Protocol

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

Date of Document: 22 November 2022

NCT03762850

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

Investigational Medicinal Product:	sparsentan
Product Code:	RE-021
Protocol Number:	021IGAN17001
IND Number:	137,918
EudraCT Number:	2017-004605-41
Clinical Trials Number:	NCT03762850
Developmental Phase:	Phase 3
Protocol Version and Date:	Amendment 6: 15 November 2022 (Version history contained in Section 15.3)
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

Medical Monitor (Travere):	[redacted] MD Nephrology Travere Therapeutics, Inc. Tel: [redacted] Medical Emergency Tel: +1-973-659-6677 or +1-570-819-8565 email: [redacted]
Medical Monitor (IQVIA):	[redacted], MD, PhD [redacted], Immunology and Internal Medicine Mobile: [redacted] 24-hour Medical Emergency (any time): US: +1-973-659-6677 (main); +1-512-652-0191 (back-up) email: [redacted]
Serious Adverse Event Reporting:	Qinecsa Solutions email: clinicalsafety.travere@qinecsa.com Fax: See Investigator Site File
Product Handling/Complaints:	Tel: +1-888-211-5014 email: InvestigationalProductComplaints@travere.com

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-group, Active-control Study of the Efficacy and Safety of Sparsentan for the Treatment of Immunoglobulin A Nephropathy

PROTOCOL NUMBER: 021IGAN17001

STUDY PHASE: Phase 3

INVESTIGATOR STUDY SITES:

Approximately 175 investigational study centers globally will participate in this study.

OBJECTIVES:

Double-blind Period

Efficacy: To determine the effect of sparsentan on proteinuria and preservation of renal function, as compared to an angiotensin receptor blocker (ARB), in patients with immunoglobulin A nephropathy (IgAN).

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

Open-label Extension Period

To assess the long-term efficacy, safety, and tolerability of open-label treatment with sparsentan in patients with IgAN.

Sparsentan + Sodium-glucose Cotransporter2 (SGLT2) Inhibitor Sub-study

The objectives of the Sparsentan + SGLT2 Inhibitor Sub-study, referred to as Sub-study, are to investigate the safety and efficacy of an SGLT2 inhibitor in combination with sparsentan on proteinuria in patients with IgAN, as compared to sparsentan alone.

METHODOLOGY:

This is a 114-week, randomized, multicenter, double-blind, parallel-group, active control study, with an open-label extension period of up to 156 weeks for a total duration of up to 270 weeks in patients with IgAN who have persistent overt proteinuria and remain at high risk of disease progression despite being on a stable dose (or doses) of an angiotensin-converting enzyme inhibitor (ACEI) and/or ARB that is (are) a maximum tolerated dose that is at least one-half of the maximum labeled dose (MLD) (according to approved labeling; see Appendix B, Section 15.2.3). The dose must have been stable for at least 12 weeks prior to study entry. Approximately 380 patients will be enrolled into the study.

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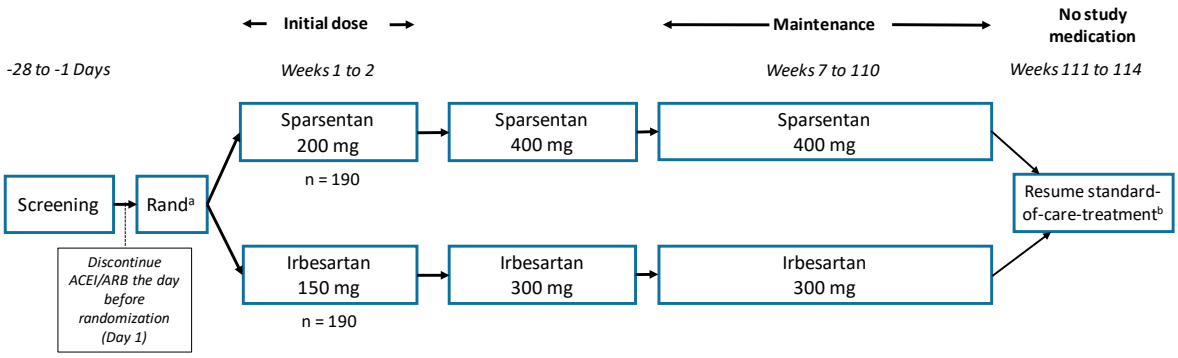
Double-blind Period

A flow chart depicting the study design is provided below.

Study 021IGAN17001 Design of the Double-blind Period



Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; RAAS = renin-angiotensin-aldosterone system; Rand = randomization

[a] On Day 1, patients will be randomized 1:1 to sparsentan or irbesartan, stratified by eGFR value (30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and urine protein excretion (≤1.75 g/day and >1.75 g/day).

[b] Resume standard-of-care treatment, including RAAS inhibitor treatment. Where possible, the same treatment regimen the patient was on at study entry (ie, the same ACEI and/or ARB at the same dose[s]) should be used, unless in the Investigator's opinion, an alternative treatment approach is warranted.

Patients who meet eligibility criteria and provide written informed consent will undergo comprehensive baseline evaluations and clinical laboratory tests and will be randomly assigned in a 1:1 ratio to receive either sparsentan or active control (irbesartan). Randomization will include stratification by estimated glomerular filtration rate (eGFR) value (30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and urine protein excretion (≤1.75 g/day and >1.75 g/day).

Standard-of-care treatment (ACEI and/or ARB therapy) and any other prohibited concomitant medications will be discontinued before the randomization (Day 1) visit (see Section 15.2.1). The final dose of an ACEI and/or ARB should be taken on the day before the randomization (Day 1) visit. The study medication (sparsentan or irbesartan) will be initiated on Day 1 according to the Dose/Route/Regimen section below. Throughout the study (including the open-label extension period), patients will be maintained on the maximum allowed dose of study medication they can tolerate while secondarily maintaining blood pressure as close as possible to a target level of 125/75 mmHg. Treatment with additional anti-hypertensive agents is encouraged during the study, with the exception of those that inhibit the renin-angiotensin-aldosterone system (RAAS) (ACEIs, aldosterone blockers, aliskiren, or ARBs) and endothelin systems (endothelin receptor antagonists [ERAs]; eg, ambrisentan and bosentan).

It is recommended that systemic corticosteroid and/or immunosuppressive therapy for the treatment of IgAN 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. Such interventions (including the duration and outcome of treatment) should be documented on the electronic case report form (eCRF).

Study visits will be conducted at 2, 4, 6, and 12 weeks after randomization and at approximately 12-week intervals thereafter. Following the 110-week blinded treatment period, treatment with study medication will be discontinued for 4 weeks. At this time, the Investigator should resume standard-of-care treatment. Where possible, the same treatment regimen the patient was on at study entry (ie, the same ACEI and/or ARB at the same dose[s]) should be used unless, in the Investigator's opinion, an alternative treatment approach is warranted.

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The Investigator may make additional adjustments in anti-hypertensive medications if considered necessary to adequately control blood pressure.

Patients will return to the site for the Week 114 visit after study medication has been discontinued (see Table 1 and Section 15.1).

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

Sparsentan or irbesartan concentrations (and possibly metabolites) in plasma will be evaluated. At specified visits, 1 trough sample will be obtained pre-dose in the clinic.

The primary analysis of proteinuria will be performed after the last patient randomized has undergone the Week 36 visit. Subsequently, all patients will continue to be followed on an intent-to-treat basis to Week 114 for the longer-term assessment of eGFR rate of change.

Open-label Extension Period

Patients may be evaluated for eligibility to participate in the open-label extension period using assessments from the Week 110 visit as screening assessments. A flow chart depicting the study design is provided in Figure 2. Patients with an eGFR value of <30 (but >20) mL/min/1.73 m^2 will be eligible for participation in the open-label extension period at the discretion of the Investigator but will require close monitoring of eGFR and serum potassium (see Exclusion Criteria for the Open-label Extension Period).

For patients who agree to participate in the open-label extension period and meet the eligibility criteria (see Inclusion/Exclusion Criteria), the Week 114 visit will also serve as the baseline visit (Day 1) for the open-label extension period. Standard-of-care treatment (ACEI and/or ARB therapy) and any other prohibited concomitant medications will be discontinued before the Week 114 visit (see Section 15.2.1). The final dose of an ACEI and/or ARB therapy should be taken on the day before the Week 114 visit. At Week 114, patients will sign a new informed consent (if not completed previously at Week 110) for the open-label extension period and will begin taking open-label sparsentan. All Week 114 (baseline visit) evaluations must be completed prior to the first dose of open-label sparsentan.

At Week 114, the starting dose is 1 tablet (200 mg) for all patients. At Week 116, the patient's dose will be titrated to either 2 tablets (2 × 200 mg) or 1 tablet (1 × 400 mg, when available), if tolerated and determined safe by the Investigator. Detailed information on the dosing regimen for the open-label extension period is included in the Dose/Route/Regimen section.

As in the double-blind period, additional anti-hypertensive agents are allowed during the open-label extension period to maintain blood pressure as close as possible to 125/75 mmHg, with the exception of those that inhibit the RAAS and endothelin systems (see Section 8.3.2 for concomitant medication considerations).

Patients will participate in the open-label extension period for up to 156 weeks (see Figure 2) for a total of 270 weeks in the study (ie, double-blind and open-label extension periods). If sparsentan becomes commercially available during the open-label extension period, patients may transition out of the study and onto commercial product before the end of the open-label extension period.

Sparsentan + SGLT2 Inhibitor Sub-study

Patients participating in the open-label extension period may be evaluated for eligibility to participate in a randomized, open-label, controlled Sub-study evaluating the safety and efficacy of an SGLT2 inhibitor in addition to stable sparsentan treatment (Sub-study). The SGLT2 inhibitor, dapagliflozin will be provided as "study medication" for the Sub-study. A flow chart depicting the Sub-study design is provided in Figure 3. In regions where dapagliflozin is licensed for the treatment of patients with progressive chronic kidney disease (CKD), patients on a stable dose of sparsentan for at least 8 weeks in the open-label extension period and fulfilling local label requirements for dapagliflozin will be eligible for participation at the discretion of the Investigator. The target and starting dose of the dapagliflozin is recommended to be 10 mg/day (see Section 8.1.3 for additional details).

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Patients who provide informed consent to participate in the Substudy and meet the eligibility criteria (see Section 7.3), will be randomly assigned to receive SGLT2 inhibitor or to receive no SGLT2 inhibitor treatment for a period of 12 weeks. Informed consent, assessment of nonlaboratory sample-based eligibility criteria and laboratory samples required to assess laboratory sample-based eligibility criteria may be provided at a routine study visit. The visit upon which eligibility is assessed will be the baseline visit. Upon receipt of central laboratory results, eligible patients will be randomized, 1:1 to receive SGLT2 inhibitor or no SGLT2 inhibitor, informed of their group allocation, and instructed, as applicable, to start dosing with 10 mg/day dapagliflozin within 14 days of the study visit, according to instructions from the Investigator. The start date of dapagliflozin dosing will be noted by the patient and recorded in the Electronic Data Capture (EDC) system.

At the discretion of the Investigator, for patients assigned to the SGLT2 inhibitor treatment group, an additional unscheduled visit may be conducted following 7 to 14 days of dosing for safety monitoring. Detailed information on the sparsentan dosing regimen for the open-label extension period is included in Section 8.1.2.

As in the double-blind period, additional anti-hypertensive agents are allowed during the open-label extension period, including the Sub-study, to maintain blood pressure as close as possible to 125/75 mmHg, with the exception of those that inhibit the RAAS and endothelin systems (see Section 8.3.2 for concomitant medication considerations). Dose reduction or discontinuation of concomitant antihypertensive medications should be considered to maintain study blood pressure targets in patients experiencing low blood pressure after the addition of dapagliflozin.

Following completion of the visit 12 weeks after the baseline visit, all patients may receive open-label dapagliflozin for up to 24 additional weeks, or through the end of the open-label extension period, whichever is shortest.

NUMBER OF PATIENTS:

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

Approximately 60 patients from the open-label extension period will be enrolled into the Sub-study.

INCLUSION/EXCLUSION CRITERIA:

Patients who provide written informed consent and meet eligibility criteria will undergo baseline assessments and be randomized into the study. 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 have 1 additional measurement on that variable through the central laboratory to assess patient eligibility.

Criteria for Double-blind Period

Inclusion Criteria for the Double-blind Period:

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

1. The patient is willing and able to provide signed informed consent.
2. The patient is male or female, aged ≥18 years.
3. The patient has biopsy-proven IgAN. The biopsy may have been performed at any time in the past.
4. The patient has a urine protein excretion value ≥1.0 g/day at screening.
5. The patient has an eGFR value of ≥30 mL/min/1.73 m^2 at screening.
6. The patient has been on a stable dose of ACEI and/or ARB therapy for at least 12 weeks prior to screening that is:
   A. the patient's maximum tolerated dose, and
   B. at least one-half of the MLD (See Appendix B, Section 15.2.3 for minimum ACEI/ARB daily dose requirements at screening).

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7. In the Investigator's opinion, the patient's blood pressure has been managed in accordance with standard-of-care using ACEI and/or ARB therapy as described in inclusion criterion 6 and additional anti-hypertensive agents if needed. At screening, the patient's systolic blood pressure must be ≤150 mmHg, and diastolic blood pressure must be ≤100 mmHg.
8. The patient is willing to undergo a change in ACEI and/or ARB and anti-hypertensive medications.
9. 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 (including open-label sparsentan). 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. 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 2) and after.

Exclusion Criteria for the Double-blind Period:

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

1. The patient has IgAN secondary to another condition (eg, systemic lupus erythematosus and liver cirrhosis) or Henoch-Schonlein purpura.
2. The patient has cellular glomerular crescents present in >25% of glomeruli on renal biopsy within 6 months prior to screening.
3. The patient has a chronic kidney disease in addition to IgAN.
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 taking any systemic immunosuppressive medications (including corticosteroids) for >2 weeks within 3 months prior to screening.
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 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.
10. 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.
11. The patient has a screening hematocrit value <27% (0.27 Volume/Volume) or hemoglobin value <9 g/dL (90 g/L).
12. The patient has a screening potassium value of >5.5 mEq/L (5.5 mmol/L).

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13. The patient has a history of alcohol or illicit drug use disorder (as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition).
14. The patient has a history of serious side effect or allergic response to any angiotensin II antagonist or ERA, including sparsentan or irbesartan, or has a hypersensitivity to any of the excipients in the study medications.
15. The female patient is pregnant, plans to become pregnant during the course of the study, or is breastfeeding.
16. 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.
17. 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 for participation in the blinded study period up to 2 additional times. Patients who are re-screened for participation in the blinded study period 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 Period

Inclusion Criteria for the Open-label Extension Period:

Based on assessments at the Week 110 and Week 114 visits, a patient must meet all of the following criteria to be eligible for the open-label extension period:

1. The patient completed participation in the double-blind period, including the Week 114 visit.
2. The patient is willing and able to provide signed informed consent for participation in the open-label extension period.
3. The patient did not permanently discontinue study medication during the double-blind period (see Section 6.3.2).
4. 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 (including open-label sparsentan). 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 the Week 114 visit until 90 days after the last dose of study medication. (For details, see Double-blind Period Inclusion Criterion 9).

Exclusion Criteria for the Open-label Extension Period:

Based on assessments at the Week 110 and Week 114 visits, a patient who meets any of the following criteria will be excluded from the open-label extension period:

1. The patient has progressed to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT).
2. The patient developed any criteria for discontinuation of study medication or discontinuation from the study as defined in Section 6.3.2 or Section 6.5, respectively, between Week 110 and Week 114.
3. The patient was unable to initiate, or developed contraindications to, treatment with RAAS inhibitors between Week 110 and Week 114.
4. The patient has an eGFR value of ≤20 mL/min/1.73 m^2 at Week 110.
5. The patient has a potassium value of >5.5 mEq/L (5.5 mmol/L).
6. The female patient is pregnant or is breastfeeding.

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NOTE: If, in the Investigator's opinion, the eGFR value at Week 110 is deemed unlikely to be representative of the patient's true status, the Investigator may repeat the eGFR measurement prior to Week 114 through the central laboratory to assess patient eligibility. Patients with an eGFR value of <30 mL/min/1.73 m^2 will require close monitoring of eGFR and serum potassium throughout the open-label extension period.

Criteria for the Sparsentan + SGLT2 Inhibitor Sub-study

Inclusion Criteria for the Sparsentan + SGLT2 Inhibitor Sub-study:

Based on assessments at a regularly scheduled open-label extension visit, a patient must meet all of the following criteria to be eligible for the Sub-study:

1. The patient is participating in the open-label extension and is willing and able to provide signed informed consent for participation in the open-label extension period Sub-study.
2. The patient has a urine protein excretion value of ≥0.3 g/day.
3. The patient has an eGFR of ≥25 mL/min/1.73m^2.
4. The patient is on a stable dose of sparsentan for ≥8 weeks in the open-label extension period that is the maximum tolerated dose.
5. The patient has ≥12 weeks of the study remaining.
6. The patient fulfils local requirements, recommendations and does not have contraindications for on-label prescription of dapagliflozin.

Exclusion Criteria for the Sparsentan + SGLT2 inhibitor Sub-study:

Based on assessments at an open-label extension visit, a patient who meets any of the following criteria will be excluded from participation in the open-label extension period Sub-study:

1. The patient has progressed to ESRD requiring RRT.
2. The patient has initiated or changed dose of a systemic immunosuppressive medication (including systemic steroids) within 12 weeks.
3. The patient has been taking an SGLT2 inhibitor within 12 weeks.
4. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the Sub-study.

DOSE FORM (TEST ARTICLE):

For the double-blind period, sparsentan doses to be administered in the study will be dispensed as 200 mg tablets over-encapsulated (blinded) with size 00 capsules.

For the open-label extension period, sparsentan will be dispensed as 200 mg or 400 mg tablets, when available.

For the Sub-study, the SGLT2 inhibitor, dapagliflozin, will be dispensed as 5 mg tablets.

DOSE FORM (REFERENCE TREATMENT):

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

Irbesartan will not be administered in the open-label extension period.

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

Double-blind Period

Standard-of-care treatment (ACEI and/or ARB therapy) and any other prohibited concomitant medications will be discontinued before the randomization (Day 1) visit (see Section 15.2.1) (unless they permanently discontinue study medication during the study; see Section 6.3.2). The final dose of an ACEI and/or ARB therapy should be taken on the day before the randomization (Day 1) visit. On Day 1, patients will be randomly assigned to either sparsentan (investigational product) or irbesartan (active control) and take study medication. The full daily dose of study medication is preferred to be taken prior to the morning meal, with the exception of the day of a study visit. On the day of a study visit, in both the double-blind and open-label extension periods (as specified in Section 15.1), including the Day 1/Randomization visit of the double-blind period, patients will take their study medication in the clinic after the pre-dose pharmacokinetic (PK) blood sample has been obtained. Allowed doses during the blinded treatment period are shown in Table 2, and the blinded dose titration scheme is provided in Figure 4.

The goal is to titrate to the target dose at Week 2. Patients will receive the initial dose (ie, one-half the target dose) for the first 2 weeks after randomization. At the Week 2 visit, the Investigator will evaluate dose tolerance in a blinded manner. The Investigator may titrate the patient's dose up to the target dose based on blood pressure and lack of adverse events (AEs) at the Week 2 visit or may titrate the patient's dose up to the target dose after the Week 2 laboratory results are available (ie, between the Week 2 and Week 4 visits). If the Investigator titrates the patient's dose at Week 2 based on blood pressure and lack of AEs, the patient's dose may be reduced once the Week 2 laboratory results are available (ie, between the Week 2 and Week 4 visits).

Patients who tolerate the initial dose after 2 weeks but display asymptomatic systolic blood pressure values ≤100 mmHg, diastolic blood pressure values ≤60 mmHg, or present with clinical symptoms of orthostatic hypotension will continue on the initial dose after the Week 2 visit without titrating up to the target dose. At the Week 2 visit, patients who do not tolerate the initial dose for any reason may discontinue study medication.

Patients who discontinue study medication (at any point in the double-blind period) should continue in the double-blind period even if they permanently discontinue study medication and, if appropriate, will be encouraged to re-start study medication throughout the double-blind period at the Investigator's discretion (see Section 6.3.1 and Section 6.3.2). However, if an End-of-Treatment (EOT)/early termination visit is completed during the double-blind period, study medication cannot be resumed. Dose titrations (up or down) are permitted at any time at the Investigator's discretion, and if appropriate, additional safety testing may be performed.

Throughout the study (including the open-label extension period), patients will be maintained on the maximum allowed dose of study medication they can tolerate while secondarily maintaining blood pressure as close as possible to the target of 125/75 mmHg. To maintain blood pressure, the Investigator will be encouraged to either treat patients with additional anti-hypertensive agents (with the exception of ACEIs, aldosterone blockers, aliskiren, ARBs, or ERAs) or withdraw anti-hypertensive agents. In the case of intolerable hypotension, withdrawal of additional anti-hypertensive agents should be accomplished before considering withdrawal or dose reduction of study medication. At the discretion of the Investigator, patients may reduce their dose in the double-blind period from 2 capsules/day to 1 capsule/day for safety or tolerability reasons.

Open-label Extension Period

The full daily dose of open-label sparsentan is preferred to be taken prior to the morning meal. Allowed doses during the open-label extension period are shown in Table 3.

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

For patients who enter the open-label extension period with an eGFR value of <30 mL/min/1.73 m^2 (ie, at Week 110), any dose titration at Week 116 will be at the Investigator's discretion based on the results of the Week 116 assessments. Patients whose dose is titrated to the 400 mg dose at Week 116 and have an eGFR value

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of <30 mL/min/1.73 m^2 will be contacted by the Investigator at Week 118 to assess tolerance of the higher dose; at the Investigator's discretion, these patients may also come in for an additional unscheduled visit at Week 118.

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

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

The urine protein/creatinine ratio (UP/C) will be determined based on a 24-hour urine sample.

Sparsentan + SGLT2 Inhibitor Sub-study

Sparsentan dosing will continue as outlined for the open-label extension period (Section 8.1.2). Patients randomized to the dapagliflozin treatment group will receive instructions on dosing from their Investigator and should commence dosing within 14 days of the study visit assessing eligibility (Screening/Randomization/Day 1 visit for the Sub-study). The target dose and recommended starting dose for patients is the maximum labeled dose (10 mg/day). For patients assigned to receive dapagliflozin, an additional unscheduled visit may be conducted following 7 to 14 days of dosing for safety monitoring. Dapagliflozin dose may be adjusted at any stage based on tolerability at the discretion of the Investigator and additional safety visits conducted as deemed necessary.

Secondarily, and in accordance with all phases of the trial, blood pressure will be maintained as close as possible to a target level of 125/75 mmHg. Treatment with additional anti-hypertensive agents is encouraged during the study, with the exception of those that inhibit the RAAS (ACEIs, aldosterone blockers, aliskiren, or ARBs) and endothelin systems (ERAs; eg, ambrisentan and bosentan). In cases of hypotension, it is recommended that dose of additional anti-hypertensives be lowered or withdrawn prior to consideration of changes in the dapagliflozin dose. Changes to sparsentan dose based on blood pressure are recommended only once all other options have been explored.

ENDPOINTS:

Efficacy Endpoints

Double-blind Period

Primary Efficacy Endpoint:

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

Key Secondary Efficacy Endpoints:

The secondary efficacy endpoints (see Section 12.7.2) are as follows:

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

Other Secondary Efficacy Endpoints:

Other secondary efficacy endpoints are as follows:

- The mean change from baseline over time in eGFR and selected proteinuria variables (based on a 24-hour urine sample) (eg, urine protein excretion, urine albumin excretion, urine albumin/creatinine ratio and UP/C) up to Week 110.
- The proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or death (ESRD is defined as initiation of RRT or sustained eGFR value of <15 mL/min/1.73 m^2).

Exploratory Endpoints – Double-blind Period:

Exploratory endpoints are as follows:

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

Safety Endpoints – Double-blind Period:

Safety evaluations include the following:

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

Open-label Extension Period Endpoints:

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

- The absolute and percent change from Week 114 in eGFR at each visit.
- The percent change from Week 114 in UP/C at each visit.
- Changes from Week 114 in QoL at each visit.
- Changes from Week 114 in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters.
- Changes from Week 114 in lipid profile (total cholesterol and triglycerides, low-density lipoprotein, and high-density lipoprotein).
- The incidence of TEAEs during the open-label extension period.

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Sparsentan + SGLT2 Inhibitor Sub-study:

For the Sub-study, the baseline visit (Day 1) is defined as the visit upon which eligibility is assessed.

Safety Endpoints:

Safety evaluations include the following:

- Changes from Sub-study baseline in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters at each visit.
- The incidence of TEAEs during the Sub-study period.

Efficacy Endpoints:

Endpoints include, but are not limited to:

- The mean change from Sub-study baseline in UP/C and UA/C based on a 24-hour urine sample at the next scheduled visit.
- Achievement of urinary protein excretion <0.3 g/day at the next scheduled visit.
- Change in absolute and percent change from Sub-study baseline in eGFR at the next scheduled visit.

STATISTICAL METHODS:

Sample Size Justification:

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

$$H_0: \Delta = 0 \text{ versus } H_1: \Delta \neq 0$$

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

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

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Analysis Sets

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

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

Per Protocol (PP) Analysis Set: The PP Analysis Set is a subset of the FAS containing patients who meet study eligibility requirements and have no protocol deviations that might impact the assessment of efficacy measurements. Patients will be analyzed according to randomized treatment assignment. The PP Analysis Set will be used for sensitivity analyses relating to efficacy. The type of protocol deviations governing exclusion from the PP Analysis Set will be determined prior to study unblinding and will be detailed in the statistical analysis plan (SAP).

Safety Analysis Set: All patients who are randomized and take at least 1 dose of randomized therapy will be included in the Safety Analysis Set. Safety analyses will be based on randomized therapy.

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

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

Sparsentan + SGLT2 Inhibitor Sub-study Analysis Set: All patients who are randomized in the Sub-study will be included in the Sub-study Analysis Set. All Sub-study efficacy and safety analyses will be based on the Sub-study Analysis Set.

Statistical Methods for Efficacy Assessment

The eGFR for each time point (visit) during the double-blind and open-label extension periods will be determined using the Chronic Kidney Disease Epidemiology (Levey 2009) formula for adults at assessment time points detailed in the Schedules of Study Events (Section 15.1).

Change from Baseline in Proteinuria at Week 36 (based on a 24-hour urine sample)

After approximately 280 patients have undergone the Week 36 visit, proteinuria (UP/C) data will be analyzed via a mixed-model repeated-measures analysis. Change from baseline during the double-blind period in UP/C on the log scale will be the dependent variable. Log baseline UP/C will be included as a covariate along with fixed effects for randomized treatment, time (ie, nominal visit in weeks), and randomized treatment-by-time interaction. Patient will be included as a random effect. The analysis will be stratified by the randomization strata. An unstructured covariance matrix will be assumed; if convergence issues arise, the following covariance structures will be employed in order until convergence is reached: heterogeneous Toeplitz, heterogeneous Compound Symmetry, heterogeneous first-order, auto-regressive, Toeplitz, Compound Symmetry, and first-order, auto-regressive. The treatment effect will be the contrast between sparsentan and irbesartan least squares (LS) means at Week 36. The LS means, treatment effect estimate (difference in LS means), 95% CI, and two-sided p-value will be extracted from the model. Results will be back-transformed to present treatment effects on the ratio scale.

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Rate of Change in eGFR Following the Acute Effect of Randomized Therapy

The rate of change in eGFR over 52 and 104 weeks (ie, following the acute effect of randomized therapy; see below) will each be analyzed via a mixed-model random coefficients analysis. Utilizing eGFR data from (i) Weeks 6 to 58 and (ii) Weeks 6 to 110, eGFR will be the dependent variable with random patient effects for intercepts and slopes. Fixed effects for randomized treatment, baseline eGFR, time (in weeks), and randomized treatment-by-time interaction will be included. The analysis will be stratified by the randomization strata. An unstructured covariance matrix will be assumed; if convergence issues arise, a first-order, auto-regressive structure will be used. The treatment effect will be the contrast between sparsentan and irbesartan marginal slope estimates. The associated slope estimates, difference in slopes, 95% CI, and two-sided p-value will be extracted from the model. Slope and the difference in slopes will be annualized for ease of presentation and interpretation.

Rate of Change in eGFR Following the Initiation of Randomized Therapy

The rate of change in eGFR over 110 weeks (ie, following the initiation of randomized therapy) will be analyzed via a mixed-model random coefficients analysis. Utilizing eGFR data from Day 1 to Week 110, eGFR will be the dependent variable with random patient effects for intercepts and slopes. Fixed effects for randomized treatment, baseline eGFR, time (in weeks), and randomized treatment-by-time interaction will be included. The analysis will be stratified by the randomization strata. An unstructured covariance matrix will be assumed; if convergence issues arise, a first-order, auto-regressive structure will be used. The treatment effect will be the contrast between sparsentan and irbesartan marginal slope estimates. The associated slope estimates, difference in slopes, 95% CI, and two-sided p-value will be extracted from the model. Slope and the difference in slopes will be annualized for ease of presentation and interpretation.

Type I Error Control for Efficacy Endpoints – Double-blind Period

At the time of the primary analysis of change from baseline in UP/C, approximately 222 patients are projected to have eGFR data up to 58 weeks. If the analysis of UP/C at Week 36 yields a two-sided p-value <0.05, analysis of key secondary endpoints will proceed.

For non-United States (US) countries, at the time of primary analysis of proteinuria, the key secondary endpoint of rate of eGFR rate of change over 6 to 58 weeks will be formally assessed at the 1% two-sided alpha level. Type I error control for the additional key secondary endpoints at confirmatory analysis will be governed at this time by a gate-keeper on the 6- to 58-week eGFR rate of change at the 1% level. The subsequent key secondary (confirmatory) endpoint analyses of eGFR rate of change over 6 to 110 weeks and eGFR rate of change over 110 weeks following initiation of randomized therapy will be tested sequentially and be assessed at the 4% two-sided alpha level if the 6- to 58-week eGFR rate of change analysis fails to achieve p<0.01; otherwise, subsequent key secondary (confirmatory) endpoint analyses will be assessed at the 5% two-sided alpha level.

For the US, at the time of the primary analysis, no formal testing will be conducted on the endpoint of eGFR rate of change over 58 weeks.

The key secondary (confirmatory) endpoint analyses of eGFR rate of change over 110 weeks following initiation of randomized therapy will be tested and be assessed at the 5% two-sided alpha level. If it is significant then key secondary (confirmatory) endpoint analyses of eGFR rate of change over 6 to 110 weeks will be tested and assessed at the 5% two-sided alpha level.

The 2 confirmatory endpoints are intended to support regulatory submissions in the US (rate of change in eGFR over 110 weeks following initiation of randomized therapy) and non-US countries (6- to 110-week eGFR rate of change); hence, no further multiplicity adjustment is necessary. The Type I error control framework for the primary proteinuria and key secondary endpoints for US and non-US countries are displayed in Figure 5. At the time of the final analysis, if all the key secondary endpoints achieve statistical significance, the other secondary endpoints will be statistically tested at the available alpha. For all other supportive efficacy endpoints, nominal p-values will be presented without Type I error control.

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Safety Data

Descriptive statistics will be used to summarize the safety data by randomized treatment group for the double-blind period. All safety evaluations will be conducted based on the Safety Analysis Set. Observed data will be listed by patient.

Clinical laboratory parameters will be measured at baseline and postbaseline visits. Each continuous laboratory variable will be summarized in terms of changes from baseline by randomized 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.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary by System Organ Class and Preferred Term. AEs 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, by severity, and by relationship to study medication. The number and percentage of patients reporting serious TEAEs, TEAEs leading to treatment discontinuation, TEAEs of interest, and cardiovascular-related TEAEs (including those resulting in death) will also be summarized for each treatment group by MedDRA System Organ Class and Preferred Term.

Interim Analysis

An unblinded interim analysis will be performed 36 weeks after randomization of at least 280 patients to evaluate the primary efficacy endpoint.

Open-label Extension Period Analyses

Analyses of the endpoints for the open-label extension period will be performed using the methods described in Section 12.7, Section 12.8, and Section 12.9, as appropriate.

Efficacy and safety endpoints for the open-label extension period will be summarized using descriptive statistics and presented overall and by original randomized treatment based on the OLEFAS. Analyses using baselines other than Week 114 (eg, prior to the first dose of study medication in the double-blind period) may be explored.

Sparsentan + SGLT2 Inhibitor Sub-study Analyses

Safety and efficacy endpoints for the Sub-study will be summarized using descriptive statistics and will be presented by the Sub-study randomized treatment group and overall based on the Sub-study analysis set.

2. TABLE OF CONTENTS

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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
ACEI	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AEOI	Adverse event of interest
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AngII	Angiotensin II
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AT_1	Angiotensin type 1 receptor
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology (formula)
COVID-19	Coronavirus disease 2019
CYP3A	Cytochrome P450 3A
CYP2B6	Cytochrome P450 2B6
DMC	Data Monitoring Committee
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*
DUPLEX	Study 021FSGS16010, NCT03493685, EudraCT 2016-00514123: *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)*
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End-of-Study
EOT	End-of-Treatment
EQ-5D-5L	EuroQol 5-dimension, 5-level Quality of Life questionnaire
ERA	Endothelin receptor antagonist
ESRD	End-stage renal disease
ET_A	Endothelin type A
ET1	Endothelin-1
ET	Early Termination

Abbreviation	Definition
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSGS	Focal segmental glomerulosclerosis
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive randomization technology
KDIGO	Kidney Disease Improving Global Outcomes
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MLD	Maximum labeled dose
NSAID	Non-steroidal anti-inflammatory drug
OLEFAS	Open-label Extension Full Analysis Set
PAS	Primary Analysis Set
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PP	Per Protocol (analysis set)
PRO	Patient-reported outcome
QoL	Quality of life
RAAS	Renin-angiotensin-aldosterone system
RRT	Renal replacement therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System
SGLT2	Sodium-glucose cotransporter-2
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SUSAR	Suspected, unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
UA/C	Urine albumin/creatinine ratio
UP/C	Urine protein/creatinine ratio
US	United States
USPI	US Prescribing Information
WOCBP	Women of childbearing potential

4. INTRODUCTION

4.1. Immunoglobulin A Nephropathy

Immunoglobulin A nephropathy (IgAN), also known as Berger's disease, is a form of glomerulonephritis originally described in 1968. Although the pathogenesis of IgAN has not been elucidated, several lines of evidence indicate that it is an autoimmune disease with an extra-renal etiology (Knoppova 2016). IgAN is diagnosed from a biopsy of cortical renal tissue and is characterized by the finding of immune deposits, predominantly containing polymeric immunoglobulin A (IgA) in the glomerular mesangium of the kidney (Boyd 2012; Le 2012; Barratt 2011; Donadio 2002a). Primary IgAN can occur at any age, but clinical onset is commonly during the second or third decades of life (Donadio 2002a).

IgAN is a serious, progressive disease in which 20% to 40% of patients progress to end-stage renal disease (ESRD) within 10 to 20 years of diagnosis (Manno 2007; Berthoux 2011; Moriyama 2014). As most patients are diagnosed in their 20s or 30s, they face the prospect of dialysis or the need for kidney transplantation in the prime of their lives. Geddes et al (Geddes 2003) conducted a retrospective analysis of patients with IgAN across 4 countries on 3 continents (Europe, North America, and Australia) to assess long-term outcome of the disease. From first clinical presentation, the overall 10-, 15-, and 20-year actuarial renal survival rates were 77.8%, 69.8%, and 55.3%, respectively. Due to the extra-renal etiology of IgAN in which the kidney is the end organ damaged by a systemic immunological condition, the incidence of IgAN recurrence following kidney transplantation is high; when posttransplant biopsies were routinely collected (regardless of symptomology), the recurrence of IgAN has been reported in 50% to 60% of patients, with an estimated 10-year incidence of graft loss due to recurrence of approximately 10% (Choy 2006).

Patients with IgAN typically present in 1 of 3 ways (Donadio 2002b; Galla 1995). Approximately 40% to 50% of patients present with 1 or recurrent episodes of visible hematuria, usually following an upper respiratory tract infection; these patients are not considered to be at risk for progression to ESRD. Less than 10% of patients present with nephrotic syndrome or acute, rapidly progressing glomerulonephritis and, in rare cases, may present with malignant hypertension. The remaining 30% to 40% of patients have persistent proteinuria that may be accompanied by microscopic hematuria, which is detected incidentally upon routine examination (Hall 2004; Topham 1994); this group is the target patient population for treatment with sparsentan and is addressed by the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis (KDIGO 2012).

While there are currently no approved medicinal products indicated for the treatment of IgAN, the cornerstone of treatment is rigorous blood pressure control using renin-angiotensin-aldosterone system (RAAS) inhibitor therapy (angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs]) to target blood pressure values <130/80 mmHg in order to reduce hemodynamic stress and proteinuria and, thereby, slow the progression of renal disease (Floege 2011; Locatelli 2006; Aucella 2009). Randomized, placebo-controlled trials have shown long-term benefit of RAAS inhibitor treatment (Ruggenenti 2000; Praga 2003; Coppo 2007), which is universally considered to be first-line standard-of-care, as outlined in the KDIGO Clinical Practice Guideline (KDIGO 2012). However, despite optimized RAAS inhibitor therapy, persistent overt proteinuria remains in

many patients, concurrent with loss of renal function and progression to ESRD. Additional treatment options are limited to those that have either a questionable benefit/risk profile (eg, high-dose systemic steroids) or limited evidence to support their use (eg, mycophenolate mofetil).

Sparsentan is a first-in-class, potent, orally-active, dual-acting ARB (angiotensin II [AngII] type 1) plus endothelin type A (ET_A) receptor blocker. Given the well-known role of AngII and endothelin-1 (ET1) in glomerulonephropathies, it is anticipated that sparsentan, as a dual antagonist, will have a positive effect on the pathophysiological changes in the glomeruli and tubulointerstitial compartment that occurs in IgAN.

4.2. Rationale for Treatment of Renal Diseases with Sparsentan

The angiotensin type 1 receptor (AT_1) receptor is expressed in renal vessels, including glomerular arterioles and glomeruli (mesangial cells and podocytes), as well as along the nephron and in cells in the renal interstitium (Allen 1999; Ardaillou 1999; Zhuo 1997; Gloy 1997; Gonçalves 2003). Thus, AngII, acting mostly via AT_1 receptors, affects practically all renal compartments and cell types. The effects of AngII include hemodynamic actions leading to vasoconstriction and elevations of intra-glomerular pressure; promoting cell growth and extracellular matrix production, resulting in glomerulosclerosis and tubulointerstitial fibrosis; pro-oxidant and inflammatory actions; and effects with implications in podocyte pathophysiology and pathogenesis of proteinuria.

ET1 also has a well-established role in renal pathophysiology. Renal ET_A receptors are expressed in renal vasculature, including glomerular arterioles, mesangial cells, and podocytes, in the proximal portion of the proximal tubule, in the distal tubule, and in collecting ducts (Kohan 2011). ET1 is stimulated by numerous factors known to trigger or to contribute to the development of kidney diseases. In general, ET1 acts as a vasoactive peptide, which also stimulates renal cell growth and proliferation, production of extracellular matrix, and inflammation (Kohan 2014) and has a major impact on tubular function (Kohan 2011). The role of ET1 in the pathogenesis of IgAN is supported by in vitro data, as well as genetic and molecular profiling of ET1 in patients with IgAN (Chen 2001; Maixnerová 2007; Tycová 2018).

Suzuki et al (Suzuki 2000) reported the effect of an ARB (valsartan) on glomerular fibrosis in renal tissue from ddY mice, a model of IgAN. A reduction in urinary albumin excretion was observed that was not statistically significant; however, the decrease in glomerular fibrosis was statistically significant ($p<0.01$). These findings were independent of the anti-hypertensive effect of valsartan. The development of histopathological lesions, urinary protein excretion, and reduction in estimated glomerular filtration rate (eGFR) was also suppressed in the ddY spontaneous IgAN mice by FR 139317, an early ET_A-specific antagonist (Nakamura 1996).

Considering well-documented roles of AngII and ET1 in renal pathophysiology and nephroprotective effects of their inhibition, there is strong rationale for dual inhibition of RAAS and endothelin systems in treatment of a variety of chronic kidney diseases (CKDs). Indeed, a combination treatment with an ACEI or ARB and endothelin receptor blocker has been shown to be more effective in a variety of aspects of experimental and clinical kidney disease compared to RAAS or endothelin inhibition alone (Komers 2016).

Finally, dual inhibition of AT_1 and ET_A by sparsentan has been demonstrated in 2 independent models of kidney injury. Sparsentan reduced proteinuria by 84% ($p<0.05$) in a 5/6 nephrectomy rat model and by 44% ($p<0.05$) in an Adriamycin-induced nephropathy rat model (data on file). Taken together, these non-clinical data demonstrate that antagonism of either AngII or ET_A can reduce kidney injury. Furthermore, data with sparsentan has demonstrated that dual antagonism of AngII and ET_A receptors has the potential to provide robust renal protection translating across multiple distinct kidney insults.

RAAS inhibitors have previously been shown to reduce proteinuria and control blood pressure in patients with IgAN, and the reduction in proteinuria levels has been associated with improvements in disease progression. Sparsentan, as an AT_1 antagonist, should demonstrate clinical effects consistent with other therapies that result in RAAS inhibition. Furthermore, as an ET_A antagonist, treatment with sparsentan should provide efficacy beyond that expected from RAAS inhibition alone. The ability of an endothelin receptor antagonist (ERA) to provide benefit beyond that observed with RAAS inhibition alone has been demonstrated in a clinical study by Dhaun (2011).

In the study by Dhaun (2011), 27 patients with chronic, non-diabetic, proteinuric kidney disease on optimized RAAS inhibitor therapy received treatment with an ET_A receptor antagonist, sitaxsentan, for 6 weeks as part of a randomized, cross-over study; treatment with sitaxsentan was compared to the calcium channel-blocker nifedipine (active control) or placebo. The study population included 14 patients with biopsy-proven IgAN; the remaining patients had diagnoses of focal segmental glomerulosclerosis (FSGS; 6 patients), membranous nephropathy (3 patients), hypertensive nephrosclerosis (2 patients), reflux nephropathy and microhematuria of presumed glomerular origin (1 patient), and unknown cause (1 patient). In the overall patient group, treatment with sitaxsentan reduced the urine protein/creatinine ratio (UP/C) and 24-hour proteinuria by approximately 30% and decreased systolic, diastolic, and mean arterial blood pressure by approximately 5 mmHg from baseline.

Based on the non-clinical and clinical results discussed above, it is anticipated that sparsentan will provide a clinical benefit to patients with IgAN who are at risk of disease progression despite prior treatment with a RAAS inhibitor at a maximum tolerated dose.

4.3. Sparsentan Clinical Development to Date

Prior to the Sponsor's acquisition of sparsentan, it was evaluated in a clinical development program targeted at the treatment of hypertension. That program consisted of 7 Phase 1 clinical safety studies and 2 randomized, double-blind, placebo-controlled Phase 2 studies in patients with Stages 1 and 2 hypertension. No serious adverse events (SAEs) or deaths were reported in the clinical pharmacology studies, and all adverse events (AEs) were reported as either mild or moderate in severity. In these studies, the most commonly reported AEs were tachycardia, dizziness, and headache. Sparsentan was also safe and well tolerated in the 2 Phase 2 studies conducted in patients with Stages 1 and 2 hypertension. The highest dose of sparsentan (800 mg once daily) produced a statistically significantly greater reduction in blood pressure than the active comparator, irbesartan, which was tested at its highest approved dose of 300 mg once daily. There were no SAEs associated with therapy. The most frequent AEs (≥5%) reported by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term were headache, edema peripheral, dizziness, fatigue, nausea, diarrhea, and abdominal pain. Headaches were

reported more in the placebo group than in the other groups, potentially due to uncontrolled high blood pressure. The clinical experience gained in these Phase 1 and Phase 2 studies supported the Sponsor's conduct of the Phase 2 DUET study in patients with FSGS.

The Phase 2 DUET study is an ongoing study in patients with FSGS (Study RET-D-001; NCT01613118; EudraCT number: 2014-002358-38). The study is designed as a 2-part study where an 8-week randomized, double-blind, active control, dose-escalation phase was followed by an open-label extension portion. The 8-week double-blind portion, which is complete, compared sparsentan administered at daily doses of 200 mg, 400 mg, or 800 mg to an active control (irbesartan) at its highest approved dose of 300 mg daily. The primary efficacy endpoint was the change in proteinuria after 8 weeks of double-blind treatment. Proteinuria was quantified using UP/C. The secondary efficacy endpoint was the proportion of patients experiencing a treatment-induced reduction in proteinuria to a UP/C of ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline after 8 weeks of double-blind treatment. Analysis of the safety and efficacy data is available through 09 June 2016, the date the last patient completed the 8-week, double-blind portion of the study; preliminary top line results are discussed below.

A total of 109 patients were enrolled and randomized in a 2:1 ratio to receive either sparsentan (N = 73) or irbesartan (N = 36) for the 8-week, double-blind period. The mean reduction in proteinuria from baseline after 8 weeks of treatment for all patients treated with sparsentan 200 mg, 400 mg, and 800 mg/day (n = 64) was 44.8%, compared to a mean reduction in proteinuria for all patients receiving irbesartan 300 mg/day (n = 32) of 18.5% (p = 0.006). Similar results were seen in DUET's secondary efficacy endpoint (ie, the proportion of patients experiencing a treatment-induced reduction in proteinuria to a UP/C of ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline in UP/C at Week 8); 18 of the 64 patients (28.13%) treated with sparsentan 200 mg/day, 400 mg/day, and 800 mg/day achieved a UP/C of ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline in UP/C at Week 8, compared to 3 of 32 patients (9.38%) receiving irbesartan 300 mg/day (p = 0.040).

Overall, during the 8-week, double-blind period, sparsentan at 200 mg/day, 400 mg/day, and 800 mg/day was safe and well tolerated. The most commonly reported treatment-emergent adverse events (TEAEs) for sparsentan were headache (19.2%), dizziness (13.7%), hypotension (13.7%), nausea (12.3%), diarrhea and vomiting (8.2%), peripheral edema (6.8%)/edema (5.5%), and abdominal pain (5.5%). The majority of all TEAEs that occurred in the sparsentan dose groups were mild or moderate (96.3%). Additional safety data beyond the 8-week, double-blind treatment period can be found in the sparsentan Investigator's Brochure.

4.4. Clinical Development of Sparsentan in IgAN

The purpose of the sparsentan IgAN clinical development program is to combine the potentially synergistic action of AngII receptor blockade with ET1 receptor antagonism for clinical use in treating IgAN. The current Phase 3 study, along with supporting data from the Phase 2 DUET study and the Phase 3 DUPLEX study, will comprise major sources of efficacy and safety data for the program.

The initial stimuli that trigger pathophysiological processes in the kidney and initial mechanisms of glomerular injury are different in IgAN and FSGS. However, as the 2 diseases progress, there is a growing number of overlaps in structural and functional consequences of initial kidney injury. In this context, segmental glomerulosclerosis and tubulointerstitial fibrosis represent

major overlapping pathologies in both disorders with devastating consequences. Glomerulosclerosis, as a result of healed necrotizing or segmental proliferative lesions, is a common consequence of IgAN, being described in up to 70% of biopsies (Tesar 2015), strongly predicting renal function outcomes in patients with IgAN (Coppo 2014). Moreover, studies have shown that IgAN immune complexes can directly induce morphological and molecular changes in podocytes and parietal epithelial cells that are practically identical to those seen in primary FSGS (Hill 2011).

Thus, there is a strong rationale for the use of sparsentan in the treatment of primary IgAN based on the overlapping pathological processes and selected structural lesions observed in IgAN and FSGS, and the current knowledge about the drug efficacy and safety in patients with primary FSGS.

4.5. 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 GFR and aldosterone inhibition. 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).

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.

Selective and non-selective endothelin ET_A/endothelin receptor subtype 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 participants and their female partners indicates that, similar to marketed ERAs and ARBs, the requirement for contraception in male study participants is not warranted.

The use of strong cytochrome P450 3A (CYP3A) inhibitors is prohibited for patients in this study, and P-glycoprotein (P-gp) inhibitors are to be used with caution as a drug-drug interaction cannot be ruled out. 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, the Investigator should contact the Medical Monitor for guidance (see Section 15.2.1).

For details regarding all non-clinical 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.

4.6. Summary of Potential Benefits

It is anticipated that sparsentan will provide a clinical benefit to patients with IgAN who are at risk of disease progression despite prior treatment with a RAAS inhibitor at a maximum tolerated dose. The current study will determine the durability of sparsentan's anti-proteinuric effect over time, as well as its ability to slow the progression of IgAN, as measured by change in eGFR compared to standard-of-care therapies.

4.7. Rationale for the Study

This study is a randomized, double-blind, parallel-group, active control clinical study to provide primary endpoint data on the change in proteinuria at Week 36 to form the basis of an application for approval of sparsentan indicated for the treatment of primary IgAN. Additionally, longer-term data on eGFR rate of change up to 114 weeks will be generated by continued follow-up of patients.

5. STUDY OBJECTIVES

5.1. Double-blind Period

5.1.1. Efficacy Objective

The efficacy objective of the double-blind period of the study is to determine the effect of sparsentan on proteinuria and preservation of renal function, as compared to an ARB, in patients with IgAN.

5.1.2. Safety Objective

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

5.2. Open-label Extension Period

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

5.3. Sparsentan + Sodium-glucose cotransporter-2 (SGLT2) Inhibitor Sub-study

The objectives of the Sparsentan + SGLT2 Inhibitor Sub-study, referred to as the Sub-study, are to investigate the safety and efficacy of an SGLT2 inhibitor in combination with sparsentan on proteinuria in patients with IgAN, as compared to sparsentan alone.

6. INVESTIGATIONAL PLAN

6.1. Endpoints

6.1.1. Efficacy Endpoints – Double-blind Period

6.1.1.1. Primary Efficacy Endpoint

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

6.1.1.2. Key Secondary Efficacy Endpoints

The secondary efficacy endpoints (see Section 12.7.2) are as follows:

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

6.1.1.3. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints are as follows:

- The mean change from baseline over time in eGFR and selected proteinuria variables based on a 24-hour urine sample (eg, urine protein excretion, urine albumin excretion, urine albumin/creatinine ratio [UA/C] and UP/C) up to Week 110.
- The proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or death (ESRD is defined as initiation of renal replacement therapy [RRT] or sustained eGFR value of <15 mL/min/1.73 m^2).

6.1.2. Exploratory Endpoints – Double-blind Period

Exploratory endpoints are as follows:

- The rate of change in eGFR over a 58-week (approximately 1 year) period following the initiation of randomized therapy (thus, the analysis is from Day 1 to 58 weeks post-randomization; eGFR total slope at 1 year).

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

6.1.3. Safety Endpoints – Double-blind Period

Safety evaluations include the following:

- Changes from- baseline in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters.
- The incidence of TEAEs.

6.1.4. Open-label Extension Period Endpoints

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

- The absolute and percent change from Week 114 in eGFR at each visit.
- The percent change from Week 114 in UP/C at each visit.
- Changes from Week 114 in QoL at each visit.
- Changes from Week 114 in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters.
- Changes from Week 114 in lipid profile (total cholesterol and triglycerides, low-density lipoprotein, and high-density lipoprotein).
- The incidence of TEAEs during the open-label extension period.

6.1.5. Sparsentan + SGLT2 Inhibitor Sub-study Endpoints

For the Sub-study, the baseline visit (Day 1) is defined as the visit upon which eligibility is assessed.

6.1.5.1. Safety Endpoints

Safety evaluations include the following:

- Changes from Sub-study baseline in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters at each visit.
- The incidence of TEAEs during the Sub-study period.

6.1.5.2. Efficacy Endpoints

Endpoints include, but are not limited to:

- The mean percent change from Sub-study baseline in UP/C and UA/C based on a 24-hour urine sample at the next scheduled visit.
- Achievement of urinary protein excretion <0.3 g/day at the next scheduled visit.
- Change in absolute and percent change from Sub-study baseline in eGFR at the next scheduled visit.

6.2. Study Design

This is a 114-week, randomized, multicenter, double-blind, parallel-group, active control study, with an open-label extension period of up to 156 weeks for a total study duration of up to 270 weeks in patients with IgAN who have persistent overt proteinuria and remain at high risk of disease progression despite being on a stable dose (or doses) of an ACEI and/or ARB that is (are) a maximum tolerated dose that is at least one-half of the maximum labeled dose (MLD) (see Appendix B, Section 15.2.3). The dose must have been stable for at least 12 weeks prior to study entry. Approximately 380 patients will be enrolled into the study. Additionally, there is an optional Sub-study during the open-label extension period that is 12 weeks in duration and is anticipated to enroll approximately 60 patients (see Section 6.2.3 for additional details).

6.2.1. Double-blind Period Design

Patients who meet eligibility criteria and provide written informed consent will undergo comprehensive baseline evaluations and clinical laboratory tests and will be randomly assigned in a 1:1 ratio to receive either sparsentan or active control (irbesartan). Randomization will include stratification by eGFR value (30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and urine protein excretion (≤1.75 g/day and >1.75 g/day).

Standard-of-care treatment (ACEI and/or ARB therapy) and any other prohibited concomitant medications will be discontinued before the randomization (Day 1) visit. The final dose of an ACEI and/or ARB should be taken on the day before the randomization (Day 1) visit (see Section 15.2.1). The study medication (sparsentan or irbesartan) will be initiated on Day 1 according to Section 8.1. Throughout the study (including the open-label extension period), patients will be maintained on the maximum allowed dose of study medication they can

tolerate while secondarily maintaining blood pressure as close as possible to the target level of 125/75 mmHg. This blood pressure target is in line with the KDIGO Clinical Practice Guideline (KDIGO 2012). Treatment with additional anti-hypertensive agents is encouraged during the study, with the exception of those that inhibit the RAAS (ACEIs, aldosterone blockers, aliskiren, or ARBs) and endothelin systems (ERAs; eg, ambrisentan, bosentan).

It is recommended that systemic corticosteroid and/or immunosuppressive therapy for the treatment of IgAN 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. Such interventions (including the duration and outcome of treatment) should be documented on the electronic case report form (eCRF).

Study visits will be conducted at 2, 4, 6, and 12 weeks after randomization and at approximately 12-week intervals thereafter. Following the 110-week blinded treatment period, treatment with study medication will be discontinued for 4 weeks. At this time, the Investigator should resume standard-of-care treatment, including RAAS inhibitor treatment. Where possible, the same treatment regimen the patient was on at study entry (ie, the same ACEI and/or ARB at the same dose[s]) should be used unless, in the Investigator's opinion, an alternative treatment approach is warranted. The Investigator may make additional adjustments in anti-hypertensive medications if considered necessary to adequately control blood pressure. Patients will return to the site for the Week 114 visit after study medication has been discontinued (see Table 1 and Section 15.1).

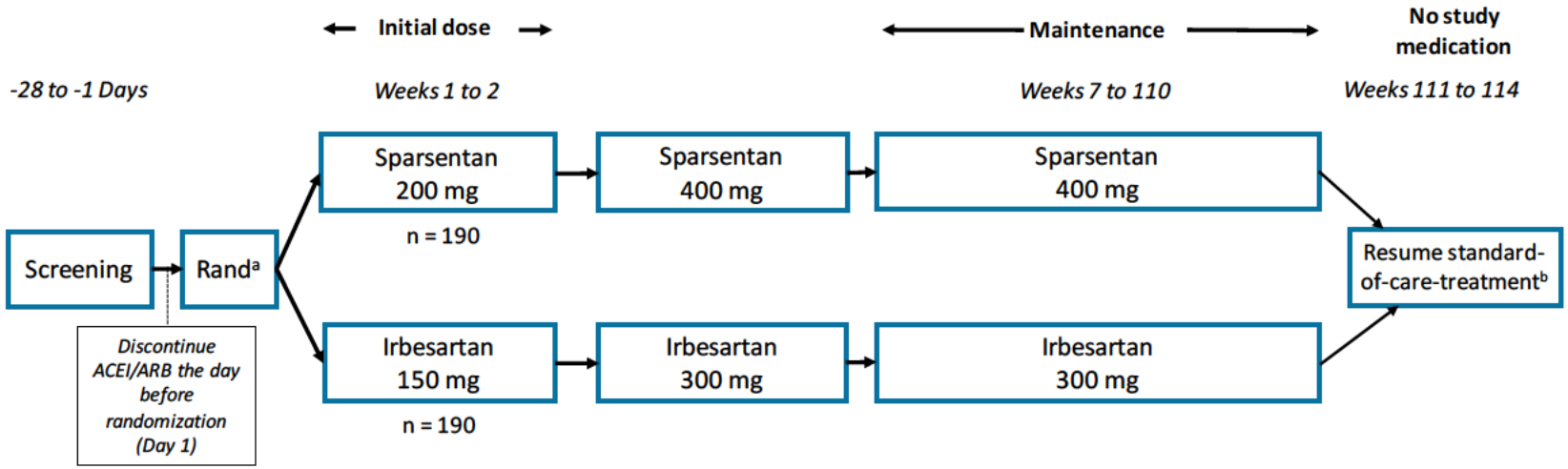
Patients who complete the double-blind period may be eligible to enroll in the open-label extension period.

Sparsentan or irbesartan concentrations (and possibly metabolites) in plasma will be evaluated. At specified visits, 1 trough sample will be obtained pre-dose in the clinic.

The primary analysis of proteinuria will be performed after the last patient randomized has undergone the Week 36 visit. Subsequently, all patients will continue to be followed on an intent-to-treat basis to Week 114 for the longer-term assessment of eGFR rate of change. Unless otherwise specified, endpoints will use the last pre-treatment value available prior to the first dose of study medication as baseline.

Flow chart and table depicting the double-blind period are provided in Figure 1 and Table 1.

Figure 1. Study 021IGAN17001 Design of the Double-blind Period



Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; RAAS = renin-angiotensin-aldosterone system; Rand = randomization

[a] On Day 1, patients will be randomized 1:1 to sparsentan or irbesartan, stratified by eGFR value (30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and urine protein excretion (≤1.75 g/day and >1.75 g/day).

[b] Resume standard-of-care treatment, including RAAS inhibitor treatment. Where possible, the same treatment regimen the patient was on at study entry (ie, the same ACEI and/or ARB at the same dose[s]) should be used unless, in the Investigator's opinion, an alternative treatment approach is warranted.

Table 1. Study 021IGAN17001 Double-blind Study Visits

Visit	**Visit 1**	**Visit 2**[b]	**Visit 3** (± 5 days)	**Visit 4** (± 5 days)	**Visit 5** (± 5 days)	**Visit 6** (± 7 days)	**Visit 7** (± 14 days)	**Visit 8** (± 14 days)
	Screening[a]	Day 1	Blinded Treatment Period					
Week	--	Randomization	W2	W4	W6	W12	W24	W36

Visit	**Visit 9** (± 14 days)	**Visit 10** (± 14 days)	**Visit 11** (± 14 days)	**Visit 12** (± 14 days)	**Visit 13** (± 14 days)	**Visit 14** (± 14 days)	**Visit 15** (± 14 days)	**Visit 16** (– 7/ + 14 days)
	Blinded Treatment Period						EOT/ET Visit	End of Double-blind Period Visit
Week	W48	W58	W70	W82	W94	W106	W110	W114

Abbreviations: EOT = End-of-Treatment; ET = Early Termination; IRT = interactive randomization technology; W = Week.
[a] Screening is from Day -28 to Day 1.
[b] At Visit 2, patients will be randomized via IRT, and the first dose will be administered in the clinic.

6.2.2. Open-label Extension Period Design

Patients may be evaluated for eligibility to participate in the open-label extension period using assessments from the Week 110 visit as screening assessments. Patients with an eGFR value of <30 (but >20) mL/min/1.73 m^2 will be eligible for participation in the open-label extension period at the discretion of the Investigator but will require close monitoring of eGFR and serum potassium (see Section 7.2.2).

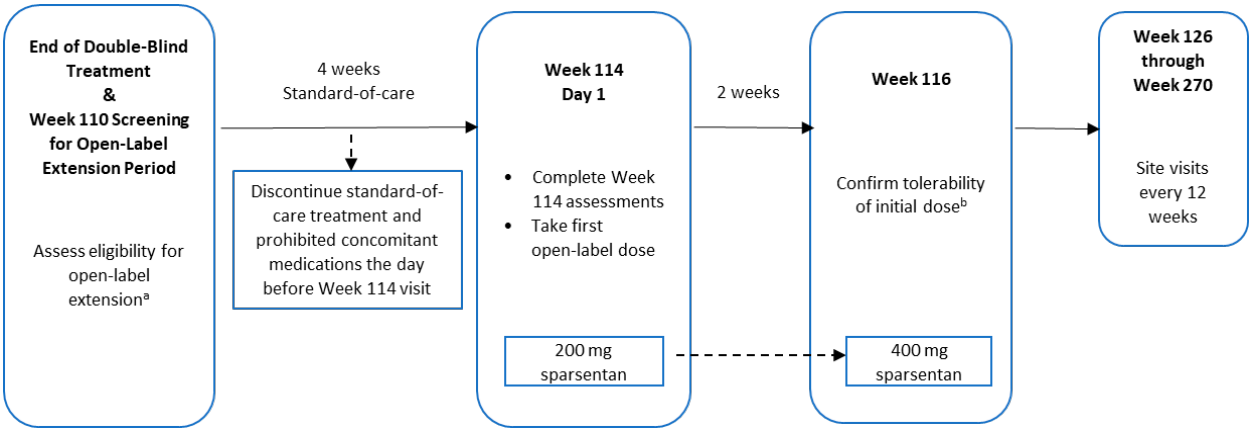
For patients who agree to participate in the open-label extension period and meet the eligibility criteria (see Section 7.2), the Week 114 visit will also serve as the baseline visit (Day 1) for the open-label extension period. Standard-of-care treatment (ACEI and/or ARB therapy) and any other prohibited concomitant medications will be discontinued before the Week 114 visit (see Section 15.2.1). The final dose of an ACEI and/or ARB therapy should be taken on the day before the Week 114 visit. At the Week 114 visit, patients will sign a new informed consent (if not completed previously at Week 110) for the open-label extension period and will begin taking open-label sparsentan. All Week 114 (baseline visit) evaluations must be completed prior to the first dose of open-label sparsentan.

At Week 114, the starting dose is 1 tablet (200 mg) for all patients. At Week 116, the patient's dose will be titrated to either 2 tablets (2 × 200 mg) or 1 tablet (1 × 400 mg, when available), if tolerated and determined safe by the Investigator. For details regarding dose titration in the open-label extension period, see Section 8.1.2; for details regarding dose modifications, see Section 8.3.2.

As in the double-blind period, additional anti-hypertensive agents are allowed during the open-label extension period to maintain blood pressure as close as possible to 125/75 mmHg, with the exception of those that inhibit the RAAS and endothelin systems (see Section 8.3.2 for concomitant medication considerations).

Patients will participate in the open-label extension period for up to 156 weeks (see Figure 2) for a total of 270 weeks in the study (ie, double-blind and open-label extension periods). If sparsentan becomes commercially available during the open-label extension period, patients may transition out of the study onto commercial product before the end of the open-label extension period.

Figure 2. Study 021IGAN17001 Overview Flow Chart of the Open-label Extension Period



Abbreviations: eGFR = estimated glomerular filtration rate

[a] See Section 7.2 for the eligibility criteria for the open-label extension period. Patients who may be eligible for the open-label extension period should be given the open-label extension period informed consent document at Week 110, if at all possible.

[b] Dose for the open-label extension will be based on tolerability as determined at Week 116. Any dose titration for patients who enter the open-label extension with an eGFR value of <30 mL/min/1.73 m^2 will be at the Investigator's discretion based on the results of the Week 116 assessments. Patients whose dose is titrated to the 400 mg dose at Week 116 and have an eGFR value of <30 mL/min/1.73 m^2 will be contacted by the Investigator at Week 118 to assess tolerance of the higher dose; at the Investigator's discretion, these patients may also come in for an additional unscheduled visit at Week 118. Doses may be modified (either 200 mg or 400 mg) at any time throughout the open-label extension for safety or tolerability reasons at the Investigator's discretion.

6.2.3. Sparsentan + SGLT2 Inhibitor Sub-study Design

Patients participating in the open-label extension may be evaluated for eligibility to participate in a randomized, open-label, controlled Sub-study evaluating the safety and efficacy of an SGLT2 inhibitor in addition to stable sparsentan treatment (Sub-study). The SGLT2 inhibitor, dapagliflozin, will be provided as "study medication" for the Sub-study. A flow chart depicting the Sub-study design is provided in Figure 3. In regions where dapagliflozin is licensed for the treatment of patients with progressive CKD, patients on a stable dose of sparsentan for at least 8 weeks in the open-label extension period and fulfilling local label requirements for dapagliflozin will be eligible for participation at the discretion of the Investigator. The target and starting dose of the dapagliflozin is recommended to be 10 mg/day (see Section 8.1.3 for additional details).

Patients who provide informed consent to participate in the Sub-study and meet the eligibility criteria (see Section 7.3), will be randomly assigned to receive SGLT2 inhibitor treatment or to receive no SGLT2 inhibitor treatment for a period of 12 weeks. Informed consent, assessment of non-laboratory sample-based eligibility criteria and laboratory samples required to assess laboratory sample-based eligibility criteria may be provided at a routine study visit. The visit upon which eligibility is assessed will be the baseline visit. Upon receipt of central laboratory results, eligible patients will be randomized 1:1 to receive SGLT2 inhibitor or no SGLT2 inhibitor, informed of their group allocation, and instructed, as applicable, to start dosing with 10mg/day dapagliflozin within 14 days of the study visit, according to instructions from the Investigator. The subject may need to return to the site to be dispensed their SGLT2 inhibitor.

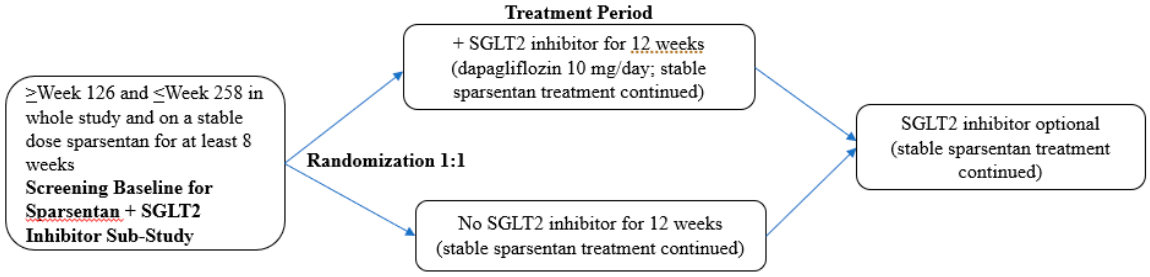
The start date of dapagliflozin dosing will be noted by the patient and recorded in the EDC system.

At the discretion of the Investigator, for patients assigned to the SGLT2 inhibitor treatment group, an additional unscheduled visit may be conducted following 7 to 14 days of dosing for safety monitoring. Detailed information on the sparsentan dosing regimen for the open-label extension period is included in Section 8.1.2

As in the double-blind period, additional anti-hypertensive agents are allowed during the open-label extension period, including the Sub-study, to maintain blood pressure as close as possible to 125/75 mmHg, with the exception of those that inhibit the RAAS and endothelin systems (see Section 8.3.2 for concomitant medication considerations). Dose reduction or discontinuation of concomitant antihypertensive medications should be considered to maintain study blood pressure targets in patients experiencing low blood pressure after the addition of dapagliflozin.

Following completion of the visit 12 weeks after the baseline visit, all patients may receive open-label dapagliflozin, for up to 24 additional weeks, or through the end of the open-label extension period, whichever is shortest.

Figure 3: Study 021IGAN17001 Overview Flow Chart of the Sparsentan + SGLT2 Inhibitor Sub-study



Abbreviations: SGLT2 = Sodium-glucose cotransporter-2.

6.3. Discontinuation of Study Medication

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 6.3.1 and Section 6.3.2). In general, patients should be encouraged to stay on study medication until they complete the study. The need for additional intervention for the treatment of IgAN or the occurrence of safety endpoints are not criteria for discontinuation of study medication. For the purposes of this protocol, sparsentan is the investigational product, and irbesartan is the active control. When referring to either investigational product (sparsentan), active control (irbesartan), or SGLT2 inhibitor (dapagliflozin), within the context of the Sub-study the term “study medication” is used.

6.3.1. 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 Schedules 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) as long as an EOT/Early Termination (ET) visit is not completed.

6.3.2. Permanent Discontinuation of Study Medication

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

- Receipt of a kidney transplant or initiation of chronic dialysis
- 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 decision to discontinue 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, Food and Drug Administration (FDA), or other regulatory authorities (see Section 13.4.5)
- Lost to follow-up

Receipt of systemic corticosteroid and/or immunotherapy intervention 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 114 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 EOT assessments listed in the Schedules of Study Events (Section 15.1) as close as possible to the patient's last dose of study medication. Alternatively, if the last dose of study medication is on a scheduled study visit (eg, Week 58), that visit will be considered an EOT/ET visit, and EOT assessments will be performed. If an EOT/ET visit is completed in the double-blind period, study medication cannot be resumed. The visit data, including the primary reason for discontinuation

of study medication, will be recorded on the EOT eCRF. Subsequent study visit data will be recorded on the visit-specific eCRF.

For patients who permanently discontinue study medication during the double-blind period, the Investigator should resume standard-of-care treatment. Where possible, the same treatment regimen the patient was on at study entry (ie, the same ACEI and/or ARB at the same dose[s]) should be used unless, in the Investigator's opinion, an alternative treatment approach is warranted. The Investigator may make additional adjustments in anti-hypertensive medications if considered necessary to adequately control blood pressure. Patients will return to the site for the Week 114 visit after study medication has been discontinued.

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 sparsentan during the open-label extension period are encouraged to return to the site for an End-of-Study (EOS) visit. Patients who discontinue dapagliflozin during the Sub-study will remain in the open-label extension period and should continue on sparsentan dosing. No additional study visits other than normally occurring protocol visits are necessary. If an EOT visit is completed, study medication cannot be resumed.

6.4. Patient Completion and Overall Study Completion

Each patient will participate in the double-blind period for up to 28 days during screening, followed by 110 weeks of blinded treatment. At the end of the 110-week treatment period, treatment with study medication will be discontinued. Patients will return to the site for the end-of-blinded-treatment-period visit, 4 weeks after study medication has been discontinued. Thus, patients will participate in the study for a total of approximately 118 weeks.

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 114.

Patients who successfully complete the Week 114 visit will complete the assessments listed in the Schedule of Events (Table 15.1-1 and Table 15.1-2). The visit data, including disposition of the patient, will be recorded on the appropriate eCRF.

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

Eligible patients may participate in the open-label extension period for up to 156 weeks. If sparsentan becomes commercially available during the extension period, patients may transition out of the study onto commercial product before the end of the open-label extension period.

The study will be considered complete when the last patient completes his/her final visit.

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 will also be discontinued from the study if the study is terminated (see Section 13.4.5).

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

- Death
- Voluntary withdrawal of patient consent (complete withdrawal of consent requires a patient's documented refusal of all methods of follow-up noted in the informed consent form [ICF])
- Termination of the study by the Sponsor, 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 (ie, through Week 114). The need for additional intervention for the treatment of IgAN or the occurrence of safety endpoints are not criteria for discontinuation from the study. A patient who permanently discontinues from the study during the double-blind period will, if possible, complete the ET assessments listed in the Schedule of Events (Table 15.1-2) as close as possible to the patient's last dose of study medication. Alternatively, if the last dose of study medication is on a scheduled study visit (eg, Week 58), that visit will be considered an EOT/ET visit, and EOT assessments will be performed. If an EOS visit is completed during the double-blind or open-label extension period (including the Sub-study), respectively, study medication (including dapagliflozin) cannot be resumed. The visit data, including the primary reason for premature discontinuation from the study, will be recorded on the ET 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 his/her 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

Patients who provide written informed consent and meet eligibility criteria will undergo baseline assessments and be randomized into the study. 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 have 1 additional measurement on that variable through the Central Laboratory to assess patient eligibility.

7.1. Criteria for the Double-blind Period

7.1.1. Inclusion Criteria for the Double-blind Period

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

1. The patient is willing and able to provide signed informed consent.
2. The patient is male or female, aged ≥18 years.
3. The patient has biopsy-proven IgAN. The biopsy may have been performed at any time in the past.
4. The patient has a urine protein excretion value ≥1.0 g/day at screening.
5. The patient has an eGFR value of ≥30 mL/min/1.73 m^2 at screening.
6. The patient has been on a stable dose of ACEI and/or ARB therapy for at least 12 weeks prior to screening that is:
   A. the patient's maximum tolerated dose and
   B. at least one-half of the MLD (see Appendix B, Section 15.2.3 for minimum ACEI/ARB daily dose requirements at screening).
7. In the Investigator's opinion, the patient's blood pressure has been managed in accordance with standard-of-care using ACEI and/or ARB therapy as described in inclusion criterion 6 and additional anti-hypertensive agents if needed. At screening, the patient's systolic blood pressure must be ≤150 mmHg and diastolic blood pressure must be ≤100 mmHg.
8. The patient is willing to undergo a change in ACEI and/or ARB and anti-hypertensive medications.
9. 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 (including open-label sparsentan). 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. 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 2) and after.

7.1.2. Exclusion Criteria for the Double-blind Period

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

1. The patient has IgAN secondary to another condition (eg, systemic lupus erythematosus, liver cirrhosis) or Henoch-Schonlein purpura.
2. The patient has cellular glomerular crescents present in >25% of glomeruli on renal biopsy within 6 months prior to screening.
3. The patient has a CKD in addition to IgAN.
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 taking any systemic immunosuppressive medications (including corticosteroids) for >2 weeks within 3 months prior to screening.
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 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.
10. 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.
11. The patient has a screening hematocrit value <27% (0.27 Volume/Volume) or hemoglobin value <9 g/dL (90 g/L).
12. The patient has a screening potassium value of >5.5 mEq/L (5.5 mmol/L).
13. The patient has a history of alcohol or illicit drug use disorder (as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition).

14. 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.
15. The female patient is pregnant, plans to become pregnant during the course of the study, or is breastfeeding.
16. 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.
17. 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 for participation in the blinded study period up to 2 additional times. Patients who are re-screened for participation in the blinded study period 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 Period

7.2.1. Inclusion Criteria for the Open-label Extension Period

Based on assessments at the Week 110 and Week 114 visits, a patient must meet all of the following criteria to be eligible for the open-label extension period:

1. The patient completed participation in the double-blind period, including the Week 114 visit.
2. The patient is willing and able to provide signed informed consent for participation in the open-label extension period.
3. The patient did not permanently discontinue study medication during the double-blind period (see Section 6.3.2).
4. 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. 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 the Week 114 visit until 90 days after the last dose of study medication. (For details, see Double-blind Period Inclusion Criterion 9).

7.2.2. Exclusion Criteria for the Open-label Extension Period

Based on assessments at the Week 110 and Week 114 visits, a patient who meets any of the following criteria will be excluded from the open-label extension period:

1. The patient has progressed to ESRD requiring RRT.
2. The patient developed any criteria for discontinuation of study medication or discontinuation from the study as defined in Section 6.3.2 or Section 6.5, respectively, between Week 110 and Week 114.
3. The patient was unable to initiate, or developed contraindications to, treatment with RAAS inhibitors between Week 110 and Week 114.
4. The patient has an eGFR value of ≤20 mL/min/1.73 m^2 at Week 110.
5. The patient has a potassium value of >5.5 mEq/L (5.5 mmol/L).
6. The female patient is pregnant or is breastfeeding.

NOTE: If, in the Investigator's opinion, the eGFR value at Week 110 is deemed unlikely to be representative of the patient's true status, the Investigator may repeat the eGFR measurement prior to Week 114 through the Central Laboratory to assess patient eligibility. Patients with an eGFR value of <30 mL/min/1.73 m^2 will require close monitoring of eGFR and serum potassium throughout the open-label extension period.

7.3. Criteria for the Sparsentan + SGLT2 Inhibitor Sub-study

7.3.1. Inclusion Criteria for the Sparsentan + SGLT2 Inhibitor Sub-study

Based on assessments at a regularly scheduled open-label extension visit, a patient must meet all of the following criteria to be eligible for the Sub-study:

1. The patient is participating in the open-label extension and is willing and able to provide signed informed consent for participation in the open-label extension period Sub-study.
2. The patient has a urine protein excretion value of ≥0.3 g/day.
3. The patient has an eGFR of ≥25 mL/min/1.73m^2.
4. The patient is on a stable dose of sparsentan for ≥8 weeks in the open-label extension period that is the maximum tolerated dose.
5. The patient has ≥12 weeks of the study remaining.
6. The patient fulfils local requirements, recommendations and does not have contraindications for on-label prescription of dapagliflozin.

7.3.2. Exclusion Criteria for the Sparsentan + SGLT2 Inhibitor Sub-study

Based on assessments at an open-label extension visit, a patient who meets any of the following criteria will be excluded from participation in the open-label extension period – Sub-study:

1. The patient has progressed to ESRD requiring RRT.
2. The patient has initiated or changed dose of a systemic immunosuppressive medication (including systemic steroids) within 12 weeks.
3. The patient has been taking an SGLT2 inhibitor within 12 weeks.
4. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the Sub-study.

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 investigational product (sparsentan), active control (irbesartan), or SGLT2 inhibitor (dapagliflozin) within the context of the Sub-study, 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 150 mg irbesartan tablets over-encapsulated (blinded) with size 00 capsules.

The doses of sparsentan to be administered in the open-label extension period will be dispensed as 200 mg or 400 mg tablets, when available. Irbesartan will not be administered in the open-label extension period.

If patient is enrolled in the Sub-study and randomized to the SGLT2 inhibitor treatment group, Investigator will instruct patient on the dispensing, daily dose, and administration according to us Prescribing Information (USPI), Summary of Product Characteristics (SmPC), or local label. (see Section 8.1.3 for additional details).

8.1.1. Treatments Administered During the Double-blind Period

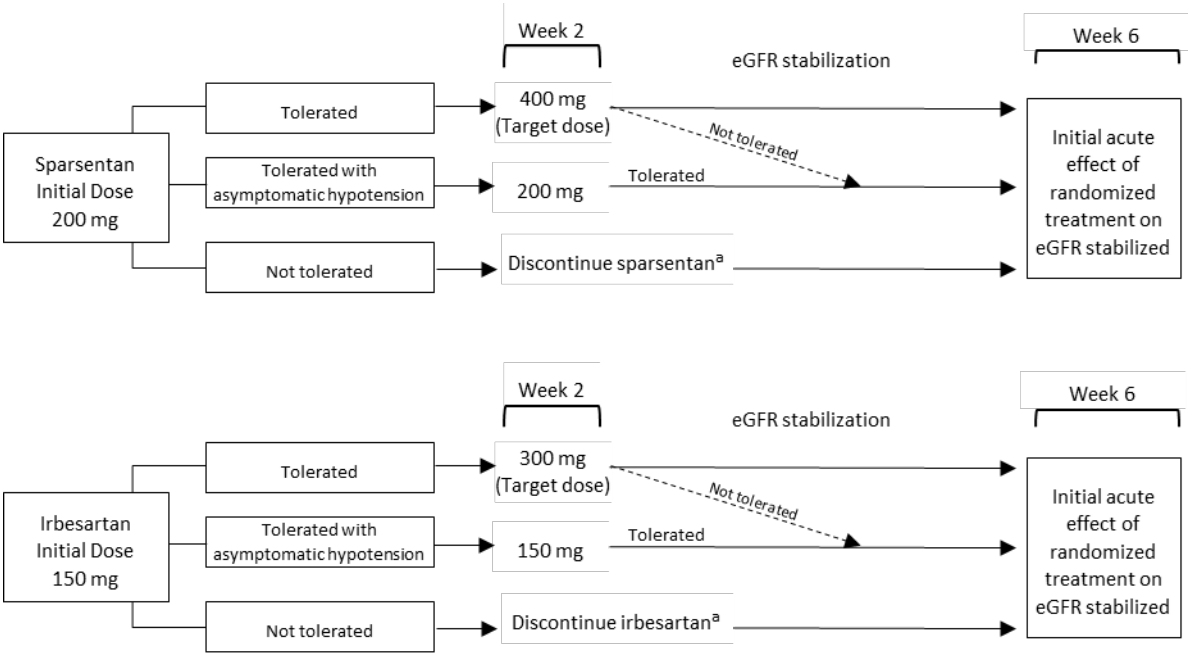
Allowed doses during the double-blind period and the number of capsules to be used for those doses are shown in Table 2. The blinded dose titration scheme is provided in Figure 4. The full daily dose of study medication is preferred to be taken prior to the morning meal, with the exception of the day of a study visit. On the day of a study visit, in both the double-blind and open-label extension periods (as specified in Section 15.1), including the Day 1/Randomization visit of the double-blind period, patients will take their study medication in the clinic after the pre-dose PK blood sample has been obtained.

Standard-of-care treatment (ACEI and/or ARB therapy) and any other prohibited concomitant medications will be discontinued before the randomization (Day 1) visit. The final dose of an ACEI and/or ARB therapy should be taken on the day before the randomization (Day 1) visit (see Section 15.2.1) (unless they permanently discontinue study medication during the study; see Section 6.3.2. On Day 1, patients will be randomly assigned to either sparsentan (investigational product) or irbesartan (active control) and take study medication. Patients who forget and take their current ACEI and/or ARB on Day 1 will take their first dose of study medication the following day at home.

Table 2. Sparsentan and Irbesartan Doses Allowed During the Double-blind Period

	Number Capsules	Randomized to:	
		Sparsentan (mg)	Irbesartan (mg)
Initial (or reduced) dose	1	200	150
Target dose	2	400	300

Figure 4. Sparsentan and Irbesartan Blinded Dose Titration Scheme



Abbreviations: EOT = End-of-Treatment; eGFR = estimated glomerular filtration rate; ET = Early Termination.

[a] Patients who do not tolerate the initial dose will be encouraged to re-start study medication throughout the double-blind period, as long as an EOT/ET visit is not completed. Patients who do not tolerate study medication should continue in the double-blind period even if they permanently discontinue study medication.

Dose tolerance is defined as systolic blood pressure >100 mmHg and diastolic blood pressure >60 mmHg after 2 weeks, and no AEs (eg, worsening edema) or laboratory findings (eg, serum potassium >5.5 mEq/L [5.5 mmol/L]).

The goal is to titrate to the target dose at Week 2. Patients will receive the initial dose (ie, one-half the target dose) for the first 2 weeks after randomization. At the Week 2 visit, the Investigator will evaluate dose tolerance in a blinded manner. The Investigator may titrate the patient's dose up to the target dose based on blood pressure and lack of AEs at the Week 2 visit or may titrate the patient's dose up to the target dose after the Week 2 laboratory results are available (ie, between the Week 2 and Week 4 visits). If the Investigator titrates the patient's dose at Week 2 based on blood pressure and lack of AEs, the patient's dose may be reduced once the Week 2 laboratory results are available (ie, between the Week 2 and Week 4 visits).

Patients who tolerate the initial dose after 2 weeks but display asymptomatic blood pressure values ≤100/60 mmHg or present with clinical symptoms of orthostatic hypotension will continue on the initial dose after the Week 2 visit without titrating up to the target dose. At the Week 2 visit, patients who do not tolerate the initial dose for any reason may discontinue study medication.

Patients who discontinue study medication (at any point in the double-blind period) should continue in the double-blind period even if they permanently discontinue study medication and, if appropriate, will be encouraged to re-start study medication throughout the double-blind period at the Investigator's discretion (see Section 6.3.1 and Section 6.3.2). However, if an EOT visit is completed, study medication cannot be resumed. Dose titrations (up or down) are

permitted at any time at the Investigator's discretion, and if appropriate, additional safety testing may be performed.

Dose modification is permitted as presented in Section 8.3.2.

8.1.2. Treatments Administered During Open-label Extension Period

The full daily dose of open-label sparsentan is preferred to be taken prior to the morning meal. Allowed doses during the open-label extension period are shown in Table 3.

Table 3. Sparsentan Doses Allowed During the Open-label Extension Period

	Number of Tablets	Sparsentan (mg)
Initial dose at Week 114	1	200
Target dose at Week 116[a]	2 or 1[b]	400

[a] Tolerability to the initial dose will be assessed at Week 116. Patients who tolerate the initial dose will have their dose titrated to the target dose at Week 116, 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 either 200 mg or 400 mg per day throughout the open-label extension period for safety or tolerability reasons, at the Investigator's discretion.

[b] At Week 116, the patient's dose will be titrated to either 2 tablets (2 × 200 mg) or 1 tablet (1 × 400 mg, when available).

At the Week 114 visit, the starting dose is 1 tablet (200 mg) for all patients. At Week 116, the patient's dose will be titrated to either 2 tablets (2 × 200 mg) or 1 tablet (1 × 400 mg, when available), if tolerated and determined safe by the Investigator. The Investigator will evaluate dose tolerance (as defined in Section 8.1.1) prior to titrating up to the target dose. If the patient tolerates the initial dose, the patient's dose will be titrated to the target dose at Week 116. Patients who display asymptomatic blood pressure values ≤100/60 mmHg or who present with clinical symptoms of orthostatic hypotension but otherwise tolerate the initial dose will continue without titrating up to the target dose after the Week 116 visit.

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

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

8.1.3. Treatments Administered During the Sparsentan + SGLT2 Inhibitor Sub-study

Sparsentan dosing will continue as outlined for the open-label extension period (Section 8.1.2). Patients randomized to the dapagliflozin treatment group will receive instructions on dosing from their Investigator and should commence dosing within 14 days of the study visit assessing eligibility (Screening/Randomization/Day 1 visit for the Sub-study). The target dose and recommended starting dose for patients is the maximum labeled dose (10 mg/day), however, Investigators may use their discretion to initiate dosing at 5 mg/day on a case-by-case basis. For patients assigned to receive dapagliflozin, an additional unscheduled visit may be conducted

following 7 to 14 days of dosing for safety monitoring. Dapagliflozin dose may be adjusted at any stage based on tolerability at the discretion of the Investigator and additional safety visits conducted as deemed necessary.

Secondarily, and in accordance with all phases of the trial, blood pressure will be maintained as close as possible to a target level of 125/75 mmHg. Treatment with additional anti-hypertensive agents is encouraged during the study, with the exception of those that inhibit the RAAS (ACEIs, aldosterone blockers, aliskiren, or ARBs) and endothelin systems (ERAs; eg, ambrisentan and bosentan). Prohibited concomitant medications are further discussed in Section 15.2.1. In cases of hypotension, it is recommended that the dose of additional anti-hypertensives be lowered or withdrawn prior to consideration of changes in the dapagliflozin dose. Changes to sparsentan dose based on blood pressure are recommended only once all other options have been explored.

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 include, 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 period, 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 bottle will have a label that will contain, but will not be limited to, the following information: 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 period, when available; details on packaging and labeling of sparsentan 400 mg tablets will be included in the Pharmacy Manual. Dapagliflozin 5 mg tablets will be used during the Sub-study, with packaging and labeling according to USPI, SmPC, or local label.

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°C and 25°C (68°F to 77°F); excursions between 15°C and 30°C (59°F and 86°F) are allowed. Dapagliflozin should be stored according to the USPI, SmPC, or local label. 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 number of study medication capsules in the double-blind period, or the appropriate number of sparsentan tablets in the open-label extension period, 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. On the day of each study visit in both the double-blind and open-label extension periods (as specified in Section 15.1), including the Day 1/Randomization visit of the double-blind period, patients will take their study medication in the clinic after the pre-dose PK blood sample has been obtained.

If an on-site visit by the patient is not feasible due to challenges related to the coronavirus disease 2019 (COVID-19) pandemic, study medication may be transported directly to a patient via courier to ensure uninterrupted treatment, if necessary. It is the responsibility of the Investigator to document this process in the patient's source documents. Refer to the Pharmacy Manual for additional details.

Patients will be instructed to swallow the sparsentan capsules or tablets whole and not to open, break, chew, crush, or split the capsule or 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), starfruit (carambola), or pomelo/shaddock throughout the study.

Patients will be instructed that if they miss a dose of sparsentan 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 sparsentan 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 given day.

In the Sub-study, patients will be instructed to follow the recommendations for how to take dapagliflozin found on the USPI, SmPC, or local label.

8.3. Dosing Considerations

8.3.1. Dose Selection Rationale

Sparsentan at doses up to 800 mg have been studied in approximately 370 healthy volunteers, and in approximately 330 patients with Stage 1 hypertension, Stage 2 hypertension, or FSGS. In these studies, sparsentan has exhibited a favorable safety profile.

For patients with IgA nephropathy, first-line treatment consists of RAAS inhibitor treatment. Sparsentan is intended as a second-line treatment for patients who do not achieve proteinuria levels <1 g/day with optimized RAAS inhibitor therapy. The 400 mg sparsentan dose was chosen for this study as an appropriate target dose for treatment of IgAN, based upon the knowledge of sparsentan PK characteristics and the perceived benefit/risk profile in this progressive disease. At a target dose of 400 mg, sparsentan is anticipated to provide significant reduction in proteinuria and reduce the rate of eGFR loss compared to 300 mg of irbesartan, with a safety and tolerability profile comparable to that of RAAS inhibitor therapy.

At the beginning of the double-blind period, patients will initially receive half of the targeted dose (defined as the initial dose) of either sparsentan or the active control, irbesartan. At Week 114, the starting dose for the open-label extension period is 1 tablet of sparsentan (200 mg) for all patients. At Week 116, the patient's dose will be titrated to either 2 tablets (2 × 200 mg) or 1 tablet (1 × 400 mg, when available), if tolerated and determined safe by the

Investigator. 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 systolic blood pressure values ≤100 mmHg, diastolic blood pressure values ≤60 mmHg, or present with clinical symptoms of orthostatic hypotension but otherwise tolerate the initial sparsentan dose will continue after the Week 2 visit (or the Week 116 visit for the open-label extension period) without titrating up to the sparsentan target dose. Patients whose sparsentan dose is not titrated up to the target dose at Week 2 (or Week 116) may titrate up to that dose at any time based on evaluation of the Investigator in consultation with the Medical Monitor as needed.

The KDIGO Clinical Practice Guideline for Glomerulonephritis (KDIGO 2012) recommends a blood pressure target of <125/75 mmHg when initial proteinuria is >1 g/day. The KDIGO recommendation reflects standard-of-care in the United States (US) and all other participating countries. This is the basis for the 125/75 mmHg blood pressure target in the double-blind period, with the goal of attaining comparable blood pressure levels between treatment groups.

Throughout the study (including the open-label extension period), patients will be maintained on the maximum allowed dose of sparsentan they can tolerate while secondarily maintaining blood pressure as close as possible to the target of 125/75 mmHg. To maintain blood pressure, the Investigator will be encouraged to either treat patients with additional anti-hypertensive agents (with the exception of ACEIs, aldosterone blockers, aliskiren, ARBs, or ERAs) or withdraw anti-hypertensive agents. In the case of intolerable hypotension, withdrawal of additional anti-hypertensive agents should be accomplished before considering withdrawal or dose reduction of study medication. At the discretion of the Investigator, patients may reduce their study medication dose in the double-blind period from 2 capsules/day to 1 capsule/day for safety or tolerability reasons.

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

Dapagliflozin dose may be modified at any time during the Sub-study for safety or tolerability reasons at the Investigator's discretion. In cases of hypotension, it is recommended that the dose of additional anti-hypertensives be lowered or withdrawn prior to consideration of changes in the dapagliflozin dose. Changes to sparsentan dose based on blood pressure are recommended only once all other options have been explored.

8.3.3. Treatment in Follow-up Period

Following the 110-week blinded treatment period, treatment with study medication will be discontinued for 4 weeks. At this time, the Investigator should resume standard-of-care treatment, including RAAS inhibitor treatment. Where possible, the same treatment regimen the patient was on at study entry (ie, the same ACEI and/or ARB at the same dose[s]) should be used, unless in the Investigator’s opinion, an alternative treatment approach is warranted. The Investigator may make additional adjustments in anti-hypertensive medications if considered necessary to adequately control blood pressure. Patients will return to the site for the Week 114 visit after study medication has been discontinued.

8.4. Prior and Concomitant Medications and Therapeutic Procedures

For enrolled patients, prior and concomitant medications and therapies will be collected from the 3 months prior to screening through the patient's final study visit. In addition, a comprehensive history of medications previously used for treatment of IgAN, including systemic corticosteroids or other systemic immunotherapeutic agents, will be collected. 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) in the double-blind period, based on a predefined randomization code (generated by the Sponsor or designee) via the interactive randomization technology (IRT) at the Day 1/Randomization visit. Randomized patients will be stratified by their screening eGFR value (30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and screening urine protein excretion (≤1.75 g/day and >1.75 g/day).

The Sub-study will be conducted in an open-label, randomized manner. Enrolled patients will be randomly assigned in a 1:1 ratio to receive either SGLT2 inhibitor treatment or no SGLT2 inhibitor treatment, based on a predefined randomization code (generated by the Sponsor or designee) via IRT at the Sub-study Screening/Randomization/Day 1 visit.

8.6. Blinding and Emergency Unblinding

The patient's treatment allocation for the double-blind period will remain blinded to all parties involved with the study throughout its course (including the open-label extension period) with the exception of the Data Monitoring Committee (DMC) (see Section 13.2) 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 IRT 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 also be made available through the IRT 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 for the double-blind period, each patient will be registered in the IRT and assigned a unique identification number, which will stay the same throughout the study, including the open-label extension period and Sub-study. Patients who are re-screened for participation in the blinded study period will be assigned a new patient number.

8.8. Treatment Compliance

For double-blind or open-label extension treatment compliance, the Investigator or designee should assess the patient's compliance with the study medication dosing at each visit after Day 1. The study medication compliance is defined as the ratio of the number of actual capsules or tablets taken over the number of capsules or tablets that should have been taken during the dosing period multiplied by 100. Patients will be asked to return all unused sparsentan or active control 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.

Dosing compliance for SGLT2 inhibitor treatment (dapagliflozin) in the 12-week Sub-study will be documented by ensuring all packs (bottles and blister packs) dispensed to a patient are returned and accounted for.

9. STUDY ASSESSMENTS

9.1. Schedules of Study Events

The Schedules of Study Events is located in Section 15.1.

For all study sites in Germany, the measures related to the COVID-19 pandemic or other unexpected circumstances should be restricted to the COVID-19 pandemic. If an on-site visit by the patient is not feasible due to the challenges related to the COVID-19 pandemic, or other unexpected circumstances as dictated by local public health authority requirements, Investigators/appropriately designated study staff will be allowed to perform study visits as remote study visits (eg, conducted via telephone and video conference). These contacts will be allowed at all protocol-required visits and at any time during the conduct of the study. However, Screening, Day 1/Randomization, Week 110, and Week 114 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 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 of 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 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 as dictated by local public health authority requirements, a verbal consent may be obtained if allowed by local regulations prior to the Home Care visit, and the signed consent form will be obtained at the next site visit. A licensed nurse will contact the patient 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, Home Care agency, and 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, 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 open-label extension periods in any situation that interrupts safety oversight.

All study sites except in Germany 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 on how to monitor and record blood pressure at home.

9.2. Study Fasting Requirements

It is strongly recommended that patients come to the study visit in a fasted state (ie, fasting for at least 8 hours prior to the visit; water is permitted during the fasting period). 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.

9.3. Screening Assessments

Screening visit assessments for the double-blind period must be performed within 28 days prior to Day 1/Randomization. Each patient will be registered in the IRT 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 period; see Section 8.7). Patients who fail screening for any reason may be re-screened for participation in the blinded study period up to 2 additional times. Patients who are re-screened for participation in the blinded study period will repeat all screening procedures and will be re-registered in the IRT and assigned a new patient number. Patients will also repeat the informed consent procedure at each re-screening.

9.4. Medical History and Demographics

Concomitant medications/therapies will be obtained 3 months prior to screening. A complete medical history will be obtained from the patient at screening, along with concomitant medications/therapies at enrollment and all prior treatments for IgAN, including systemic corticosteroids or other systemic immunotherapeutic agents. Demographic characteristics will include age, race, ethnicity, and sex.

9.5. Physical Examination

Physical examinations will be performed according to the Schedules of Study Events in Section 15.1. Full physical examinations will be performed at screening, Day 1, Week 58, and Week 110 visits; a symptom-directed targeted physical examination will be performed at all other visits. Peripheral edema will be assessed at all visits using the semi-quantitative scale in Appendix B (Section 15.2.4).

9.6. Vital Signs

Vital signs, including blood pressure, heart rate, temperature, respiration rate, weight, and height, will be performed according to the Schedules of Study Events in Section 15.1. Height will only be recorded at screening of the double-blind period. Vital signs should be measured prior to phlebotomies for clinical laboratory evaluations.

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; the mean of the last 2 readings will be recorded. In addition to these blood pressure measurements, measurements of blood pressure intended to detect possible orthostatic hypotension will be performed at each visit according to US Centers for Disease Control and Prevention guidelines (US CDC 2017). Heart rates will be measured with each positional blood pressure reading for orthostatic hypotension detection. This should be done after the sitting blood pressure measurements have been taken. 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. A decrease in systolic blood pressure of ≥20 mmHg or diastolic blood pressure of ≥10 mmHg in either of the standing measurements or the presence of lightheadedness or dizziness during the test is considered abnormal and may justify a change in study medication dose at the Investigator's discretion.

9.7. Electrocardiogram

Twelve-lead electrocardiograms (ECGs) will be conducted at screening for the double-blind period and at Week 110 or Week 114 visit for the open-label extension period, depending on the day/visit of ICF signing.

According to the requirements for Germany only, 12-lead ECGs will be conducted in triplicate at screening and randomization for the double-blind period, and at every visit throughout the study except Visit 4 and Visit 17, depending on the day/visit of ICF signing.

9.8. Clinical Laboratory Assessments

For the double-blind and open-label extension periods, it is strongly recommended that patients should remain fasted until their blood samples have been collected (ie, fasting for at least 8 hours prior to the visit; water is permitted during the fasting period). 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 Schedules 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 patients with clinically significant abnormal test results will be followed regularly until the values return to normal ranges, until a valid reason other than study medication-related AE is identified, 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 with kits for the home collection of quantitative urinalysis samples (24-hour collection). They will also receive full instructions regarding the proper collection of those samples.

Protein and albumin excretion, creatinine, sodium, and urea will be determined from the 24-hour urine samples as specified in the Schedules of Study Events (Section 15.1). The eGFR for each time point (visit) will be determined using the Chronic Kidney Disease Epidemiology (CKD-EPI) formula (Levey 2009), which is as follows:

$$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

where
S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1

If necessary, due to the challenges related to the COVID-19 pandemic, a patient may transport the 24-hour urine samples to the site via courier. If a patient cannot come into the site, safety laboratory assessments may be tested at a local laboratory. It is the responsibility of the Investigator to document this process in the patient's source documents.

According to current international standards, the CKD-EPI formula is the recommended method for estimating GFR in adults across the baseline GFR range intended for the population in this study and is calculated based on 4 required variables: serum creatinine, age, sex, and race.

The list of clinical laboratory analytes to be tested is presented in Section 15.2.5.

9.9. Contraception Requirement and Pregnancy Testing

WOCBP 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.

WOCBP must not become pregnant, and so beginning at menarche, they 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 (including open-label sparsentan). Highly reliable contraception methods are defined as those that can achieve a failure rate of <1% per year; these methods include:

- Stable oral, implanted, transdermal, or injected contraceptive hormones associated with inhibition of ovulation
- An intrauterine device in place for at least 3 months

One additional barrier method must also be used during sexual activity from Day 1/Randomization until 90 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 male 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 6 visit, and beginning at Week 116 through the open-label extension period. 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.

9.10. Patient-reported Outcomes

The Kidney Disease Quality of Life questionnaire and the EuroQol, 5-dimension QoL questionnaire, version 5L will be used to evaluate the effects of sparsentan (as compared to irbesartan) on health-related QoL (where available). These questionnaires should be completed prior to any other assessment at study visits.

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 period who did not complete the questionnaires at Day 1 of the double-blind period should complete them at Week 114 (as baseline assessments for the open-label extension) and throughout the open-label extension.

9.11. Pharmacokinetic Assessments

Samples enabling assessment of sparsentan and irbesartan in plasma will be taken during the double-blind period according to the Schedules of Study Events in Table 15.1-1 and Table 15.1-2. At applicable visits, 1 sample will be taken pre-dose in the clinic.

9.12. Biorepository Samples

With patient consent, blood 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.

Samples collected should be labeled for "Biorepository" and will be collected at visits specified in the Schedules of Study Events during both the double-blind and open-label extension periods

of the study, as specified in Section 15.1. Additional information is provided in the Laboratory Manual.

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 directions in the Laboratory Manual. The samples will be destroyed 5 years after the clinical study report is finalized.

9.13. Renal Biopsy Slide Scoring

Where slides or digital images from previous renal biopsies are available and with patient consent, these slides or digital images will be provided for central reader histological analysis including scoring according to the Oxford Classification of IgA nephropathy (Coppo 2014; Trimarchi 2017). This analysis may enable evaluation of the relationship between histological profile and response to treatment. Biopsy slides will be returned after central scoring.

9.14. Safety Assessments

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

10. ADVERSE EVENT REPORTING

10.1. Adverse Event

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, which 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.

All AEs, irrespective of seriousness, should be collected from the day of patient signing the informed consent until the follow-up/EOS visit in both the double-blind and open-label extension periods as specified in the Schedules of Study Events (Section 15.1).

AEs may include the following:

- 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 114 for the open-label extension period) 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 114 for the open-label extension period) that have either worsened or recurred following resolution

It is anticipated that some patients will have a worsening of the underlying condition of the disease, such as increasing proteinuria or rapidly declining renal function. Any such worsening of the underlying condition should be reported as AEs.

The patient will be evaluated for new AEs and the status of existing AEs at each study visit, including screening, 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.

10.2. Serious Adverse Event

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

10.3.1. Abnormal Liver Function Test Results

Abnormal liver function test results that meet at least one of the following criteria below will be considered AEOIs and must be reported to the Sponsor's Medical Monitor within 24 hours of awareness:

- 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.
- 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 period (ie, Week 114) 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, liver-specific alkaline phosphatase (ALP), and total bilirubin within 48 to 72 hours to confirm the abnormalities.
3. If the abnormality is confirmed by repeat results, the following should be done:
   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] and 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 the following:

- 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 of >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).

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

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.
- The ALT or AST elevations are accompanied by a total bilirubin >2 times the ULN or INR of >1.5 without initial findings of cholestasis (elevated serum liver-specific ALP).

10.3.2. COVID-19 Adverse Events

If a patient is diagnosed with COVID19 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 COVID19 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 form stating the reason the timeline was not adhered to.

10.4. Acute Kidney Injury

KDIGO guidelines for diagnosing AKI are as follows:

- Increased serum creatinine of ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours.
- Increased serum creatinine of ≥1.5 times the baseline (which is known or presumed to have occurred within the prior 7 days),
- Urine volume of <0.5 mL/kg/h for 6 hours or more (KDIGO 2012).

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 studies, 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 that 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 his/her 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 participant.
- 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 the following:

- 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 eg, 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

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

For patients who discontinue study medication (see Section 6.3.1 and Section 6.3.2) but are not withdrawn from the study, AEs will continue to be recorded until the patient completes the study (see Section 6.4 for definition of patient completion).

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

AEs will be recorded using MedDRA by System Organ Class and Preferred Term. 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.
- A completed SAE Report Form containing a detailed written description of the event along with available supporting documents (eg, discharge summary, autopsy report, and 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.
- 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 6.4), 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.

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.

SAEs 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 AE/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 and the pregnancy reporting form. 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 the 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 or the patient's partner). 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 and medical history will be coded using MedDRA. Similarly, prior and concomitant medications and concomitant therapies will be coded using the World Health Organization Drug Dictionary.

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 9.4 or later of Statistical Analysis System (SAS®). Data summaries will use descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency and percentage for categorical and ordinal variables. Unless otherwise specified, endpoints will use the last pre-treatment value available prior to the first dose of study medication as baseline. All data collected will be included in patient data listings.

This section on statistical methodology outlines the principal statistical features pertaining to the analysis of the main efficacy endpoints and summary of safety data. A more detailed statistical analysis plan (SAP) will be prepared and finalized prior to the first planned efficacy analysis.

12.2. Sample Size Justification

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

$$H_0: \Delta = 0 \text{ versus } H_1: \Delta \neq 0$$

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

Approximately 380 patients will be required to detect an underlying treatment effect in the rate of change in eGFR over 110 weeks following the initiation of randomized therapy (eGFR total slope at 2 years) of 2.9 mL/min/1.73 m^2 per year with 90% power. In addition, approximately 380 patients provide 80% power to detect a smaller treatment effect on eGFR total slope at 2 years of 2.55 mL/min/1.73 m^2 per year. Consequently, approximately 380 patients provide more than 90% power to detect an underlying treatment effect in the rate of change in eGFR over 104 weeks following the initial acute effect of randomized therapy (eGFR chronic slope at 2 years) of 3.15 mL/min/1.73 m^2 per year. With this sample size, the observed annualized treatment difference to yield a p-value of <0.02 is 1.8 mL/min/1.73 m^2 per year. These sample size and power calculations follow the method described by Dupont (Dupont 1998), with

one-sided $\alpha = 0.02$ and residual error of 5.8 mL/min/1.73 m^2 estimated from a random coefficient analysis of the Leicester University Hospital Registry. The projected treatment effects on the rate of change in eGFR were based on a meta-analysis of clinical studies in IgAN using the methodology presented by Inker (Inker 2019).

To investigate the safety and efficacy of SGLT2 inhibitors in combination with sparsentan on proteinuria in patients with IgAN, as compared to sparsentan alone, approximately 30 patients in each of the two treatment groups (total 60 patients) will be enrolled in the Sub-study. The sample size of the Sub-study is determined empirically without formal statistical assumptions.

12.3. Analysis Sets

The analysis datasets to be used for the evaluation of efficacy and safety are defined in the following sections.

12.3.1. Full Analysis Set

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

12.3.2. Primary Analysis Set

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

12.3.3. Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set is a subset of the FAS containing patients who meet study eligibility requirements and have no protocol deviations that might impact the assessment of efficacy measurements. Patients will be analyzed according to randomized treatment assignment. The PP Analysis Set will be used for sensitivity analyses relating to efficacy. The type of protocol deviations governing exclusion from the PP Analysis Set will be determined prior to study unblinding and will be detailed in the SAP.

12.3.4. Safety Analysis Set

All patients who are randomized and take at least 1 dose of randomized therapy will be included in the Safety Analysis Set. Safety analyses will be based on randomized therapy.

12.3.5. Pharmacokinetic Analysis Set

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

12.3.6. Open-label Extension Full Analysis Set

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

12.3.7. Sparsentan + SGLT2 Inhibitor Sub-study Analysis Set

All patients who are randomized in the Sub-study will be included in the Sub-study Analysis Set. All Sub-study efficacy and safety analyses will be based on the Sub-study Analysis Set.

12.4. Demographics and Baseline Characteristics

Demographic data and baseline characteristics for the FAS, PAS, PP Analysis Set, Safety Analysis Set, OLEFAS, and Sub-study Analysis Set will be summarized by treatment group using descriptive statistics.

12.5. Patient Accountability and Disposition

For the double-blind period, patient disposition will be summarized by the numbers and percentages of patients who screened, failed screening, enrolled, were randomized, received randomized treatment, completed randomized treatment, discontinued randomized treatment early (including reasons), completed the study, and discontinued from the study (including reasons). Data will be presented overall and by treatment group.

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

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

12.6. Study Medication Usage and Compliance

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

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

Compliance rates will be summarized for the Safety Analysis Set using summary statistics and numbers and percentages within categories (eg, 0-<20%, 20-<40%, 40-<60%, 60-<80%, 80-<100%, 100-<120%, ≥120%) by treatment group and overall.

Duration of treatment in weeks, defined as follows:

(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 period, compliance will be calculated using an analogous approach as above but using dosage strength instead of number of tablets. Compliance will be summarized overall for the OLEFAS.

The above approaches will be applied to UP/C and eGFR values in the open-label extension period.

12.7. Efficacy Analyses

Efficacy analyses during the double-blind period will be based on the FAS. The primary and key secondary endpoint analyses only will be repeated in the PP Analysis Set as supportive analyses.

As UP/C is a highly right-skewed variable, analyses will be performed on log-transformed data.

The eGFR for each time point (visit) will be determined using the CKD-EPI (Levey 2009) formula for adults based on age, sex, race, and serum creatinine values from the visit. The eGFR will be determined at screening and at assessment time points detailed in the Schedules of Study Events (Section 15.1).

12.7.1. Analysis of the Primary Endpoint: Change from Baseline in Proteinuria at Week 36

After approximately 280 patients have undergone the Week 36 visit, proteinuria (UP/C) data will be analyzed via a mixed-model repeated-measures analysis. Change from baseline during the double-blind period in UP/C on the log scale will be the dependent variable. Log baseline UP/C will be included as a covariate along with fixed effects for randomized treatment, time (ie, nominal visit in weeks), and randomized treatment-by-time interaction. Patient will be included as a random effect. The analysis will be stratified by the randomization strata. An unstructured covariance matrix will be assumed; if convergence issues arise, the following covariance structures will be employed in order until convergence is reached: heterogeneous Toeplitz, heterogeneous Compound Symmetry, heterogeneous first-order, auto-regressive, Toeplitz, Compound Symmetry, and first-order, auto-regressive. The treatment effect will be the contrast between sparsentan and irbesartan least squares (LS) means at Week 36. The LS means, treatment effect estimate (difference in LS means), 95% CI, and two-sided p-value will be extracted from the model. Results will be back-transformed to present treatment effects on the ratio scale.

12.7.2. Analysis of Key Secondary Efficacy Endpoints

12.7.2.1. Rate of Change in eGFR Following the Acute Effect of Randomized Therapy

The rate of change in eGFR over 52 and 104 weeks (ie, following the acute effect of randomized therapy; see Section 12.7.4) will each be analyzed via a mixed-model random coefficients analysis. Utilizing eGFR data from (i) Weeks 6 to 58 and (ii) Weeks 6 to 110, eGFR will be the dependent variable with random patient effects for intercepts and slopes. Fixed effects for randomized treatment, baseline eGFR, time (in weeks), and randomized treatment-by-time interaction will be included. The analysis will be stratified by the randomization strata. An unstructured covariance matrix will be assumed; if convergence issues arise, a first-order, auto-regressive structure will be used. The treatment effect will be the contrast between sparsentan and irbesartan marginal slope estimates. The associated slope estimates, difference in slopes, 95% CI, and two-sided p-value will be extracted from the model. Slope and the difference in slopes will be annualized for ease of presentation and interpretation.

12.7.2.2. Rate of Change in eGFR Following Initiation of Randomized Therapy

The rate of change in eGFR 110 weeks (ie, following initiation of randomized therapy) will each be analyzed via a mixed-model random coefficients analysis. Utilizing eGFR data from Day 1 to Week 110, eGFR will be the dependent variable with random patient effects for intercepts and slopes. Fixed effects for randomized treatment, baseline eGFR, time (in weeks), and randomized treatment-by-time interaction will be included. The analysis will be stratified by the randomization strata. An unstructured covariance matrix will be assumed; if convergence issues arise, a first-order, auto-regressive structure will be used. The treatment effect will be the contrast between sparsentan and irbesartan marginal slope estimates. The associated slope estimates, difference in slopes, 95% CI, and two-sided p-value will be extracted from the model. Slope and the difference in slopes will be annualized for ease of presentation and interpretation.

12.7.2.3. Type I Error Control for Efficacy Endpoints – Double-blind Period

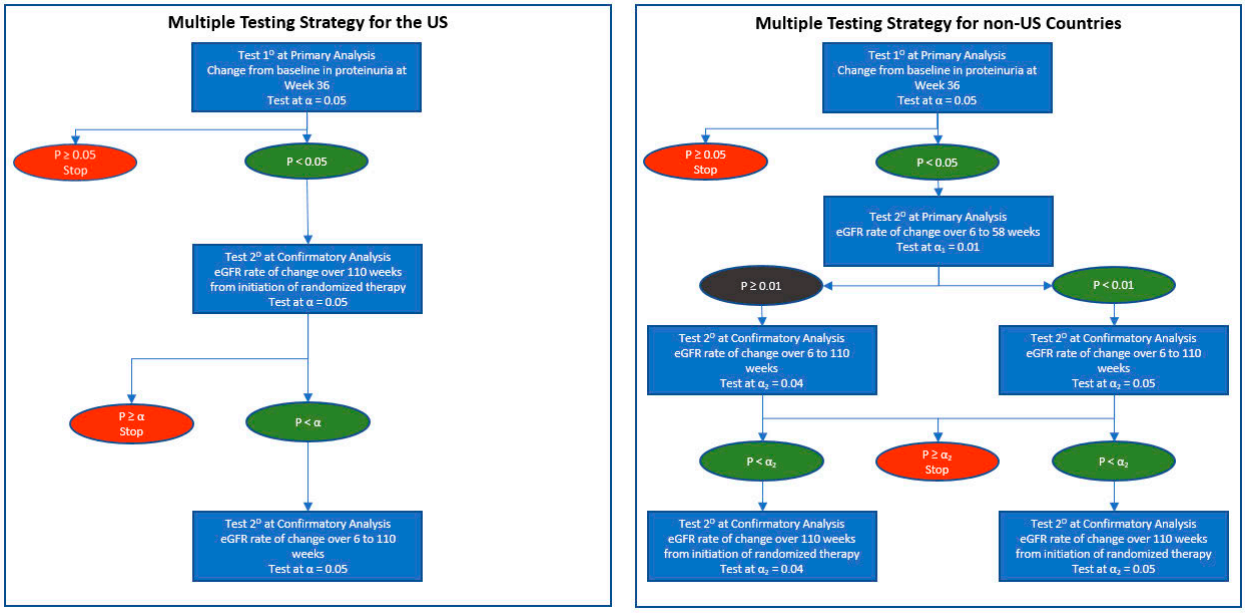
At the time of the primary analysis of change from baseline in UP/C, approximately 222 patients are projected to have eGFR data up to 58 weeks. If the analysis of UP/C at Week 36 yields a two-sided p-value <0.05, analysis of the key secondary endpoints will proceed.

For non-US countries, at the time of primary analysis of proteinuria, the key secondary endpoint of rate of eGFR rate of change over 6 to 58 weeks will be formally assessed at the 1% two-sided alpha level. Type I error control for the additional key secondary endpoints at confirmatory analysis will be governed at this time by a gate-keeper on the 6- to 58-week eGFR rate of change at the 1% level. The subsequent key secondary (confirmatory) endpoint analyses of eGFR rate of change over 6 to 110 weeks and eGFR rate of change over 110 weeks following initiation of randomized therapy will be tested sequentially and be assessed at the 4% two-sided alpha level if the 6- to 58-week eGFR rate of change analysis fails to achieve p<0.01; otherwise, subsequent key secondary (confirmatory) endpoint analyses will be assessed at the 5% two-sided alpha level.

For the US, at the time of primary analysis of proteinuria, the endpoint of rate of change over 58 weeks will not be formally tested. The key secondary (confirmatory) endpoint analyses of eGFR rate of change over 110 weeks following initiation of randomized therapy and eGFR rate of change over 6 to 110 weeks will be tested sequentially and assessed at the 5% two-sided alpha level.

The 2 confirmatory endpoints are intended to support regulatory submissions in the US (rate of change in eGFR over 110 weeks following initiation of randomized therapy) and non-US countries (6- to 110- week eGFR rate of change); hence, no further multiplicity adjustment is necessary. The Type I error control framework for the primary proteinuria and key secondary endpoints for US and non-US countries are displayed in Figure 5. At the time of the final analysis, if all the key secondary endpoints achieve statistical significance, the other secondary endpoints will be statistically tested at the available alpha. For all other supportive efficacy endpoints, nominal p-values will be presented without Type I error control.

Figure 5. Type I Error Control for the Primary and Key Secondary Efficacy Endpoints



Abbreviations: eGFR = estimated glomerular filtration rate; US = United States

12.7.3. Primary and Sensitivity Analyses to Address Missing Data in the Primary and Key Secondary Efficacy Endpoints

For the primary analysis of the primary endpoint and key secondary endpoints of eGFR change from baseline and slope, missing data will be imputed using the multiple imputation procedure (Ouyang 2017; Rubin 1987). The SAP will provide full detail of the methodologies that will be used to execute primary and sensitivity analyses to assess the influence of missing primary and/or key secondary endpoint data. Briefly, these methodologies will include multiple imputation under an assumption of missing not at random and tipping-point analyses to explore how extreme the difference between randomized treatments would have to be among patients with missing data to overwhelm the treatment effect obtained in the primary and key secondary endpoint analyses described above. In these analyses, the multiple imputation approach will be expanded to allow for varying impact of missing data by incorporating a shift parameter in the imputation model. The range of values for the shift parameter will explore the varying missing data assumptions, including the scenario where the imputation model is completely based on the control group (ie, control-based imputation).

12.7.4. Analyses of Other Efficacy and Exploratory Endpoints

The other efficacy endpoints are provided in Section 6.1.1.3, and exploratory endpoints are provided in Section 6.1.2.

The following endpoints will be analyzed using a mixed-model repeated-measures analysis as described for the primary endpoint (see Section 12.7.1):

- The mean change from baseline over time for eGFR and urine protein excretion, urine albumin excretion, UA/C, and UP/C based on a 24-hour urine sample.

- The mean change from baseline in QoL, measured via PRO at each visit.
- Changes from baseline in blood pressure at each visit.

The change from baseline to 4 weeks post-cessation of randomized treatment (114 weeks) will be analyzed via analysis of covariance. The dependent variable will be the change from pre-treatment baseline eGFR at Week 114, 4 weeks following planned discontinuation of randomized treatment. Fixed effects for randomized treatment and baseline eGFR will be included. 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.

Change from baseline in eGFR at 6 weeks post-randomization will be analyzed using analysis of covariance on the change in eGFR from randomization to Week 6; this analysis will be performed to assess the acute effect of randomized treatment. The change in eGFR from randomization to Week 6 will be the dependent variable, with a fixed effect for randomized treatment and baseline eGFR included as a covariate. 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. Similarly, the change from EOT in eGFR at 4 weeks following cessation of treatment will be analyzed using analysis of covariance; the dependent variable will be the change from EOT.

The following endpoints, considered as simple binary outcomes, will be analyzed using a logistic regression analysis with a fixed effect for randomized treatment and baseline eGFR included as a covariate. The analysis will be stratified by the randomization strata. The treatment effect estimate from the model will be the contrast between sparsentan and irbesartan log odds. The treatment effect estimate, and its 95% CI will be back-transformed to provide results on the odds ratio scale, and the associated two-sided p-value will be presented as follows:

- The proportion of patients achieving a urinary protein excretion of <0.3 g/day up to Week 110.
- The proportion of patients achieving a urinary protein excretion of <1.0 g/day up to Week 110.
- The proportion of patients requiring systemic immunosuppressive medication during the study.
- The frequency of hospitalizations (for any reason and for reasons related to the kidney).

The proportion of patients reaching a confirmed 40% change from baseline in eGFR, ESRD, or death will be analyzed via PROC PHREG in SAS in terms of the time to the first of a confirmed 40% change from baseline in eGFR, ESRD, or death using a Cox regression model stratified for the randomization stratification factors and with a fixed effect term for randomized treatment. The hazard ratio along with its 95% CI and two-sided p-value will be provided. The data will also be displayed by randomized treatment group using Kaplan-Meier estimates of the cumulative density function.

The use of systemic immunosuppressive medication and the frequency of hospitalizations will also be analyzed in terms of the number of systemic immunosuppressive medications and the

number of hospitalizations for any reason per patient, using a Negative Binomial regression model via PROC GENMOD in SAS. The model will be stratified for the randomization stratification factors and will include a fixed effect term for randomized treatment. The analyses will be adjusted for duration of exposure to randomized treatment. Estimated event rates will be extracted from the model for each randomized treatment. The treatment effect will be presented as the ratio of event rates together with the associated 95% CI and two-sided p-value.

The total duration of hospitalizations for any reason per patient will be further analyzed using analysis of covariance with a fixed effect term for randomized treatment and baseline eGFR included as a covariate. The analysis will be stratified by the randomization factors. 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.

The proportion of patients with hematuria at each visit will be analyzed using a generalized, mixed-model, repeated-measures analysis using PROC GLIMMIX in SAS. Fixed effects will be included for baseline eGFR value (30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and urine protein excretion (≤1.75 g/day and >1.75 g/day), as well as for randomized treatment, visit, and randomized treatment-by-time interaction. Patient will be included as a random effect. A logit link function will be used with distribution set to binomial. An unstructured covariance matrix will be assumed; if convergence issues arise, a first-order, auto-regressive structure will be used. Treatment effect estimates will be extracted from the model at each visit in terms of the difference between randomized treatments in log odds, together with the associated 95% CI and two-sided p-values. Treatment effects and CIs will be back-transformed to provide results on the odds ratio scale.

12.8. Safety Evaluation

Descriptive statistics will be used to summarize the safety data by randomized treatment group for the double-blind period. All safety evaluations will be conducted based on the Safety Analysis Set. Observed data will be listed by patient.

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. Body weight will be summarized as changes from baseline.

The presence and staging of edema will be summarized by frequency counts and percentages based on semi-quantitative evaluation of edema findings (see Section 15.2.4). A shift table indicating changes in edema from baseline to each postbaseline 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 pre-specified in the SAP. Vital sign abnormalities for each treatment will be summarized using shift tables.

12.8.2. Clinical Laboratory Tests

Clinical laboratory parameters will be measured at baseline and postbaseline visits. Each continuous laboratory variable will be summarized in terms of changes from baseline by randomized 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

All AEs will be coded using MedDRA by System Organ Class and Preferred Term. AEs 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, by severity, and by relationship to study medication. The number and percentage of patients reporting serious TEAEs, TEAEs leading to treatment discontinuation, TEAEs of interest, and cardiovascular-related TEAEs (including those resulting in death) will also be summarized for each treatment group by MedDRA System Organ Class and Preferred Term.

12.9. Other Analyses

12.9.1. Prior and Concomitant Medications

Concomitant medications and therapies will be coded using the World Health Organization Drug Dictionary. The incidence of prior and concomitant medications and therapies will be listed and summarized by randomized treatment group using frequency and percentage for the double-blind period and separately for the open-label extension period.

12.9.2. Pharmacokinetics

Trough plasma levels for sparsentan and irbesartan will be summarized by visit using descriptive statistics.

12.10. Interim Analysis

An unblinded interim analysis will be performed 36 weeks after randomization of at least 280 patients to evaluate the primary efficacy endpoint.

12.11. Analyses for the Open-label Extension Period

Analysis of endpoints for the open-label extension period will be performed using the methods described in Section 12.7, Section 12.8, and Section 12.9, as appropriate.

Efficacy and safety endpoints for the open-label extension period will be summarized using descriptive statistics and presented overall and by original randomized treatment based on the OLEFAS. Analyses using baselines other than Week 114 (eg, prior to the first dose of study medication in the double-blind period) may be explored; details will be provided in the SAP.

12.12. Analyses for the Sparsentan + SGLT2 Inhibitor Sub-study

Sub-study data analysis will be conducted after approximately 60 patients completed the Sub-study.

Safety and efficacy endpoints for the Sub-study will be summarized using descriptive statistics and will be presented by the Sub-study randomized treatment group and overall based on the Sub-study Analysis Set.

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 GCP, 1996; ICH Guidelines for Safety Data Management, 1994; the US Code of Federal Regulations (CFR 21 Parts 50, 56, and 312); and the European Union 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). Documentation of any applicable approval(s) and the approved ICF will be received by the Sponsor or its designee prior to enrollment of patients and release of study medication.

13.2. Data Monitoring Committee

This 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 bi-annually 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 designees 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 treatment discontinuation. 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, CFR 21 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, CFR 21 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, CFR 21 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 ICF and when obtaining consent from the patient. 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 using an IRB/IEC-approved consent form.

The Investigator will ensure that each patient 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 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 signed ICF will be obtained from patients who participate in the open-label extension period. A separate signed ICF will be obtained from patients who participate in the Sub-study.

If necessary, due to the challenges related to the COVID-19 pandemic, a patient may provide informed consent 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 process within the source documents. The patient 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 patient outcomes. 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 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. Non-compliance 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 the challenges related to the COVID-19 pandemic, monitoring activities may be performed remotely as dictated by local public health authority requirements.

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 that 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 study site does not randomize any patients into the double-blind period of the study, has no patients who participate in the open-label extension period, and has no patients participating in the open-label extension period who 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 EOS procedures.

13.4.6. Study Medication Control

The following section applies to sparsentan and active control medication as well as the dapagliflozin, which will be supplied by the Sponsor.

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

The following applies to sparsentan and active control medication as well as the dapagliflozin, which will be supplied by the Sponsor.

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

The following applies to sparsentan and active control medication as well as the dapagliflozin for the Sub-study.

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 his/her designee.

13.4.7. Product Handling and Complaints Reporting

The following applies to sparsentan and active control medication as well as the dapagliflozin for the Sub-study.

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.

13.4.8. 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.

13.4.9. 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.

The Investigator will maintain a list of patient names and identifying information (eg, patient hospital number, and unique patient number). This list will not be collected by the Sponsor.

The written participant information sheet will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data protection laws. All data that is computer processed by the Sponsor or designee will be identified only by unique patient number/randomization code/patient initials/site number.

When personal patient data are stored in or processed by computer, the data must be protected to prevent their disclosure to unauthorized third parties. Pertinent sections of national data protection laws will be complied with in full, according to the country of conduct.

The ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IEC/IRB may require direct access to parts of the hospital or study site records relevant to the study, including patient medical history.

A description of this study will be available on http://www.clinicaltrials.gov, as required by US law. However, no personal patient information will be included on this website.

13.4.10. Clinical Study Report

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

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15. APPENDICES

15.1. Appendix A: Schedules of Study Events

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

Table 15.1-1. Double-blind Period: Schedules of Study Events from Screening Through Week 36

	Screening	Randomization	Blinded Treatment Period					
Week	--	**Day 1**	**Week 2**	**Week 4**	**Week 6**	**Week 12**	**Week 24**	**Week 36**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Visit Window	**28 Days Prior to Day 1**	--	**14 ± 5 days**	**± 5 days**	**± 5 days**	**± 7 days**	**± 14 days**	**± 14 days**
Informed Consent	X							
Inclusion/Exclusion	X							
Medical History	X							
Demographics	X							
Full Physical Examination	X	X						
Targeted Physical Examination			X	X	X	X	X	X
Peripheral Edema Assessment[a]	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X
Screening Tests[c]	X							
Clinical Laboratory Assessments Panel A[d]	X	X			X	X	X	X
Clinical Laboratory Assessments Panel B[e]			X	X				
Lipid Panel[f]	X[f]				X	X	X	X
NT-proBNP	X		X		X	X	X	X
Aldosterone, Renin		X			X	X	X	
Endothelin		X			X	X	X	
Biorepository Samples (blood and urine, if consented)		X				X		X
Coagulation Tests (Prothrombin Time, INR)	X				X		X	
Quantitative urinalysis (24-hour collection)[g]	X	X		X	X	X	X	X
Calculate eGFR[h]	X	X	X	X	X	X	X	X

	Screening	Randomization	Blinded Treatment Period					
Week	--	**Day 1**	**Week 2**	**Week 4**	**Week 6**	**Week 12**	**Week 24**	**Week 36**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Visit Window	**28 Days Prior to Day 1**	--	**14 ± 5 days**	**± 5 days**	**± 5 days**	**± 7 days**	**± 14 days**	**± 14 days**
PK plasma levels (sparsentan, irbesartan)[i]					X	X		X
Pregnancy Test[j]	X	X	X	X	X	X	X	X
QoL Questionnaire[k]		X					X	
12-lead Electrocardiogram[l]	X							
Dispense Urine Pregnancy Tests[m]					X	X	X	X
Study Medication Dispensing[n]		X	X	X	X	X	X	X
Study Medication Accountability			X	X	X	X	X	X
Randomization		X						
Adverse Event Assessment	----------Continuous Monitoring ----------							
Concomitant Medications/Therapies	----------3 Months prior to screening followed by Continuous Monitoring ----------							

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EOT = End-of-Treatment; EQ-5D-5L = EuroQol 5-dimension, 5-level Quality of Life questionnaire; HDL = high-density lipoprotein; INR = international normalized ratio; IRT = interactive randomization technology; KDQoL-36 = Kidney Disease Quality of Life Questionnaire; 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; PK = pharmacokinetics; QoL = Quality of life; SF-12 = 12-Item Short Form Health Survey (QoL questionnaire); WBC = white blood cell; WOCBP = women of childbearing potential.

[a] Peripheral edema assessment guidance provided in Section 15.2.4.

[b] Vital signs should 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. In addition to these blood pressure measurements, measurements of blood pressure intended to detect possible orthostatic hypotension will 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 (height measured only at screening) will also be recorded. Heart rates will be measured with each positional blood pressure reading for orthostatic hypotension detection.

[c] Includes hepatitis B surface antigen, hepatitis B "e" antigen, anti-hepatitis C antibody, hepatitis C ribonucleic acid (performed if anti-hepatitis C antibody is positive), drug/alcohol screen, and plasma follicle-stimulating hormone level (in females to confirm menopausal status only).

[d] Includes clinical chemistry (serum sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, phosphate, glucose, hemoglobin A1c, cystatin, uric acid, BUN, creatinine [including calculation of eGFR], bilirubin [total, direct, and indirect], ALT, AST, ALP, gamma glutamyltransferase, creatine kinase, amylase, and lipase); hematology (red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, WBC, and WBC differential [neutrophils, eosinophils, basophils, lymphocytes, and monocytes, percentage and absolute]); and routine urinalysis (color, appearance, and dipstick [pH, specific gravity, protein, glucose, ketones, bilirubin, blood, urobilinogen, and leukocyte esterase]). 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. If the patient has not been fasting, it should be documented accordingly in the eCRF.

[e] Includes clinical chemistry (same as footnote d but excluding phosphate, hemoglobin A1c, cystatin, and uric acid); hematology (same as footnote d but excluding WBC differential); and routine urinalysis (same as footnote d). 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. If the patient has not been fasting, it should be documented accordingly in the eCRF.

[f] Includes total cholesterol, LDL (direct), HDL (direct), and triglycerides (direct). At screening, only total cholesterol and triglycerides are required.

[g] For screening, patients will be given supplies for collection of a 24-hour urine sample at Visit 1 and will return with the collected sample within the visit window. For other visits, the sample will be collected 24 hours immediately prior to the visit. Patients who forget to collect this sample the 24 hours immediately prior to the visit may collect and return it within the visit window. Protein and albumin excretion, creatinine, sodium, and urea will be measured from this sample. If the sample for the screening visit is collected within 14 days prior to Visit 2, the sample (and calculation of eGFR) for Visit 2 is not necessary.

[h] Calculated using the CKD-EPI formula based on age, sex, race, and serum creatinine values from the visit.

[I] A blood sample for plasma PK will be drawn prior to study medication administration. Once EOT is completed for a patient, PK samples will not be collected.

[j] Serum pregnancy tests will be performed on WOCBP at screening. Urine pregnancy tests will be performed at all other visits and monthly between visits. A positive urine pregnancy test will be confirmed by a serum test.

[k] QoL questionnaires should be completed prior to any other assessment. The questionnaires will be the KDQoL-36 (which consists of the first 12 questions of the SF-12 and 24 questions [questions 13-36] from the KDQoL-36) and the EQ-5D-5L. 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 period who did not complete the questionnaires at Day 1 of the double-blind period should complete them at Week 114 (as baseline assessments for the open-label extension) and throughout the open-label extension.

[l] For Germany only, 12-lead electrocardiograms will be conducted in triplicate at screening and randomization for the double-blind period, and at every visit throughout the study except visit 4 and visit 17.

[m] Sites will provide WOCBP with 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.

[n] At Visit 2 (Day 1), patients will be randomized via IRT, and the first dose will be administered in clinic. Patients will be instructed to take their study medication in the clinic on the days of office visits. All other days, study medication should be taken prior to the morning meal. Patients will be instructed to swallow the capsules whole. Patients will also be instructed to avoid drinking or eating anything that contains grapefruit, Seville oranges (bitter oranges often used as marmalade), starfruit (carambola), or pomelo/shaddock throughout the study.

Table 15.1-2. Double-blind Period: Schedules of Study Events from Week 48 Through End of Double-blind Period

	Blinded Treatment Period							End-of-Blinded Treatment Period
Week	**Week 48**	**Week 58**	**Week 70**	**Week 82**	**Week 94**	**Week 106**	**Week 110/EOT/ET[a]**	**Week 114**
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Visit Window	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**– 7/ + 14 days**
Full Physical Examination		X					X	
Targeted Physical Examination	X		X	X	X	X		X
Peripheral Edema Assessment[b]	X	X	X	X	X	X	X	X
Vital Signs[c]	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments Panel A[d]	X	X	X	X	X	X	X	X
Lipid Panel[e]	X	X	X	X	X	X	X	X
NT-proBNP	X	X	X	X	X	X	X	X
Aldosterone, Renin, Endothelin	X		X		X		X	X
Biorepository Samples (blood and urine, if consented)		X		X			X	X
Coagulation Tests (Prothrombin Time, INR)	X		X				X	
Quantitative Urinalysis (24-hour collection)[f]	X	X	X	X	X	X	X	X
Calculate eGFR[g]	X	X	X	X	X	X	X	X
PK Plasma Levels[h]	X		X		X		X	
Pregnancy Test[i]	X	X	X	X	X	X	X	X
QoL Questionnaires[j]	X		X		X		X	
Dispense Urine Pregnancy Tests[k]	X	X	X	X	X	X	X	
Informed Consent for OLE[l]							X	X
Study Medication Dispensing[m]	X	X	X	X	X	X		
Study 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 ----------							

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EOT = End-of-Treatment; EQ-5D-5L = EuroQol 5-dimension, 5-level QoL Questionnaire; ET = Early Termination; HDL = high-density lipoprotein; INR = international normalized ratio; KDQoL-36 = Kidney Disease QoL Questionnaire; 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; PK = pharmacokinetics; QoL = Quality of life; SF-12 = 12-Item Short Form Health Survey (QoL questionnaire); WBC = white blood cell; WOCBP = women of childbearing potential.

[a] Assessments at this visit will be used as screening for patients entering the open-label extension period. All Week 110 evaluations must be completed prior to the first dose of open-label sparsentan.

[b] Peripheral edema assessment guidance provided in Section 15.2.4.

[c] Vital signs should 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. In addition to these blood pressure measurements, measurements of blood pressure intended to detect possible orthostatic hypotension will 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. Heart rates will be measured with each positional blood pressure reading for orthostatic hypotension detection.

[d] Includes clinical chemistry (serum sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, phosphate, glucose, hemoglobin A1c, cystatin, uric acid, BUN, creatinine [including calculation of eGFR], bilirubin [total, direct, and indirect], ALT, AST, ALP, gamma glutamyltransferase, creatine kinase, amylase, and lipase); hematology (red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, WBC, and WBC differential [neutrophils, eosinophils, basophils, lymphocytes, and monocytes, percentage and absolute]); and routine urinalysis (color, appearance, and dipstick [pH, specific gravity, protein, glucose, ketones, bilirubin, blood, urobilinogen, and leukocyte esterase]). 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. If the patient has not been fasting, it should be documented accordingly in the eCRF.

[e] Includes total cholesterol, LDL (direct), HDL (direct), and triglycerides (direct).

[f] Sample will be collected 24 hours immediately prior to the visit. Patients who forget to collect this sample the 24 hours immediately prior to the visit may collect and return it within the visit window. Protein and albumin excretion, creatinine, sodium, and urea will be measured from this sample.

[g] Calculated using the CKD-EPI formula based on age, sex, race, and serum creatinine values from the visit.

[h] A blood sample for plasma PK will be drawn prior to study medication administration. Once EOT is completed for a patient, PK samples will not be collected.

[i] WOCBP only. Urine pregnancy tests will be performed at all visits and monthly between visits. A positive urine pregnancy test will be confirmed by a serum test.

[j] QoL questionnaires should be completed prior to any other assessment. The questionnaires will be the KDQoL-36 (which consists of the first 12 questions of the SF-12 and 24 questions [questions 13-36] from the KDQoL-36) and the EQ-5D-5L. 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 period who did not complete the questionnaires at Day 1 of the double-blind period should complete them at Week 114 (as baseline assessments for the open-label extension) and throughout the open-label extension.

[k] Sites will provide WOCBP with 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.

[l] Patients who may be eligible for the open-label extension period should sign the open-label extension period informed consent form at Week 110. Patients may also sign the OLE period informed consent form at Week 114, if not completed previously at Week 110.

[m] Dispense study medication. Patients will be instructed to take their study medication in the clinic on the day of office visits. All other days, study medication should be taken prior to the morning meal. Patients will be instructed to swallow the capsules whole. Patients will also be instructed to avoid drinking or eating anything that contains grapefruit, Seville oranges (bitter oranges often used as marmalade), starfruit (carambola), or pomelo/shaddock throughout the study. The patient will be instructed to bring all sparsentan tablets and their original containers to the next clinic visit.

Table 15.1-3. Open-label Extension Period and Sparsentan + SGLT2 Inhibitor Sub-study: Schedules of Study Events from Week 110 Through Week 186

Week	Open-label Treatment								
	Week 110 Screening	Week 114 Baseline/ Day 1	Week 116	Week 126	Week 138	Week 150	Week 162	Week 174	Week 186
Visit	15	16	17	18	19	20	21	22	23
Visit Window	± 14 days	– 7/ + 14 days	– 7/ + 14 days	± 28 days	± 28 days	± 28 days	± 28 days	± 28 days	± 28 days
Informed Consent for OLE[a]	X	X							
Informed Consent for Sub-Study (Baseline Sub-study Visit) and Randomization[m]				As early as Week 126 (Visit 18) but no later than Week 258 (Visit 29)					
Full Physical Examination	X								
Targeted Physical Examination		X	X	X	X	X	X	X	X
Peripheral Edema Assessment[b]	X	X	X	X	X	X	X	X	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments Panel A[d]	X	X		X	X	X	X	X	X
Clinical Laboratory Assessments Panel B[e]	X	X	X						
Lipid Panel[f]	X	X				X	X	X	X
NT-proBNP	X	X	X	X	X	X	X	X	X
Quantitative Urinalysis (24-hour collection)[g]	X	X		X	X	X	X	X	X
QoL Questionnaire[h]	X	X		X	X	X	X	X	X
Pregnancy Test[i]	X	X		X	X	X	X	X	X
Dispense Urine Pregnancy Tests[i]			X	X	X	X	X	X	X
Biorepository Samples (blood and urine, if consented)	X	X		X	X	X	X	X	X
Study Medication Dispensing[j,l]		X	X	X	X	X	X	X	X
Study Medication Accountability[n]		X	X	X	X	X	X	X	X
12-lead Electrocardiogram[k,o]	X	X							
Adverse Event Assessment	----------Continuous Monitoring----------								
Concomitant Medications/Therapies	----------Continuous Monitoring----------								

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol, 5-dimension 5-level QoL Questionnaire; HDL = high-density lipoprotein; ICF = Informed consent form; KDQoL-36 = Kidney Disease QoL Questionnaire; 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; SGLT2 = Sodium-glucose cotransporter-2; SmPC = summary of product characteristics; USPI = US prescribing information; WBC = white blood cell; WOCBP = women of childbearing potential

[a] Patients who may be eligible for the OLE period should sign the OLE period ICF at Week 110. Patients may also sign the OLE period ICF at Week 114, if not completed previously at Week 110.

[b] Peripheral edema assessment guidance is provided in Section 15.2.4.

[c] Vital signs should 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. In addition to these blood pressure measurements, 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. Heart rates will be measured with each positional blood pressure reading for orthostatic hypotension detection.

[d] Includes clinical chemistry (serum 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 glutamyltransferase, creatine kinase, and amylase); hematology (red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, WBC, and WBC differential [percentage and absolute: neutrophils, eosinophils, basophils, lymphocytes, and monocytes]); and routine urinalysis (color, appearance, and dipstick [pH, specific gravity, protein, glucose, ketones, bilirubin, blood, urobilinogen, and leukocyte esterase]). All chemistry and hematology analytes are shown in Section 15.2.5.

[e] Includes clinical chemistry (same as footnote d but excluding phosphate, cystatin, and uric acid); hematology (same as footnote d); and routine urinalysis (same as footnote d). 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. If the patient has not been fasting, it should be documented accordingly in the eCRF.

[f] Includes total cholesterol, LDL (direct), HDL (direct), and triglycerides (direct). Lipid analytes are shown in Section 15.2.5

[g] Urine protein excretion and creatinine. Sample will be collected 24 hours immediately prior to the visit. Patients who forget to collect this sample 24 hours immediately prior to the visit may collect and return it within the visit window. Protein excretion and creatinine will be measured from this sample.

[h] Patients will complete the KDQoL-36t. All patients will also complete the EQ-5D-5L. Patients participating in the OLE period who did not complete the questionnaires at Day 1 of the double-blind period should complete them at Week 114 (as baseline assessments for the OLE) and throughout the OLE.

[i] Urine pregnancy tests will be performed at all visits and monthly between visits. A positive urine pregnancy test will be confirmed by a serum test. Urine pregnancy tests will be dispensed to WOCBP to conduct pregnancy testing at home between study visits. Sites will provide the patients 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.

[j] Patients will be instructed to take their sparsentan in the clinic on the day of office visits. On all other days, sparsentan should be taken at approximately the same time each day, preferably prior to the morning meal. For each patient, the time when sparsentan was taken should be recorded in the eCRF. Patients will be instructed to swallow the tablets whole and to not 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), starfruit (carambola), or pomelo/shaddock throughout the study. The patient will be instructed to bring all sparsentan tablets and their original containers to the next clinic visit.

[k] Electrocardiogram to be done at Week 110 or Week 114 visit depending on the day/visit of ICF signing.

[l] If patient is enrolled in the Sub-study and randomized to the SGLT2 inhibitor treatment group, Investigator will instruct patient on the dispensing, daily dose, and administration according to USPI, SmPC, or local label. The patient will be instructed to bring all packs (bottles or blister packs) to the next clinic visit.

[m] Only patients who want to participate in the Sub-study must sign a specific consent. Patients enrolled in the Sub-Study and randomized to receive SGLT2 inhibitors may need to return to the study site to be dispensed the SGLT2 inhibitor and may have a safety visit between 7 to 14 days after beginning dosing with the SGLT2 inhibitor.

[n] This will be derived from medication dispensed to a patient in the Sub-Study are returned.

[o] For Germany only, 12-lead electrocardiograms will be conducted in triplicate at screening and randomization for the double-blind period, and at every visit throughout the study except Visit 4 and Visit 17.

Table 15.1-4. Open-label Extension Period: Schedules of Study Events from Week 198 Through End-of-Study

Week	Open-label Treatment						
	Week 198	Week 210	Week 222	Week 234	Week 246	Week 258	Week 270 End-of-Study
Visit	24	25	26	27	28	29	30
Visit Window	± 28 days	± 28 days	± 28 days	± 28 days	± 28 days	± 28 days	± 28 days
Optional Informed Consent for SGLT2i Sub-Study (Baseline SGLT2i visit) and Randomization[j]	As early as Week 126 (Visit 18) but no later than Week 258 (Visit 29)						
Full Physical Examination							
Targeted Physical Examination	X	X	X	X	X	X	X
Peripheral Edema Assessment[a]	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X
Clinical Laboratory Assessments Panel A[c]	X	X	X	X	X	X	X
Lipid Panel[d]	X	X	X	X	X	X	X
NT-proBNP	X	X	X	X	X	X	X
Quantitative Urinalysis (24-hour collection)[e]	X	X	X	X	X	X	X
QoL Questionnaires[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,i]	X	X	X	X	X	X	
Study Medication Accountability[k]	X	X	X	X	X	X	X
Adverse Event Assessment	----------Continuous Monitoring----------						
Concomitant Medications/Therapies	----------Continuous Monitoring----------						

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol, 5-dimension 5-level QoL Questionnaire; ET = early termination; HDL = high-density lipoprotein; KDQoL-36 = Kidney Disease QoL Questionnaire; 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; SGLT2 = Sodium-glucose cotransporter-2; SmPC = summary of product characteristics; USPI = US prescribing information; WBC = white blood cell; WOCBP = women of childbearing potential

[a] Peripheral edema assessment guidance is provided in Section 15.2.4.

[b] Vital signs should 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. Heart rates will be measured with each positional blood pressure reading for orthostatic hypotension detection.

[c] Includes clinical chemistry (serum 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 glutamyltransferase, creatine kinase, and amylase); hematology (red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, WBC, and WBC differential [percentage and absolute: neutrophils, eosinophils, basophils, lymphocytes, and monocytes]), and routine urinalysis (color, appearance, and dipstick [pH, specific gravity, protein, glucose, ketones, bilirubin, blood, urobilinogen, and leukocyte esterase]). All chemistry, hematology, and urinalysis analytes are shown in Section 15.2.5.

[d] Includes total cholesterol, LDL (direct), HDL (direct), and triglycerides (direct). Lipid analytes are shown in Section 15.2.5

[e] Urine protein excretion and creatinine. Sample will be collected 24 hours immediately prior to the visit. Patients who forget to collect this sample 24 hours immediately prior to the visit may collect and return it within the visit window. Protein excretion and creatinine will be measured from this sample.

[f] Patients will complete the KDQoL-36. All patients will also complete the EQ-5D-5L.

[g] Urine pregnancy tests will be dispensed to WOCBP to conduct pregnancy testing at home between study visits. Sites will provide the patients 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.

[h] Dispense sparsentan. Patients will be instructed to take their sparsentan in the clinic on the day of office visits. On all other days, sparsentan 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 to not open, break, chew, crush, or split the tablet prior to taking. For each patient, the time when sparsentan was taken should be recorded in the eCRF. Patients will also be instructed to avoid drinking or eating anything that contains grapefruit, Seville oranges (bitter oranges often used as marmalade), starfruit (carambola), or pomelo/shaddock throughout the study. The patient will be instructed to bring all sparsentan tablets and their original containers to the next clinic visit.

i If patient is enrolled in the Sub-study and randomized to the SGLT2 inhibitor treatment group, Investigator will instruct patient on the dispensing, daily dose, and administration according to USPI, SmPC, or local label. The patient will be instructed to bring all packs (bottles or blister packs) to the next clinic visit.

[j] Patients enrolled in the Sub-study and randomized to receive SGLT2 inhibitors may have a safety visit between 7 to 14 days after beginning dosing with the SGLT2 inhibitor.

[k] This will be derived from medication dispensed to a patient in the Sub-study are returned.

Table 15.1-5. Sparsentan + SGTL2 Inhibitor Sub-study: Schedule of Study Events

Please see information contained within the open-label extension Schedule of Study Events (Table 15.1-3).

15.2. Appendix B: Supplemental Study Information

15.2.1. Concomitant Medication Considerations

A. While Taking Study Medication (ie, Day 1 Through Week 110)

1. Prohibited Medications While Taking Study Medication (ie, Day 1 Through Week 110)

- Inhibitors of the RAAS.
  - Examples include (not all inclusive) the following: ACEIs, aldosterone blockers, ARBs, spironolactone, eplerenone, and aliskiren.
- Inhibitors of the endothelin system (bosentan, macitentan, and ambrisentan).
- Potassium-sparing diuretics (eg, amiloride and triamterene).
- Selected anti-diabetic drugs (thiazolidinediones and SGLT2) 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.
- Amphetamines, amphetamine derivative agents, and prescribed weight loss medications, including orlistat (eg, Alli® and 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 (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.
- The following medications are prohibited for <u>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™ and Septra®), cimetidine, pyrimethamine, cetirizine, cobicistat, probenecid, vandetanib, dolutegravir, ranolazine, dronedarone, ritonavir, and telaprevir cannot be used within at least 7 days prior to any visit at which eGFR is assessed.
  - Fibrates.

2. Medications to Be Used With Caution While Taking Study Medication (ie, Day 1 Through Week 110)

It is recommended that systemic corticosteroid and/or immunosuppressive therapy for the treatment of IgAN 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.

- 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.
- Cytochrome P450 2B6 (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.
- 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.
- 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.

- 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 CYP 2B6 substrates) can be found at: http://medicine.iupui.edu/clinpharm/ddis/main-table/

B. Prohibited Medications Following Discontinuation of Study Medication (ie, Non-Treatment Period from Week 110 Through Week 114)

- Selected anti-diabetic drugs (thiazolidinediones and sodium-glucose cotransporter-2 inhibitors) 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.
- Amphetamines and amphetamine derivative agents.
- 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™ and Septra®), cimetidine, pyrimethamine, cetirizine, cobicistat, probenecid, vandetanib, 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 110

- 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™ and Septra®), cimetidine, pyrimethamine, cetirizine, cobicistat, probenecid, vandetanib, 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 114)

1. Prohibited Medications While Taking Study Medication (ie, During the Open-label Extension Period (Starting at Week 114)

- 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 114)

It is recommended that systemic corticosteroid and/or immunosuppressive therapy for the treatment of IgAN 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. For patients enrolled into the Sub-study, no SGLT2 inhibitor should be prescribed during this period.
- 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 CYP 2B6 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 of >5.5 mEq/L (5.5 mmol/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, rule out measurement errors or likely reasons for the increase (eg, sample hemolysis, metabolic acidosis, discontinuation of diuretic 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 scenario 2a and 2b, adjust the dose of diuretic accordingly after 1 week. If the patient's serum potassium value is still >5.5 mEq/L (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 mEq/L (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. Minimum ACEI/ARB Daily Dose Requirements at Screening

Inclusion criterion 6 requires that patients have been on a stable, maximum tolerated dose of ACEI and/or ARB therapy for at least 12 weeks prior to signing of the informed consent. The criterion also requires the maximum tolerated dose to be at least one-half the MLD. The application of inclusion criterion 6 is intended to ensure that only patients with the potential to tolerate the minimum doses of study medication, in terms of anti-hypertensive effect, are enrolled in the study.

The table below shows the minimum daily doses for the most common ACEI or ARBs to guide eligibility screening. Values in the table represent 50% of the MLD of these drugs in most participating countries (in some countries [eg, the US], MLDs may be higher than in other countries). These values are considered approximately equivalent to the minimum daily dose of the active comparator for the treatment phase of the study (ie, irbesartan 150 mg/day).

If a patient is on a combination of an ACEI and an ARB, the sum of the individual doses (as a percentage of the MLD on the table) should be at least 50% (eg, 2.5 mg/day Ramipril [25%] + 25 mg losartan [25%] = 50% in total).

For patients taking an ACEI and/or ARB not presented in the table, the Investigator is advised to contact the Medical Monitor to discuss patient eligibility.

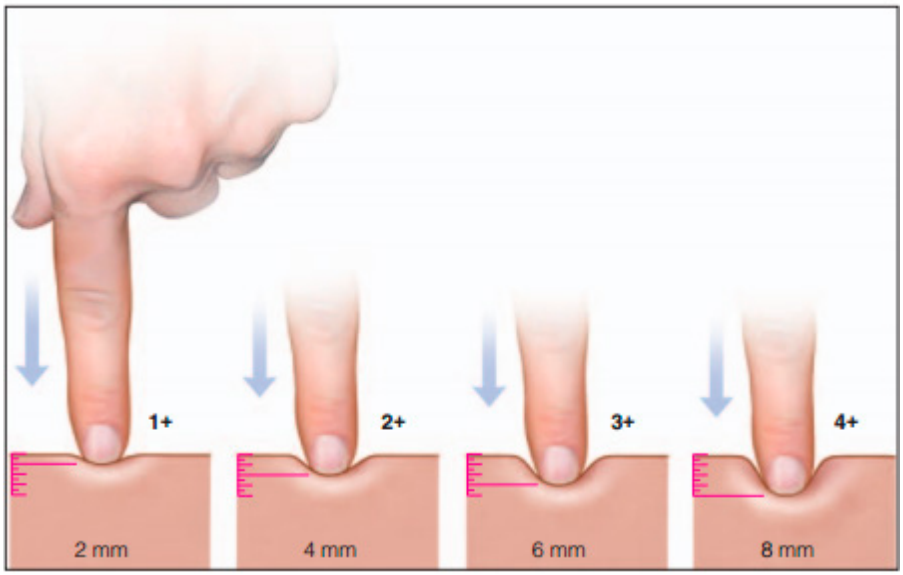
ACEI	Minimum Daily Dose at Screening	ARB	Minimum Daily Dose at Screening
Benazepril	20 mg	Candesartan	16 mg
Captopril	75 mg	Eprosartan	300 mg
Enalapril	20 mg	Irbesartan	150 mg
Fosinopril	20 mg	Losartan	50 mg
Moexipril	15 mg	Valsartan	160 mg
Perindopril	4 mg	Telmisartan	40 mg
Quinapril	20 mg	Olmesartan	20 mg
Ramipril	5 mg	Azilsartan	40 mg
Trandolapril	2 mg		
Lisinopril	20 mg		
Zofenopril	30 mg		
Cilazapril	5 mg		
Delapril	60 mg		
Imidapril	10 mg		

15.2.4. 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 – 4 mm somewhat deeper pitting, disappears in 10 – 15 seconds (Mild)
3+	4 – 6 mm noticeably deep pit, lasts 1 to 2 minutes (Moderate)
4+	6 – 8 mm: very deep pit, lasts 2 to 5 minutes (Severe)

Adapted from the Guelph General Hospital Congestive Heart Failure Pathway



15.2.5. Clinical Laboratory Assessments Performed During the Study

Table 15.2-1. Clinical Laboratory Assessments During the Double-blind Period

Clinical Chemistry

Sodium
Potassium
Chloride
Bicarbonate
Total protein
Albumin
Calcium
Phosphate
Glucose
HbA1c
Cystatin
Uric acid
Blood urea nitrogen
Creatinine, including eGFR
Total bilirubin
Direct bilirubin
Indirect bilirubin
ALT
AST
ALP
Gamma glutamyltransferase
Creatine kinase
Amylase
Lipase

Screening Tests

Hepatitis B surface antigen
Hepatitis B "e" antigen
Anti-hepatitis C antibody
Hepatitis C RNA (performed if anti-hepatitis C antibody is positive)
Drug/Alcohol screen
Plasma follicle-stimulating hormone level >40 mIU/mL

Hematology

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

- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

Coagulation Tests

Prothrombin Time, INR

Other Tests

Aldosterone
Renin
NT-proBNP
Endothelin

Lipid Panel

Total Cholesterol
LDL (direct)
HDL (direct)
Triglycerides (direct)

Pharmacokinetics

Sparsentan
Irbesartan

Quantitative Urine

Protein excretion
Albumin excretion
Creatinine
Sodium
Urea

Routine Urinalysis (dipstick)

Color
Appearance
pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Blood
Urobilinogen
Leukocyte esterase

Pregnancy Tests

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

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; 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; RNA = ribonucleic acid; WBC = white blood cells

All laboratory assessments are intended to be performed by a Central Laboratory.

Table 15.2-2. Clinical Laboratory Assessments During the Open-label Extension Period

Clinical Chemistry

Sodium
Potassium
Chloride
Bicarbonate
Total protein
Albumin
Calcium
Phosphate

Pregnancy Tests

Urine pregnancy test
(Serum pregnancy test for confirmation of positive urine pregnancy test)

Other Tests

NT-proBNP

Lipid Panel

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

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 (percentage and absolute)

- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

ALT
AST
ALP
GGT
Creatine kinase
Amylase

Quantitative Urinalysis (24-hour urine samples)

Protein excretion
Creatinine

Routine Urinalysis

Color
Appearance
pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Blood
Urobilinogen
Leukocyte esterase

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; GGT = gamma glutamyltransferase; HDL = high-density lipoprotein; 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: Protocol History

Protocol Version	Date Issued	Rationale for Update
Amendment 6 – Global	15 November 2022	• Added Sparsentan + SGLT2 Inhibitor Sub-study to the protocol • Global consolidation of protocol • Updated information for COVID-19 Adverse Event/Serious Adverse Event reporting
Amendment 5-DE (country specific for Germany)	03 May 2021	• Revised efficacy endpoints • Specified single-tablet consumption based on availability during OLE period • Included Interim Analysis • Revised Schedules of Study Events • Updated information for Physical Examination and specified measurement of heart rate for orthostatic hypotension detection • Revised clinical laboratory assessments and removed serum pregnancy test for OLE period • Specified condition when study medication cannot be resumed • Added ECG measurements for all visits except visit 4 for DB period from screening through Week 36, for all visits for DB period from Week 48 through End of DB period, and for OLE period from Week 110 through Week 186, except for Week 116 • Added minor edits throughout
Amendment 5 – Global	06 April 2021	• Revised efficacy endpoints • Specified single-tablet consumption based on availability during open-label extension period • Included Interim Analysis • Revised Schedules of Study Events • Updated information for Physical Examination and specified measurement of heart rate for orthostatic hypotension detection

Protocol Version	Date Issued	Rationale for Update
		• Revised clinical laboratory assessments and removed serum pregnancy test for open-label extension period • Specified condition when study medication cannot be resumed • Revised list of concomitant medications for both double-blind and open-label extension periods • Added minor edits throughout
Amendment 4-DE (country specific for Germany)	13 July 2020	• Added open-label extension period to protocol • Updated overall sample size and removed the sample size assessment • Added guidance for working with restrictions related to COVID-19
Amendment 4 – Global	13 July 2020	• Added open-label extension period to protocol • Updated overall sample size and removed the sample size assessment • Added guidance for working with restrictions related to COVID-19
Amendment 3-DE (country specific for Germany)	10 March 2020	Addition of orthostatic hypotension blood pressure measurements, per Data Monitoring Committee recommendations.
Amendment 3 – Global	10 March 2020	Addition of orthostatic hypotension blood pressure measurements, per Data Monitoring Committee recommendations.
Amendment 2-DE (country specific for Germany)	15 August 2019	Removal of mandate for contraception in male patients.
Amendment 1-DE (country specific for Germany)	24 June 2019	Added ECG measurements at additional visits.
Amendment 2 – Global	07 May 2019	Removal of mandate for contraception in male patients.
Amendment 1 – Global	07 March 2019	Global harmonization of protocol. Also addressed comments from FDA. This amendment was submitted to FDA, BfArM, and the German Central EC only.
Original Protocol – France	14 December 2018	Added justification for collecting race data.
Original Protocol (Version 1.0, US)	10 September 2018	Addressed FDA comments for DUPLEX protocol prior to submitting protocol to IND.

Protocol Version	Date Issued	Rationale for Update
Original Protocol – United Kingdom	30 May 2018	Addressed comments from MHRA.
Original Protocol	06 April 2018	N/A

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