappa and lambda light chains (plasma/urine)
Serum/urine PEP
Complement components 3 and 4
Rheumatoid factor
Anti-double stranded DNA

Pregnancy Tests
Urine pregnancy test
Serum pregnancy test (at Screening and for confirmation of positive urine pregnancy test)

Glucose
Cystatin
Uric Acid
Blood urea nitrogen
Creatinine, including eGFR
Total bilirubin
Direct bilirubin
Indirect bilirubin

Hematology
Red blood cells
Hemoglobin
Hematocrit
MCV, MCH, MCHC
Platelets
White blood cells
WBC differential (% and absolute)
- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

Coagulation
Prothrombin time, INR

Other Tests
Aldosterone
Plasma renin activity
NT-proBNP
Endothelin

Lipid Panel
Total cholesterol
LDL (direct)
HDL (direct)
Triglycerides (direct)
VLDL-C (indirect)

ALT
AST
ALP
GGT
Creatine kinase
Amylase
Lipase
Bile acids

Pharmacokinetics
Sparsentan
Irbesartan

Quantitative Urinalysis (first morning void samples)
Total protein
Albumin
Creatinine
Sodium
Urea

Routine Urinalysis
Color
Appearance
pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Blood
Urobilinogen
Leukocyte esterase
Microscopic examination (performed if blood, protein, or leukocyte esterase is abnormal in urine)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; GGT = gamma glutamyl transferase; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; INR = international normalized ratio; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PEP = protein electrophoresis; RNA = ribonucleic acid; VLDL-C = very low-density lipoprotein cholesterol; WBC = white blood cells

Table 9: Clinical Laboratory Assessments During the Open-Label Extension

Clinical Chemistry

Sodium
Potassium
Chloride
Bicarbonate
Total protein
Albumin
Calcium
Phosphate
Glucose
Cystatin
Uric acid
Blood urea nitrogen
Creatinine, including eGFR
Total bilirubin
Direct bilirubin
Indirect bilirubin
ALT
AST
ALP
GGT
Creatine kinase
Amylase

Pregnancy Tests

Urine pregnancy test
Serum pregnancy test (at Screening and for confirmation of positive urine pregnancy test)

Other Tests

NT-proBNP

Lipid Panel

Total cholesterol
LDL (direct)
HDL (direct)
Triglycerides (direct)

Hematology

Red blood cells
Hemoglobin
Hematocrit
MCV, MCH, MCHC
Platelets
White blood cells
WBC differential (% and absolute)

- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

Quantitative Urinalysis (first morning void samples)

Total protein
Creatinine
Microalbumin
Microalbumin/Creatinine Ratio
Urine Protein/Creatinine Ratio

Routine Urinalysis

Color
Appearance
pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Blood
Urobilinogen
Leukocyte esterase
Microscopic examination (performed if blood, protein, or leukocyte esterase is abnormal in urine)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; GGT = gamma glutamyl transferase; HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; WBC = white blood cells

15.3. Appendix C: Germany-Specific Requirements

This appendix provides language for Germany-specific regulatory requirements and other procedures to follow in the execution of the global study.

The summary of changes outlined in the table below:

- provides Germany-specific protocol language (in **bold** text) that replaces the corresponding language in the body of the global protocol and applies only for Germany.
- specifies requirements for sites and patients participating in Germany.

Table 10: Germany Summary of Changes

Protocol Section	Germany Text (revised text in bold)
Synopsis Supportive Measures for Coronavirus Disease 2019/Unexpected Circumstances	**Supportive Measures for Coronavirus Disease 2019** **Study sites will be permitted to send study medication to patients' homes via a traceable courier and/or shipping provider to ensure continuing medication. Prior to shipping, study sites will be instructed to acquire and document verbal consent from the patient as well as verify the patient's correct shipping address and their availability to receive the shipment. Additionally, a second physically signed consent from the patient to send study medication to the patient's home will also be obtained at the next site visit. The study site will call the patient to confirm receipt of the study medication. The patient will be instructed to return all unused study medication at their next site visit.** Details are included in the protocol.
Section 8.2.3 Preparation and Administration of the Study Medication Paragraph 3	**Shipment of Study Medication from Study Sites Directly to Patients** **Study sites will be permitted to send** study medication to patients' homes via a traceable courier and/or shipping provider to ensure **continuing medication**. **Prior to shipping, study** sites will be instructed to acquire **and document** verbal **consent** from the patient **as well as verify the patient's** correct shipping address and **their** availability to receive the shipment. **Additionally, a second physically signed consent from the patient to send study medication to the patient's home will also be obtained at the next site visit. Study medication will be shipped and stored between 20° and 25°C (68° to 77°F); excursions between 15°and 30°C (59° to 86°F) are allowed. Further guidance is provided in the Pharmacy Manual. The study site will call the patient to confirm receipt of the study medication.** Confirmation of receipt will be **obtained over the phone by the study site and** documented in the source documentation. **The patient will also sign the Study Patient Acknowledgement of Receipt of Study Drug form.** The patient's identity and personal information will continue to be kept confidential and will not be shared with the Sponsor. **The patient will be instructed to return all unused study medication at their next site visit.**
Section 9.1 Schedule of Study Events	**The Sponsor is taking all necessary measures to ensure data integrity while implementing the home care visit by requiring that a licensed and qualified home care nurse (Service Provider) is trained to perform specific study assessments per GCP and Good Documentation Practice standards. Study procedure instructions for the Service Provider will be provided in the home care visit training manual, which has been developed by the Sponsor in collaboration with the home care agency to follow protocol-mandated study procedures.**

Protocol Section	Germany Text (revised text in bold)
	Given the importance of ongoing laboratory and clinical tests for safety evaluations, and to reduce the risk of COVID-19 infection during the pandemic, the Sponsor is contracting with a home care agency to assist with study visits as permitted during the COVID-19 pandemic. **The Principal Investigator (PI) will confirm that the Service Provider assigned to perform study procedures during the home care visit is qualified and has the appropriate education, training, and experience to perform the specified tasks. This will be documented by a current signed and dated curriculum vitae or resume and license and/or certificates of qualification, documentation of completion of study-specific training, and documentation of compliance with study-specific requirements, GCP/ICH guidelines, Patient Privacy Laws, General Data Protection Regulation, Health Insurance Portability and Accountability Act, International Air Transport Association Dangerous Goods local and national regulations, and the home care agency's SOPs relating to services, as applicable.** **The PI may request to speak to or meet with the Service Provider prior to the home care visit and request to review and approve the adequate qualification of the Service Provider as well as review their practical performance according to local legal requirements. The PI will be responsible for ensuring that the Service Provider is properly trained on study-related procedures and the protocol and training will be documented in the site-specific training log, but the Service Provider will be trained on study-related procedures and the protocol by the Country Coordinator from the Training Manual.** **The PI and the patient will assess if it is necessary to implement the home care visit in the event the patient is unable to visit the site for the conduct of the study visit due to the COVID-19 pandemic. The PI may decline implementation of the home care visit at their site at any time. If the PI agrees with the patient to utilize the home care services, the PI will send the study-specific Service Request Form (Physician Orders) to the home care agency to initiate the request. The PI will delegate study-specific procedures to the Service Provider and document the delegated procedures in the site-specific delegation log for the study.** **In order to conduct the home care visit, the Country Coordinator (home care agent responsible for managing and coordinating ambulant care services within their country), and the Service Provider (responsible for conducting the study-specific services ordered by the PI and in compliance with the protocol and the Ambulant Care Training Manual) will have access to the patient's personal data including their individually identifiable protected health information, such as the patient's name, address, or phone number. This type of information will only be used by**

Protocol Section	Germany Text (revised text in bold)
	the Service Provider or home care Country Coordinator as necessary to contact the patient to schedule their home care visit and will not be provided to the Sponsor. The Service Provider will communicate the date and time of the home care visit to the study site. The site must be available during the conduct of the home care visit; furthermore, the site will provide the Service Provider with an emergency phone number where the PI can be reached during the home care visit should there be the need to speak to the PI. **Home care visits may be implemented at Week 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, and 108 during the double-blind treatment period of the study. Home care visits are not allowed to be utilized for screening, Day 1 (randomization), and Week 112 (end of double-blind treatment visit/first open-label extension visit). Study procedures conducted at these visits may not be delegated to the Service Provider and are required to be conducted at the site.** **Home care visits may be implemented at Week 114, 124, 136, 148, 160, 172, 184, 196, 208, 220, 232, 244, 256, and 268 during the open-label extension treatment period of the study.** **The PI may delegate and supervise the following study procedures to the Service Provider to be conducted during the home care visit:** **• Measure vital signs (blood pressure, heart rate, respiratory rate, body weight, and body temperature)** **• Measure orthostatic vitals (heart rate and blood pressure), as applicable. If any signs of orthostatic hypotension are observed, the Service Provider must promptly communicate this to the Investigator at site by telephone call during the visit** **• Collect biologic specimens (including processing, packaging, and shipment to the designated laboratory) to include the following: hematology, chemistry, chemistry with N-terminal prohormone of brain natriuretic peptide; serum pregnancy test; aldosterone, plasma renin; endothelin; pre-dose PK; quantitative urinalysis; urinalysis; urine pregnancy test; and collection of biomarker samples (serum, plasma, and urine samples).** **• Perform body system assessment per local regulations (only peripheral assessment allowed in European Union countries)** **• Perform 12-lead ECG, as applicable**

Protocol Section	Germany Text (revised text in bold)
	• Confirm receipt of site package (study medication, home pregnancy kit, and urine collection cups) **• Assess changes in signs and/or symptoms and promptly communicate these changes to the Investigator site by telephone call during the visit** **• Assess changes in concomitant medications** **• Perform documentation, communication, and records retention** **The Service Provider will complete the services ordered by the PI, including collection of laboratory samples, and document the services provided during the home care visit in the Ambulant Care Source Documents (source documents). Following the home care visit, source documents will be reviewed for quality and completeness by the home care Country Coordinator. The electronic copy of the source documents will be sent to the site within 48 hours of the visit, followed by the original hard copy sent to the study site via courier, and the study site will review the source documents. The PI will contact the patient over the phone to assess the patient's health and safety. The home care agency, Country Coordinator, or Service Provider will not share patient data with the Sponsor. Study data will be source verified by the Study Monitor as per study monitoring plan, and any missed study procedures will be documented as a protocol deviation and reported accordingly. Although the home care services are delegated to the Service Provider, the PI holds responsibility for ensuring the quality of the data and the well-being of the patient for the procedures performed as per legal requirements.** **The urgent safety measures will be temporary and revert to on-site procedures as soon as the situation allows. However, these urgent safety measures may be implemented again if the need arises (ie, an additional wave of COVID-19) as dictated by local public health authority requirements. The Sponsor acknowledges that German regulations do not permit the use of the urgent safety measures outside of the COVID-19 pandemic. Therefore, these urgent safety measures will only be in effect during the COVID-19 pandemic.** **Phone and Video Contact with Patients** Investigators **may interface with patients via telephone or live** video **conferencing using a secured system chosen by the study site. Telephone or video conferences will not be recorded or screenshot.** These contacts will be allowed at all protocol-required visits and at any time during the conduct of the study. The sites will discuss the patient's current health status, AEs, concomitant medications, and medication compliance during the phone and video contacts. Patients

Protocol Section	Germany Text (revised text in bold)
	will be instructed to contact the site personnel with any health concerns. Results of these patient contacts will be fully documented in the patient source documents. Patients will return for an on-site visit as soon as the **PI** and patient determine it is appropriate and safe. **Subject to prior agreement by the study sites/Investigators, these urgent safety measures will only be implemented in cases where on-site patient visits are not possible due to COVID-19-related challenges, without awaiting approval of this submission by German Regulatory Authorities and Ethics Committees.**
Section 9.6 Vital Signs Paragraph 2	**The Sponsor may implement home blood pressure monitoring to allow for further safety assessment. If requested by the PI, the Sponsor will supply blood pressure cuffs to the study site to be provided to the patients for monitoring of blood pressure at home. The PI will be responsible for providing the patient with instructions on how to monitor and record blood pressure at home.** At all protocol-specified time points, blood pressure will be measured after the patient has been sitting comfortably in a chair for at least 5 minutes prior to obtaining 3 readings, using the same arm for each reading, and the mean of the last 2 readings will be recorded. At the Day 1/Randomization visit, vital signs will be obtained prior to dosing and at 1, 2, 3, and 4 hours after the first dose of study medication.
Section 9.8 Clinical Laboratory Assessments Paragraph 5	Patients will be provided kits for the home collection of quantitative urinalysis samples. They will also receive full instructions regarding the proper collection of those samples. If necessary, due to challenges related to the COVID-19 pandemic, a patient or parent/legal guardian may transport the first morning void samples to the site via courier service for processing and shipment to the central laboratory. If a patient cannot come to the site, safety labs may be tested at a local laboratory. It is the responsibility of the Investigator to document this process in the patient's source documents.
Section 9.8 Clinical Laboratory Assessments Paragraph 9	If the patient is unable to visit the site, the patient may use a courier to transport the first 3 morning urine void samples to the site. The PI will be responsible for providing the patient with instructions and making the transport arrangements with the courier. The list of clinical laboratory analytes to be tested is presented in Section 15.2.4.

Protocol Section	Germany Text (revised text in bold)
Section 13.4.1 Patient Informed Consent Paragraph 3	**The following should apply to Germany regarding patient informed consent for pandemic-related measures. Pandemic-related measures will be explained to the patient in the supplementary patient information and ICFs. If due to current COVID-19 circumstances the patient is not scheduled to come to the site for a visit soon, the study site staff will provide them the supplementary patient information and ICF via post mail and will discuss the details of these documents with the patient via phone or video conference. Verbal consent will be taken over the phone and recorded within the patient's medical records. In addition, the patient's written consent will be obtained remotely. If the patient agrees with this approach, the Investigator will ask the patient to send their signed and dated ICF by courier service (eg, DHL) or by registered mail (so that a signature is available as proof of delivery) to the study site. The pandemic-related procedures described below are carried out only after written consent has been obtained and if the signed and dated supplementary patient information and ICF have been received by the study site.**
Section 13.4.4 Monitoring Paragraph 2	If necessary, due to challenges related to the COVID-19 pandemic, monitoring activities may be performed remotely as dictated by local public health authority requirements. An emergency remote data verification (rDV) process is being implemented in countries where this is allowed, according to local laws and regulations. **Please note that the rDV process will not be utilized in Germany.** Alternative ways of monitoring the data, where allowed, will be implemented. It is intended that this process will facilitate adequate ongoing oversight of the conduct of clinical studies in order to identify and eliminate any immediate risk to study patients while on-site monitoring activities cannot be performed due to COVID-19 restrictions.
Table 4 Double-Blind Period: Schedule of Events from Screening Through Week 12 Footnote a	If an on-site visit is not feasible due to challenges related to the COVID-19 pandemic, Investigators/appropriately designated study staff will be allowed to perform study visits as remote study visits (eg, conducted via telephone **or** video conference). These contacts will be allowed at all protocol-required visits and at any time during the conduct of the study. However, Screening, Washout, and Day 1 visits must be conducted at the study site.

15.4. Appendix D: Protocol History

Protocol Version	Date Issued	Rationale for Update
Amendment 9	18 January 2024	Removed the extension of the open-label extension period past Week 268 that was added in Protocol Amendment 8, as a result of a business decision to not extend the study.
Amendment 8	31 March 2023	Added Table 8 to the Schedule of Activities to extend the open-label extension by 2 years, with visits every 6 months. Revised Section 8.2.1 to add that 30-count bottles are also available for the open-label extension. Revised Section 10.3.2 to change COVID SAE reporting procedure to follow normal SAE reporting procedure. Added Section 15.3 to allow for global consolidation of protocol. Minor edits were done for consistency as applicable
Amendment 7-DE	08 February 2022	Updated Study Contact Information as per protocol administration letter dated 27 Jan 2021. Removed Global Safety officer contact details as per protocol administration letter dated 27 Jan 2021 Revised Section 8.2.1 to add information regarding new presentation of 30-count bottles. Updated Section 8.2.3, Section 9.1, Section 9.6, Section 9.8, and Section 13.4.1 as per Germany Addendum. Removed “or other unexpected circumstances” from Synopsis, Section 8.2.3, Section 9.1, Section 9.8, Section 13.4.1, Section 13.4.4, and Section 15.1 due to restrictions in Germany on the implementation of these special measures for any reason other than the COVID-19 pandemic and any reference to other times when they could be used are being removed. Updated Section 10.7.2 to include information for recording of SAEs during the open-label extension. Due to recent positive results of large clinical studies with sodium-glucose cotransporter 2 inhibitors (SGLT2i) in non-diabetic patients with proteinuric kidney diseases, these drugs are being used with increasing frequency. It has been concluded that there is no contraindication to the use of SGLT2i and sparsentan and with this amendment, SGLT2i use is being allowed in the open-label

Protocol Version	Date Issued	Rationale for Update
		portion of the study. Revised Section 15.2.1 to include information regarding SGLT2i. Minor edits were done for consistency as applicable.
Amendment 7	02 November 2021	Updated Study Contact Information as per protocol administration letter dated 27 Jan 2021. Removed Global Safety officer contact details as per protocol administration letter dated 27 Jan 2021. Revised Section 8.2.1 to add information regarding new presentation of 30-count bottles. Updated Section 10.7.2 to include information for recording of SAEs during open-label extension. Due to recent positive results of large clinical studies with sodium-glucose cotransporter 2 inhibitors (SGLT2i) in non-diabetic patients with proteinuric kidney diseases, these drugs are being used with increasing frequency. It has been concluded that there is no contraindication to the use of SGLT2i and sparsentan and with this amendment, SGLT2i use is being allowed in the open-label portion of the study. Revised Section 15.2.1 to include information regarding SGLT2i. Minor edits were done for consistency as applicable.
Amendment 6	01 December 2020	Updated protocol to reflect Sponsor rebranding from “Retrophin” to “Travere Therapeutics”. Clarified the timing for discontinuing standard-of-care treatment. Added guidance for working with restrictions related to COVID-19. Added home care visit for patient retention in the double-blind and open-label extension periods. Updated with GBR Protocol Amendment 5 specifications. Updated study endpoints per FDA recommendation.
Amendment 5	23 January 2020	Added open-label extension period to protocol.
Amendment 5-GBR	08 April 2020	Added open-label extension period to the United Kingdom version of the protocol.
Amendment 4-GBR	21 November 2019	Allowed enrollment of pediatric patients in the United Kingdom.
Amendment 3	06 June 2019	Removed mandate for contraception in male patients; see Amendment 3 Summary of Changes, Attachment 1. Added a minimum weight requirement to inclusion criteria.

Protocol Version	Date Issued	Rationale for Update
		Harmonized with PROTECT Protocol Amendment 2.
Amendment 2	07 January 2019	Streamlined endpoints and statistical methods, added guidance and testing related to safety monitoring.
Amendment 1	26 June 2018	Harmonized with PROTECT Protocol and addressed comments from regulatory agencies.
Original Protocol	19 January 2018	N/A

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Approval Task	[redacted] Medical 27-Jan-2024 01:06:34 GMT+0000
Approval Task	[redacted] Biostatistics 29-Jan-2024 17:30:16 GMT+0000
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