Protocol

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

Date of Document: 21 February 2023

NCT05856760

CLINICAL STUDY PROTOCOL

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

Protocol Number:	TVTX-RE021-204
Compound:	sparsentan (RE-021)
Brief Title:	A study to investigate safety and effect of Sparsentan in combination with SGLT2 inhibition in adult participants with IgAN
Study Phase:	2
Acronym:	SPARTACUS
Sponsor Name and Legal Registered Address:	Travere Therapeutics, Inc. 3611 Valley Centre Drive, Suite 300 San Diego, CA 92130 USA
Regulatory Agency Identifier Number(s):	**Registry** **ID** IND 137918
Version:	Original
Approval Date:	13 February 2023

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse event
AEOI	Adverse event of interest
AESI	Adverse event of special interest
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine transferase
AngII	Angiotensin II
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AT_1R	Angiotensin II type 1 receptor
BP	Blood pressure
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology
CONSORT	Consolidated Standards of Reporting Trials
CRFs	Case report forms
CTFG	Clinical Trial Facilitation Group
CYP3A	Cytochrome P450 3A
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 Participants 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 Participants with Primary Focal Segmental Glomerulosclerosis (FSGS)*
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate

Abbreviation	Definition
EOS	End of Study
EOT	End of Treatment
ERA	Endothelin receptor antagonist
ET_AR	Endothelin type A receptor
ET1	Endothelin-1
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FMV	First morning void
FSGS	Focal segmental glomerulosclerosis
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMR	Geometric mean ratio
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDFU	Investigational Directions for Use
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology system
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
KDIGO	Kidney Disease Improving Global Outcomes
KF	Kidney failure
LAM	Lactational amenorrhea method
MLD	Maximum labeled dose
MMRM	Mixed Model Repeated Measures
MRA	Mineralocorticoid receptor antagonist

Abbreviation	Definition
MTD	Maximum tolerated dose
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PP	Per Protocol (analysis set)
QD	Once daily
RAAS	Renin-angiotensin-aldosterone system
RAASi	Renin-angiotensin-aldosterone system inhibitor
SAE	Serious adverse event
SAP	Statistical analysis plan
SGLT2	Sodium glucose cotransporter-2
SGLT2i	Sodium glucose cotransporter-2 inhibitor
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
UA/C	Urine albumin-to-creatinine ratio
UP/C	Urine protein-to-creatinine ratio
US	United States

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A multicentered, single-group Phase 2, exploratory, open-label study to investigate safety and effect of sparsentan in combination with sodium glucose cotransporter-2 (SGLT2) inhibition in the treatment of adult participants with Immunoglobulin A nephropathy (IgAN)

Brief Title:

A study to investigate safety and effect of sparsentan in combination with SGLT2 inhibition in adult participants with IgAN

Regulatory Agency Identifier Number(s):

Registry	ID
IND	137918

Protocol Number:	**Compound:**	**Type of Study:**
TVTX-RE021-204	Sparsentan (RE-021)	Phase 2

Total Number of Study Site(s) Projected:

Approximately 30 multinational sites.

Name of Sponsor/Company:
Travere Therapeutics, Inc.
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USA

Study Rationale

Due to their antiproteinuric and long-term nephroprotective effects, SGLT2 inhibitors are being increasingly used in the treatment of patients with both diabetic and non-diabetic chronic kidney diseases including IgAN. Sparsentan, a non-immunosuppressive single molecule with dual antagonism of the endothelin type A receptor (ET_AR) and the angiotensin II type 1 receptor (AT_1R), is being developed for the treatment of IgAN.

An interim analysis of data from the randomized, controlled, Phase 3 PROTECT (021IGAN17001) study in participants with IgAN at risk of progression to kidney failure (KF) despite optimized renin-angiotensin-aldosterone system inhibitor (RAASi) demonstrated a significantly greater antiproteinuric effect of sparsentan as compared to the angiotensin receptor blocker (ARB), irbesartan, used as an active control. This observation suggests long-term nephroprotective potential of sparsentan in IgAN, a hypothesis which will be tested by analysis of long-term estimated glomerular filtration rate (eGFR) based confirmatory endpoints of the PROTECT trial.

With more widespread use of sodium glucose cotransporter-2 inhibitor (SGLT2i) and the possibility of concomitant use of SGLT2i and sparsentan in patients with IgAN, there is an increasing need to study the safety and effect of a combination of these 2 therapeutic approaches. The current study, SPARTACUS, has been designed to determine the safety and effect of such a combination of therapies.

Objectives and Endpoints	
Objectives	**Endpoints**
Safety:	
To assess the safety and tolerability of sparsentan in participants with IgAN on chronic stable treatment with an SGLT2 inhibitor.	The incidence of treatment-emergent AEs (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to treatment discontinuation, and adverse event of interest (AEOIs). Changes from baseline in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters.
Primary (Efficacy):	
To evaluate the effect of sparsentan on albuminuria in participants with IgAN on SGLT2 inhibitor medication.	The change from baseline (Day 1) in urine albumin-to-creatinine ratio (UA/C) at Week 24.
Secondary (Efficacy):	
To evaluate the effect of sparsentan on proteinuria variables, eGFR and blood pressure (BP), in participants with IgAN on SGLT2 inhibitor medication over the duration of the study.	Achievement of UA/C of <0.2 g/g at Week 24. Achievement of 30% and 50% reduction from baseline in UA/C at Week 24. The change from baseline in UA/C, urine protein-to-creatinine ratio (UP/C), eGFR, and BP at each visit.

Overall Design:

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

Participants who provide written informed consent will be assessed for eligibility and will undergo baseline evaluations including clinical laboratory tests. Per the eligibility criteria, all participants are required to be on a stable dose(s) of angiotensin converting enzyme inhibitor (ACEI) and/or ARB and on a stable dose of a SGLT2 inhibitor at screening and will continue their stable treatments through the screening period. Eligible participants entering the study will remain on the stable dose of the SGLT2 inhibitor for the duration of the study, however, they will discontinue ACEI and/or ARB therapy before the Day 1 visit. The final dose of an ACEI and/or ARB should be taken on the day before the Day 1 visit. Baseline evaluations will be taken on Day 1 prior to administration of the first dose of the study intervention (sparsentan) according to Section 6.1.

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

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

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

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows are outlined in the Schedule of Activities (SoA) in Section 1.3. Details of each procedure are provided in Section 8.

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

Health Measurement/Outcome: The purpose of this study is to evaluate safety and effect of sparsentan in combination with SGLT2 inhibitors in adult participants with IgAN.

Study Intervention and Intervention Form: Sparsentan tablets

Condition/Disease: IgAN

Study Duration: The duration of the study for a participant will be up to 34 weeks.

Treatment Duration: The study design included a screening period of up to 6 weeks, treatment period of 24 weeks, and a follow-up period of 4 weeks.

Visit Frequency: Site visits will be conducted for screening, at Day 1 (baseline), and at weeks 2, 4, 12, and 24 following Day 1. Following the 24-week treatment period, study intervention will be discontinued for 4 weeks. At this time, the Investigator should resume standard of care treatment, including RAAS inhibitor treatment. Participants will return to the site for a visit at Week 28 for the safety follow-up visit.

Number of Participants:

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

Note: Enrolled means participants', or their legally acceptable representatives', agreement to participate in a clinical study following completion of the informed consent. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Arms and Duration:

This study includes 3 periods: a screening period (up to 42 days), a treatment period (24 weeks) and a follow-up period (4 weeks).

All participants will be on stable doses of standard of care ACEI and/or ARB and an SGLT2 inhibitor at study entry, with prohibited concomitant medications discontinued before the baseline (Day 1) visit. The full daily dose of study intervention (sparsentan) is preferred to be taken prior to the morning meal, with the exception of the day of a study visit. Allowed doses of sparsentan during the treatment period are 200 mg and 400 mg. The goal is to titrate from the initial dose of 200 mg (Day 1) to the target dose of 400 mg at Week 2.

Planned maximum duration for each participant in this study is 34 weeks.

- Screening period of up to 6 weeks.
- Treatment period of 24 weeks.
- Safety follow-up visit 4 weeks after the final dose.

Key Eligibility Criteria

For a full list of eligibility criteria, please refer to Section 5.

Inclusion Criteria

- Participant aged ≥18 years at the time of signing the informed consent.
- Participant has biopsy-proven IgAN. The biopsy may have been performed at any time in the past.
- Participant has a UA/C ≥0.3 g/g at screening.
- Participant has an eGFR value of ≥25 mL/min/1.73m^2 at screening.
- The participant has been on a stable dose of an SGLT2 inhibitor for at least 12 weeks prior to screening.
- Participant has been on a stable dose of ACEI and/or ARB therapy for at least 12 weeks prior to screening that is:
  - The participant's maximum tolerated dose (MTD), and
  - at least one half of the maximum labeled dose (MLD)

Exclusion Criteria

- Participant has IgAN secondary to another condition or immunoglobulin A (IgA) vasculitis.
- Participant has undergone any organ transplant, with the exception of corneal transplants.
- Participant has a documented history of heart failure, clinically significant cardiovascular or liver disease.
- Participant has been taking high dose (defined as >10 mg/day prednisone) or other any systemic immunosuppressive medications within 12 weeks of prior to screening.

Statistical Considerations:

Sample Size Justification

To investigate the safety and effect of sparsentan in participants with IgAN on chronic stable treatment with an SGLT2 inhibitor, approximately 60 participants will be enrolled in the study. The sample size of the study is determined empirically without formal statistical assumptions. A sample size of 60 is sufficient to detect at least one adverse event with probability 95%, assuming an expected adverse event incidence of 5% using the binomial distribution.

Analysis Sets

Full Analysis Set (FAS): All participants who take at least 1 dose of sparsentan will be included in the FAS. All efficacy analyses will be based on the FAS.

Per Protocol (PP) Analysis Set: The PP analysis set is a subset of the FAS containing participants who meet study eligibility requirements and have no protocol deviations that might impact the assessment of efficacy measurements. The 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 database lock and will be detailed in the statistical analysis plan (SAP).

Efficacy Analyses

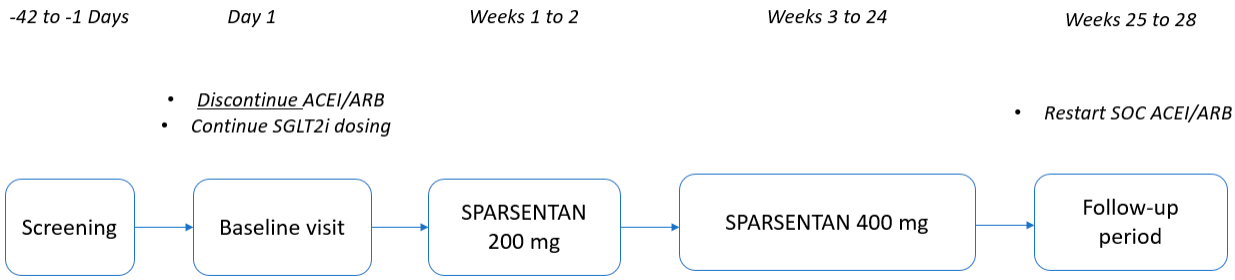
All efficacy analyses will be done descriptively on the FAS as well as PP analysis set in observed case. Change from baseline will be summarized with mean and 95% confidence interval (CI) as

appropriate. For categorical efficacy endpoints, the proportion of participants in the category will be presented along with corresponding 95% CI. Safety Analyses All safety analyses will be based on the FAS. Descriptive statistics will be presented. TEAE will be summarized by system organ class and preferred terms, by severity, and by relationship to study intervention. Changes from baseline in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters will be summarized and/or listed. In addition, shifts in laboratory parameters and peripheral edema will be summarized.
Data Monitoring/Other Committee: No

1.2. Schema

A study schema is provided in Figure 1.

Figure 1: Study Design



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

1.3. Schedule of Activities (SoA)

	Screening	Baseline	Study Treatment Period				Safety Follow-up Visit
Week	**--**	**Day 1**	**Week 2**	**Week 4**	**Week 12**	**Week 24/ EOT**	**Week 28/4-week Safety Visit**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Window	**Day –42 to Day –1**	**--**	**± 5 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**
Informed Consent	X						
Inclusion/Exclusion	X						
Screening Tests[a]	X						
IRT	X	X					
Medical History	X						
Demographics	X						
Peripheral Edema Assessment[b]	X	X	X	X	X	X	X
Vital Signs[c]	X	X	X	X	X	X	X
Clinical Laboratory Assessments[d]	X	X	X	X	X	X	X
Lipid Panel[e]	X	X			X	X	
Physical Examination[f]	X	X	X	X	X	X	X
Adverse Event Assessment	----------Continuous Monitoring ----------						
Concomitant Medications/Therapies	----------3 Months prior to screening followed by Continuous Monitoring----------						
RAAS Inhibitor Treatment[g]	X					X	
SGLT2 Inhibitor Treatment	----------Continuous Treatment ----------						
Quantitative urinalysis	X	X		X	X	X	X
Calculate eGFR[h]	X	X	X	X	X	X	X
Study Intervention Dispensing		X	X	X	X		
Study Intervention Accountability			X	X	X	X	
Pregnancy Test[i]	X	X	X	X	X	X	X
Dispense Urine Pregnancy Test[j]				X	X		

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; EOT = end of treatment;

HDL = high-density lipoprotein; IRT = interactive response technology system; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; pH = potential for hydrogen; RAAS = renin-angiotensin-aldosterone system; SOC = standard of care; SGLT2 = sodium glucose cotransporter-2; WBC = white blood cell.

[a] Includes plasma follicle stimulating hormone level (to confirm menopausal status only).

[b] Peripheral edema assessment guidance provided in Section 10.4.

[c] Vital signs should be measured prior to having blood drawn for laboratory evaluations. BP will be measured after participants 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. Weight, heart rate, temperature, respiration rate, and height (height measured only at screening) will also be recorded.

[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 glutamyl transferase, 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 10.3.

[e] Includes total cholesterol, LDL (direct), HDL (direct), and triglycerides (direct). All lipid analytes are shown in Section 10.3.

[f] Full physical examination will be performed at screening. A symptom directed targeted physical examination will be performed for all other visits.

[g] After Week 24/EOT, participants are expected to restart SOC treatment. The restart of RAAS inhibitor is at the discretion of the Investigator.

[h] The day before visit, participants should avoid strenuous exercise and a high protein meal, and participants should maintain a stable water intake.

[i] At screening, serum pregnancy tests will be performed on participants who can become pregnant. 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.

[j] Sites will provide participants who can become pregnant 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.

2. INTRODUCTION

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 extrarenal etiology (Knoppova 2016). IgAN is a serious, progressive disease in which 20% to 40% of patients progress to kidney failure (KF) 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 extrarenal 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 KF. 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 2021).

While there are currently no approved medicinal products specifically indicated for the treatment of IgAN, the cornerstone of treatment is rigorous blood pressure (BP) control using renin-angiotensin-aldosterone system inhibitor (RAASi) therapy, (angiotensin converting enzyme inhibitors [ACEIs], or angiotensin receptor blockers [ARBs]) to target BP 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 RAASi 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 2021). However, despite optimized RAASi therapy, persistent overt proteinuria remains in many patients, concurrent with loss of renal function and progression to KF.

Recently conducted large randomized controlled trials in patients with diabetic and non-diabetic chronic kidney disease (CKD) on stable RAASi treatment, have shown the sodium glucose cotransporter-2 (SGLT2) inhibitors, dapagliflozin and empagliflozin, to reduce proteinuria, slow progression of kidney function loss and reduce risk of KF (Heerspink 2020; Herrington 2022; Baigent 2022). Pre-specified sub-group analyses, show the benefit for IgAN patients to be consistent with the overall CKD population (Wheeler 2021; Herrington 2022; Baigent 2022).

As a consequence of these findings, there is increasing use of SGLT2 inhibitors for the treatment of IgAN in addition to standard of care renin-angiotensin-aldosterone system (RAAS) inhibition.

2.1. Study Rationale

Due to their antiproteinuric and long-term nephroprotective effects, SGLT2 inhibitors are being increasingly used in the treatment of patients with both diabetic and non-diabetic chronic kidney diseases including IgAN. Sparsentan, a non-immunosuppressive single molecule with dual antagonism of the endothelin type A receptor (ET_AR) and the angiotensin II type 1 receptor (AT_1R), is being developed for the treatment of IgAN.

An interim analysis of data from the randomized, controlled, Phase 3 PROTECT (021IGAN17001) study in participants with IgAN at risk of progression to KF despite optimized RAASi demonstrated a significantly greater antiproteinuric effect of sparsentan as compared to the ARB, irbesartan, used as an active control. This observation suggests long-term nephroprotective potential of sparsentan in IgAN, a hypothesis which will be tested by analysis of long-term estimated glomerular filtration rate (eGFR) based confirmatory endpoints of the PROTECT trial.

With more widespread use of sodium glucose cotransporter-2 inhibitor (SGLT2i) and the possibility of concomitant use of SGLT2i and sparsentan in patients with IgAN, there is a need to study the safety and effect of a combination of these 2 therapeutic approaches. The current study, SPARTACUS, has been designed to determine the safety and effect of such a combination of therapies.

2.2. Background

Sparsentan is a non-immunosuppressive single molecule with dual antagonism of ET_AR and AT_1R. Given the well-known role of angiotensin II (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.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

The potential risks for patients treated with sparsentan are a consequence of its dual antagonist properties of both angiotensin and endothelin receptor blockade.

Due to its ARB properties, sparsentan imparts a potential risk of acute kidney injury (AKI) due to reductions in intracapillary glomerular pressure and a risk of hyperkalemia due to lower glomerular filtration rate (GFR) and aldosterone inhibition. 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 endothelin receptor antagonists (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 type A/endothelin receptor subtype B 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.

Table 1: Risk Assessment

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s): Sparsentan		
Transaminase elevations.	Elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3x upper limit of normal (ULN) have been observed in studies of sparsentan, though concurrent elevation of bilirubin has not been observed.	Sparsentan can be discontinued in participants with clinically relevant aminotransferase elevations or if aminotransferase elevation is accompanied by a greater than 2x ULN increase in bilirubin or by clinical symptoms of hepatotoxicity.
Hyperkalemia.	Participants with advanced kidney disease or taking concomitant potassium-increasing drugs are at increased risk for hyperkalemia.	Potassium will be monitored at each visit for clinical evidence of electrolyte imbalance, with the course of action dependent on the potassium level and likely cause of increase. Management includes modifications in diet, diuretics, or potassium lowering medications. Sparsentan can be held or discontinued in participants who develop clinically significant hyperkalemia.
AKI.	Changes in kidney function and impaired kidney function can be caused by drugs that inhibit the RAAS system. Participants with renal artery stenosis, CKD, severe CHF, or volume depletion may be at particular risk of developing clinically significant AKI. The combination of sparsentan and SGLT2 inhibitors may enhance the risk of AKI.	Kidney function will be monitored periodically in this clinical study.Sparsentan can be held or discontinued in participants who develop clinically significant disease.

Table 1: Risk Assessment (Continued)

Identified/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypotension.	Hypotension has been observed in patients treated with ARBs and ERAs and has been observed in clinical studies of sparsentan. The combination of sparsentan and SGLT2 inhibitors may enhance the risk of hypotension.	In patients at risk for hypotension, consider eliminating or adjusting other anti-hypertensive medications.If hypotension develops despite elimination or reduction of other anti-hypertensive medications, the dose of sparsentan can be reduced or interrupted.
Fluid retention.	Fluid retention is observed in patients with IgAN and may occur with drugs that antagonize ET_AR. Fluid retention has been observed in clinical studies of sparsentan. Treatment with ERAs is associated with increased rates of edema and CHF in patients with diabetic nephropathy.	If clinically significant fluid retention develops, diuretics may need to be initiated or modified. The dose of sparsentan can also be reduced.Sparsentan should be used with caution in patients with Stage 3/4 CKD and with extreme caution in patients with Stage 5 CKD. Sparsentan should be avoided in patients with Stage 2-4 CHF.
Fetal harm.	Selective and non-selective endothelin type A/endothelin receptor type B antagonists are expected to cause fetal harm. ARBs reduce fetal renal function and increase fetal and neonatal morbidity and death during the second and third trimesters of pregnancy.	Participants will be advised of the risks and pregnancy testing will be conducted monthly.
Study Procedures		
Venipuncture will be performed during the study.	There is risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

Abbreviations: AKI = acute kidney injury; ARBs = angiotensin receptor blockers; CHF = congestive heart failure; CKD = chronic kidney disease; ERAs = endothelin receptor antagonists; ET_AR = Endothelin type A receptor; IgAN = Immunoglobin A nephropathy; SGLT2 = sodium glucose cotransporter-2.

2.3.2. Benefit Assessment

In an interim analysis of data from PROTECT, sparsentan had an early and sustained effect on reducing proteinuria compared to participants in the irbesartan arm. Consistent reduction of proteinuria in PROTECT was observed across pre-specified baseline subgroups. Additionally, preliminary eGFR analyses suggest the rate of eGFR decline is attenuated in participants taking sparsentan may further reduce residual proteinuria in patients treated with a combination of RAASi and SGLT2i.

2.3.3. Overall Benefit/Risk Conclusion

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

However, sparsentan has demonstrated a clinically meaningful benefit in reducing proteinuria in an interim analysis of data from PROTECT. In PROTECT, no new safety signals were identified; the nature, severity, and frequency of adverse events (AEs) were generally consistent with the safety profile of sparsentan in participants with focal segmental glomerulosclerosis (FSGS) (DUET, DUPLEX studies). Thus, the potential risks and benefits identified in association with sparsentan and participation in this study support a favorable benefit-risk analysis for sparsentan in this study population.

Additional details regarding specific benefits and risks for participants of this clinical study may be found in the accompanying Investigator's Brochure (IB) and informed consent form (ICF).

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints
Safety	
To assess the safety and tolerability of sparsentan in participants with IgAN on chronic stable treatment with an SGLT2 inhibitor.	The incidence of treatment-emergent AEs (TEAEs), serious adverse events (SAEs), AEs leading to treatment discontinuation, and adverse event of interest (AEOIs). Changes from baseline in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters.
Primary (Efficacy)	
To evaluate the effect of sparsentan on albuminuria in participants with IgAN on SGLT2 inhibitor medication.	The change from baseline in urine albumin-to-creatinine ratio (UA/C) at Week 24.
Secondary (Efficacy)	
To evaluate the effect of sparsentan on proteinuria variables, eGFR and BP, in participants with IgAN on SGLT2 inhibitor medication over the duration of the study.	Achievement of UA/C of <0.2 g/g at Week 24. Achievement of 30% and 50% reduction from baseline in UA/C at Week 24. The change from baseline in UA/C, urine protein-to-creatinine ratio (UP/C), eGFR, and BP at each visit.

3.1. Primary Estimand

Not applicable. No estimands are developed for this study.

3.2. Secondary Estimand(s)

Not applicable. No estimand(s) are developed for this study.

4. STUDY DESIGN

4.1. Overall Design

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

Participants who provide written informed consent will be assessed for eligibility and will undergo baseline evaluations including clinical laboratory tests. Per the eligibility criteria, all participants are required to be on a stable dose(s) of ACEI and/or ARB therapy and on a stable dose of a SGLT2 inhibitor at screening and will continue their stable treatments through the screening period. Eligible participants entering the study will remain on the stable dose of the SGLT2 inhibitor for the duration of the study, however, they will discontinue ACEI and/or ARB therapy before the Day 1 visit. The final dose of an ACEI and/or ARB therapy should be taken on the day before the Day 1 visit. Baseline evaluations will be taken on Day 1 prior to administration of the first dose of the study intervention (sparsentan) according to Section 6.1.

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

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

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

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for Endpoints

4.2.1.1. Safety Endpoints

Safety parameters commonly used for evaluating investigational CKD treatments are included as safety endpoints, but not limited to, the incidence of causality and outcomes of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed and defined according to severity. Severity of AEs are defined in Section 10.5.

4.2.1.2. Efficacy Endpoints

The primary and secondary endpoints evaluate change from baseline in albuminuria and achievement of remission of albuminuria at 24 weeks. Albuminuria is not only a major symptom of IgAN but also an established risk factor for disease progression and KF in IgAN (Reich 2007;

Le 2011). Meta-analyses of randomized controlled trials in IgAN have established mean percentage change in albuminuria from baseline as a surrogate endpoint for rate of loss of eGFR and risk of KF (Inker 2016; Thompson 2019; Inker 2021) and the change in albuminuria from baseline is therefore applied as the primary efficacy endpoint.

A secondary endpoint analysis will determine additional measures of antialbuminuric and antiproteinuric effects of sparsentan, such as the proportion of participants achieving 30% and 50% reductions in albuminuria, which, based on the meta-analyses, reflect thresholds for clinically meaningful benefit (Inker 2016; Inker 2021; Thompson 2019). Additionally, achievement of remission of albuminuria, is associated with low risk of KF (Reich 2007). Changes in eGFR, as a measure of renal function, and BP, the major determinant of the risk of CKD progression, from baseline will be evaluated over the duration of the study as secondary endpoints.

4.2.2. Rationale for Study Population

The study enrolls an adult population of biopsy-proven participants with IgAN, remaining proteinuric despite combination treatment with RAASi and SGLT2 inhibitor, who might benefit from further reduction or normalization of proteinuria by sparsentan.

4.3. Justification for Dose

As of August 2021, Sparsentan has been studied in approximately 1320 healthy volunteers, and in approximately 550 patients with Stage 1 hypertension, Stage 2 hypertension, FSGS or IgAN. In these studies, sparsentan has exhibited a favorable safety profile.

In this study, sparsentan treatment is planned to be initiated at a dose of 200 mg once daily (QD) by mouth for 14 days, and then increased to the recommended target dose of 400 mg QD, as tolerated.

This same dosing scheme is applied in PROTECT, PROTECT is an ongoing randomized, controlled Phase 3 study investigating the safety and efficacy of sparsentan, as compared to irbesartan, in 404 participants with IgAN at high risk of progression to KF. Participants are randomized 1:1 to receive either sparsentan or irbesartan with target doses of 400 mg and 300 mg, respectively, for a treatment period of 110 weeks. The target dose of 400 mg sparsentan was chosen for this study as an appropriate target dose for treatment of IgAN, based upon the knowledge of sparsentan pharmacokinetics (PK) characteristics and the perceived benefit/risk profile in this progressive disease.

At a pre-specified interim analysis, triggered 36 weeks after the Randomization of 280 participants, the primary efficacy endpoint of change from baseline in UP/C at Week 36 was met. Subjects receiving sparsentan achieved a mean reduction in proteinuria from baseline of 50%, compared with a mean reduction in proteinuria from baseline of 15% for irbesartan-treated subjects. This observed reduction in proteinuria corresponds to a clinically meaningful and significantly higher relative reduction from baseline of 41% in favor of sparsentan compared with irbesartan (geometric mean ratio [GMR] = 0.59, $p<0.0001$). Key secondary endpoints will evaluate the rate of change in eGFR after 1 and 2 years of treatment once all participants complete the double-blind phase of the study.

4.4. End of Study (EOS) Definition

The EOS is defined as the date of the last visit of the last participant in the study.

4.5. End of Treatment (EOT) Definition

The EOT is defined as the end of the study intervention treatment period. EOT may be at Week 24 (participant completes the study intervention treatment period as planned) or at the timepoint when a participant discontinues the study intervention permanently. In both circumstances, the EOT electronic case report form (eCRF) will be completed at the associated visit (see Section 7.1).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Informed Consent

Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Age

1. Participant must be ≥18 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participant has biopsy-proven IgAN. The biopsy may have been performed at any time in the past.
3. Participant has a UA/C ≥0.3 g/g at screening.
4. Participant has an eGFR value of ≥25 mL/min/1.73 m2 at screening

Contraceptive/Barrier Requirements

5. Participants who can become pregnant, 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 intervention until 30 days after the last dose of study intervention. Highly reliable contraception methods include stable oral, implanted, transdermal, or injected contraceptive hormones associated with inhibition of ovulation, or an intrauterine device (IUD) in place for a duration defined as effective in product labeling. If hormonal contraception is used, one additional barrier method must also be used during sexual activity, such as a diaphragm or diaphragm with spermicide (preferred), or male condom or male condom with spermicide (preferred), from Day 1/Randomization until 30 days after the last dose of study intervention. Hormonal implants do not require an

additional barrier method to be used. Participants who can become pregnant 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 12 consecutive months without an alternative medical cause; participants on hormone replacement therapy must have a documented plasma follicle stimulating hormone level >40 mIU/mL. All participants who can become pregnant 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 baseline (Visit 2) and after. See Section 10.7 for additional details on contraceptive and barrier guidance.

Other Inclusion Criteria

6. Participant has been on a stable dose of ACEI and/or ARB therapy for at least 12 weeks prior to screening that is:
    a. The participant's maximum tolerated dose (MTD), and
    b. at least one half of the maximum labeled dose (MLD) (See Section 10.2 for minimum ACEI/ARB daily dose requirements at screening).
7. The participant has been on a stable dose of an SGLT2 inhibitor for at least 12 weeks prior to screening.
8. Participant systolic BP must be ≤160 mmHg, and diastolic BP must be ≤110 mmHg at screening.
9. For participants receiving chronic low dose systemic corticosteroids (defined as ≤10 mg/day prednisone or equivalent), or an enteric formulation of budesonide and/or a mineralocorticoid receptor antagonist (MRA), the dosage must be stable for ≥12 weeks prior to screening.
10. The participant is willing to undergo a change in ACEI and/or ARB and anti hypertensive medications.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participant has IgAN secondary to another condition (eg, systemic lupus erythematosus and liver cirrhosis) or immunoglobulin A (IgA) vasculitis.
2. Participant has undergone any organ transplantation, with the exception of corneal transplants.
3. Participant has a documented history of heart failure [New York Heart Association (NYHA) Class II-IV] and/or previous hospitalization for heart failure or unexplained dyspnea, orthopnea, paroxysmal nocturnal dyspnea, ascites, and/or peripheral edema (see Section 10.4 for assessment of peripheral edema).

4. Participant 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 3 months prior to screening.
5. Participant has jaundice, hepatitis, or known hepatobiliary disease (excluding asymptomatic cholelithiasis), or ALT and/or AST >2 times the ULN range at screening.
6. Participant has a history of malignancy other than adequately treated basal cell or squamous cell skin cancer or cervical carcinoma within the past 2 years.
7. Participant has a history of serious side effect or allergic response to any AngII antagonist, ERA or sparsentan, or has a hypersensitivity to any of the excipients in the study intervention.

Prior/Concomitant Therapy

8. Participant requires any of the prohibited concomitant medications (Section 10.6).
9. Participant has been taking high dose systemic corticosteroids (defined as >10 mg/day prednisone or equivalent) or other any systemic immunosuppressive medications or enteric budesonide greater than the MLD and/or a MRA greater than the MLD within 12 week prior to screening.

Prior/Concurrent Clinical Study Experience

10. Treatment with sparsentan within 12 weeks prior to screening
11. Participant 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.

Diagnostic Assessments

12. Participant has a screening hematocrit value <27% (0.27 Volume/Volume) or hemoglobin value <9 g/dL (90 g/L).
13. Participant has a screening potassium value of >5.5 mEq/L (5.5 mmol/L).

Other Exclusion Criteria

14. The participant is pregnant, plans to become pregnant during the course of the study, or is breastfeeding.
15. The participant, in the opinion of the Investigator, is unable to adhere to the requirements of the study, including the ability to swallow the study intervention capsules whole.

Participants 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 participant for enrollment. If, in the Investigator's opinion, a laboratory value at screening is deemed unlikely to be representative of the participant's true status, the Investigator may have 1 additional measurement on that variable through the Central Laboratory to assess participant eligibility. Participants who fail screening may be rescreened according to Section 5.4.

5.3. Lifestyle Considerations

The full daily dose of study intervention is preferred to be taken prior to the morning meal, with the exception of the day of a study visit.

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Participants who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 additional times. Rescreened participants should be assigned a new participant number for every screening/rescreening event and will need to repeat all screening tests. Participants will also repeat the informed consent procedure each time they are rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 2.

Table 2: Study Intervention(s) Administered

Intervention Label	Sparsentan
Intervention Name	Sparsentan
Intervention Description	Week 1: Starting dose will be 1 tablet (1 x 200 mg) taken prior to the morning meal. Starting Week 3: Dose will be titrated to 1 tablet (1 × 400 mg) taken prior to the morning meal, if tolerated and determined safe by the Investigator.
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	200 mg or 400 mg
Dosage Level(s)	Week 1: Starting dose will be 1 tablet (1 x 200 mg) taken prior to the morning meal. Starting Week 3: Dose will be titrated to 1 tablet (1 × 400 mg) taken prior to the morning meal, if tolerated and determined safe by the Investigator.
Route of Administration	Oral
Use	Experimental
Investigational Medicinal Product (IMP)/Non-Investigational Medicinal Product (NIMP)	IMP
Sourcing	Provided centrally by the Sponsor.
Packaging and Labeling	Study intervention will be provided in container. Each container will be labeled as required per country requirement. Additional details about packaging and labeling can be found in the Pharmacy Manual.

Definition of IMP and NIMP is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

Table 3: Study Arm

Arm Title	**Sparsentan**
Arm Type	Experimental
Arm Description	At Week 1, the starting dose will be 1 tablet (1 x 200 mg) for all participants. At Week 3, the sparsentan dose will be titrated to 1 tablet (1 × 400 mg), if tolerated and determined safe by the Investigator.

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Dose Preparation

Details about administration of sparsentan are provided in the Pharmacy Manual.

6.2.2. Handling, Storage, and Accountability

The Investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided by the Sponsor in a Pharmacy Manual.

6.3. Assignment to Study Intervention

This is an open-label study. All participants will be centrally assigned to study intervention using an interactive response technology system (IRT). Before the study is initiated, the log-in information and directions for the IRT will be provided to each site.

6.4. Blinding and Masking

This is an open-label study.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of sparsentan dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.6. Dose Modification

The Investigator may titrate up the participant's dose to the target dose based on BP and lack of AEs at Week 2. Participants who tolerate the initial dose after 2 weeks but display asymptomatic systolic BP values ≤100 mmHg, or diastolic BP values ≤60 mmHg will continue the initial dose after the Week 2 visit without titrating up to the target dose. Participants who do not titrate up to the target dose at Week 2 for any reason, may titrate up to target dose at any time thereafter based on evaluation of the Investigator and if allowed by BP and lack of AEs in consultation with the Medical Monitor as needed. Participants who do not tolerate the initial dose for any reason at the Week 2 visit may discontinue study intervention.

Throughout the study, participants will be maintained on the maximum allowed dose of study intervention they can tolerate while secondarily maintaining BP as close as possible to the target of 125/75 mmHg. To maintain BP, the Investigator will be encouraged to either treat participants with additional anti-hypertensive agents [with the exception of ACEIs, aliskiren, ARBs, or ERAs (see Section 10.6)] 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 intervention.

Doses may be modified (titrate up or down) at any time throughout the study for safety or tolerability reasons at the Investigator's discretion, and if appropriate, additional safety testing may be performed.

6.7. Treatment of Overdose

There is limited clinical experience with sparsentan overdose in participants. Sparsentan has been administered in doses of up to 1600 mg/day in healthy subjects without evidence of dose limiting toxicities.

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether the study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.

6.8. Prior and Concomitant Therapy

For enrolled patients, prior and concomitant medications and therapies will be collected from the 3 months prior to screening through the participant'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.

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Prohibited

Medications specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the Investigator, the Sponsor, and the participant.

Prohibited concomitant medications and other concomitant medication considerations during study participation are outlined in Section 10.6.

For details regarding all non-clinical and clinical data on sparsentan, as well as warnings, precautions, and contraindications, the Investigator should refer to the IB.

6.8.2. Rescue Medication

No rescue or supportive medications are specified for use in this study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.

7.1. Discontinuation of Study Intervention

During the course of the study, it may be necessary for a participant to permanently discontinue study intervention prematurely. If study intervention is permanently discontinued prematurely, the participants should return to the site for a visit as close as possible to the participant’s last dose of study intervention. This visit may be a regularly scheduled visit or an unscheduled visit, and all assessments for this visit are to be completed per the regular scheduled visit or the Week 24 visit/EOT for an unscheduled visit, respectively, as listed in the SoA (Section 1.3). At this visit, the primary reason for premature discontinuation from study intervention, will be recorded on the EOT eCRF. Following this visit, participants are to complete the safety

follow-up visit as listed in the SoA (Section 1.3) within approximately 4 weeks after the last dose of study intervention.

The discontinuation of the SGLT2 inhibitor at any point during the study is not a reason for participant removal from protocol-required investigational product(s) or procedural assessments.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by Sponsor.
- Lost to follow-up.
- Death.
- Ineligibility determined.
- Protocol deviation.
- Noncompliance.
- Adverse event.
- Participant request.
- Pregnancy.
- Receipt of a kidney transplant or initiation of chronic dialysis.
- Diagnosis of NYHA Class II-IV CHF.
- Hyperkalemia that is resistant to treatment (see Section 10.8).

The need for additional intervention for the treatment of IgAN or the occurrence of safety endpoints are not, by themselves, criteria for discontinuation of study intervention.

The primary reason for discontinuation of study intervention, will be recorded on the EOT eCRF. Subsequent study visit data will be recorded on the visit specific eCRF (either a regular scheduled visit or unscheduled visit). Once the EOT eCRF is completed, study intervention cannot be resumed.

Additional details regarding temporary interruption or permanent discontinuation of the study intervention are outlined in Section 7.1.2 and Section 7.2.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Section 10.9 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in the best interest of the participant.

Additional details regarding suggested actions and follow-up assessments for liver safety are outlined in Section 10.9.

7.1.2. Temporary Discontinuation

Participants who temporarily interrupt study intervention will be encouraged to restart study intervention at the Investigator's discretion and should continue in the study. Participants who

temporarily interrupt study intervention prior to completion of the study will continue with study visits and assessments according to the SoA (Section 1.3). Unless contraindicated, treatment should be resumed (titrated at the Investigator's discretion) whenever possible (including between visits) as long as the EOT eCRF has not completed.

7.1.3. Study Intervention Restart

Study intervention restart after temporary interruption or after liver chemistry stopping criteria are met is allowed in this study. Refer to Section 7.1.2 for details on temporary discontinuation. Refer to Section 7.1.3.1 and Section 10.9 for details on study intervention restart after liver chemistry stopping criteria are met.

7.1.3.1. Study Intervention Restart or Rechallenge After Liver Chemistry Stopping Criteria Are Met

Study intervention restart after liver chemistry stopping criteria is met is allowed in this study. If the participant meets liver chemistry stopping criteria, do not restart the participant with study intervention unless:

Monitoring indicates abnormalities have resolved or stabilized.

Refer to Section 10.9 Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines for details on the restart process.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw consent and/or discontinue participation in the study at any time without prejudice to subsequent standard of care treatment. A participant's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor. Participants will also be discontinued from the study if the study is terminated (see Section 10.1.10). The Investigator is to discuss with the participant appropriate procedures for withdrawal from the study and must document the participant's decision to withdraw in the participant's medical records.

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, the visit data, including the primary reason for premature discontinuation from study intervention, will be recorded on the EOT eCRF. See SoA (Section 1.3) for data to be collected at the time of study discontinuation.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

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

- Death.
- Voluntary withdrawal of participant consent (complete withdrawal of consent requires a participant's documented refusal of all methods of follow-up noted in the ICF).
- Termination of the study by the Sponsor, FDA, or other regulatory authorities.
- Lost to follow-up.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.

8.1. Administrative and General Procedures

8.1.1. Informed Consent

All participants or their legally authorized representative must sign (wet-ink or electronically, if permitted) and date the Institutional Review Board (IRB)/independent ethics committee (IEC) approved informed consent before any study specific procedures are performed.

8.1.2. Inclusion/Exclusion Criteria

For a full list of eligibility criteria, please refer to Section 5.

8.2. Screening and Baseline Procedures

8.2.1. Screening Assessments

Screening visit assessments must be performed within 6 weeks prior to Day 1; the screening window begins on the day of the patient's first in-clinic study procedure. Each participant will be registered in the IRT as screening and assigned a unique identification number which will stay the same throughout the study. If, in the Investigator's opinion, a laboratory value at screening is deemed unlikely to be representative of the participant's true status, the Investigator may have 1 additional measurement on that variable through the Central Laboratory to assess participant eligibility. Participants who fail screening may be rescreened according to Section 5.4.

Participants who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 additional times. Rescreened participants should be assigned a new participant number for every screening/rescreening event and will need to repeat all screening tests. Participants will also repeat the informed consent procedure each time they are rescreened.

8.2.2. Demographics

Demographic data collection including sex, age, race, and ethnicity (as allowed by local regulations) will be collected.

8.2.3. Medical History

A complete medical history will be obtained detailing other comorbid conditions and history of complications of IgAN, including the following:

- All prior treatments for IgAN, including systemic corticosteroids, other systemic immunotherapeutic agents, and SGLT2 inhibitors.
- Current ongoing concomitant medications, including over the counter and other non-IgAN medications. See Section 6.8 for additional details on prior and concomitant medications.

8.3. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.3.1. Quantitative Urinalysis

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

Participants will be provided kits for the home collection of quantitative urinalysis samples. They will also receive full instructions regarding the proper collection of those samples.

8.3.2. eGFR Calculation

The list of clinical laboratory analysis to be tested is presented in Section 10.3 and includes serum creatinine for the estimation of GFR. The eGFR for each time point (visit) will be determined using the Chronic Kidney Disease Epidemiology (CKD-EPI) race free equation (Inker 2021).

8.4. Safety Assessments

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

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.4.1. Physical Examinations

Physical examinations will be performed according to the SoA in Section 1.3. Full physical examinations will be performed at screening; a symptom directed targeted physical examination will be performed at all other visits.

8.4.2. Peripheral Edema

Peripheral edema will be assessed at all visits using the semi-quantitative scale in Section 10.4.

8.4.3. Vital Signs

Vital signs should be measured prior to having blood drawn for laboratory evaluations. BP will be measured after participants 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. Weight, heart rate, temperature, respiration rate, and height (height measured only at screening) will also be recorded.

8.4.4. Clinical Safety Laboratory Tests

Routine blood and urine samples for laboratory assessments will be collected at the visits specified in the SoA in Section 1.3. 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 intervention 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.

- See Section 10.3 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or until EOS should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Section 10.3, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.4.5. Pregnancy Testing

Participants who can become pregnant, as defined in Section 10.7 , must not become pregnant. Acceptable forms of contraception are also defined in Section 10.7 .

At screening, serum pregnancy tests will be be performed on participants who can become pregnant. Urine pregnancy tests will be performed at all other visits and monthly between visits. Urine pregnancy tests will be dispensed to participants who can become pregnant to conduct pregnancy testing at home once per month until the next scheduled study visit. If the urine pregnancy test is positive, study intervention 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 participant will be followed to pregnancy outcome as outlined in Section 8.5.5.

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) is to be conducted every 4 weeks during intervention.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for contraception in Section 5.1 Inclusion Criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4.6. Suicidal Ideation and Behavior Risk Monitoring

No known risk of suicidal ideation associated with the use of sparsentan. If suicidal ideation and/or behavior risk monitoring is to occur, participant should refer to mental health services.

8.5. AEs SAEs, and Other Safety Reporting

The participant will be evaluated for new AEs and the status of existing AEs per the SoA (Section 1.3) and any time contact is made with the participant outside of a scheduled visit.

The definitions of AEs and SAEs can be found in Section 10.5.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.5.

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF until the follow-up visit at the timepoints specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.5. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.5.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.5.7) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.5.

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure/Investigational Directions for Use (IDFU)/package insert and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.5.5. Pregnancy

- Details of all pregnancies in participants will be collected after the start of study intervention and until 90 days following the final dose of study intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the participant's pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will discontinue study intervention.

Participants will be instructed to discontinue study intervention and 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 (Section 10.1.1) of this protocol or by fax to the number in the Investigator Site File.

All pregnancies in participants 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 participant that the Sponsor or its designee is required to gather information regarding the course and outcome of the pregnancy after exposure to the study intervention. 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 participant). 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 (Section 10.1.1) 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 participant and the participant decides to continue in the study after permanently discontinuing study intervention, the event will be processed per routine study guidelines. However, if the participant 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 (Section 10.1.1) 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.

8.5.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

All events, whether typically associated with the disease under study or not, will be reported according to the standard process for expedited reporting of AEs/SAEs. Disease-related events reporting is not applicable to this study.

8.5.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) (serious or nonserious) are listed below and are focused on liver safety. These events warrant further investigation and documentation in order to appropriately characterize the relationship of these events to study intervention treatment.

- Abnormal liver function test results that meet specific criteria (see Section 10.9) will be considered AEOIs and must be reported to the Sponsor's Medical Monitor within 24 hours of awareness.

If a reported AE/SAE falls under these AEOI criteria, additional information on the AE/SAE should be entered on the AESI form in the eCRF.

8.6. Pharmacokinetics

PK parameters are not evaluated in this study.

8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8. Genetics

Genetics are not evaluated in this study.

8.9. Biomarkers

Biomarkers are not evaluated in this study.

8.10. Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to first planned analysis, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.1. Statistical Hypothesis

There is not a pre-specified statistical hypothesis for efficacy for this study.

9.1.1. Multiplicity Adjustment

Not applicable. Multiplicity control is not relevant for the study.

9.2. Analysis Sets

Full Analysis Set (FAS): All participants who take at least 1 dose of sparsentan will be included in the FAS All efficacy analyses will be based on the FAS.

Per Protocol (PP) Analysis Set: The PP analysis set is a subset of the FAS containing participants who meet study eligibility requirements and have no protocol deviations that might impact the assessment of efficacy measurements. The 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 database lock and will be detailed in the SAP.

9.3. Statistical Analyses

9.3.1. Procedures for Handling Missing Data

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

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

9.3.2. Definition of Endpoint(s)

The safety endpoints include:

- Incidence of TEAEs, SAEs, AEs leading to treatment discontinuation, and AEOIs.
- Changes from baseline in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters.

The primary efficacy endpoint is:

- The change from baseline in UA/C at Week 24.

The secondary efficacy endpoints are:

- Achievement of UA/C of <0.2 g/g at Week 24.

- Achievement of 30% and 50% reduction from baseline in UA/C at Week 24.
- Change from baseline in UA/C, UP/C, eGFR, and BP at each visit.

9.3.3. Main Analytical Approach

The general analytical approach for all endpoints will be descriptive in nature. Although no formal statistical hypothesis testing will be conducted, the change from baseline in UA/C may be analyzed using mixed model repeated measures (MMRM). Details description will be presented in the SAP as appropriate.

For continuous variables, descriptive statistics will include means, standard deviations, medians, minimums, maximums, and the numbers of non-missing values. For categorical variables, descriptive statistics will include counts and percentages per category. Unless otherwise specified, endpoints will use the last non-missing observation prior to the first dose of study intervention as baseline. All data collected will be included in data listings.

All efficacy analyses will be done descriptively on the FAS as well as PP analysis set in observed case. Change from baseline will be summarized with mean and 95% confidence interval (CI) as appropriate. For categorical efficacy endpoints, the proportion of participants in the category will be presented along with corresponding 95% CI.

All safety analyses will be based on the FAS. Descriptive statistics will be presented. TEAE will be summarized by system organ class and preferred terms, by severity, and by relationship to study intervention. Changes from baseline in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters will be summarized and/or listed. In addition, shifts in laboratory parameters and peripheral edema will be summarized.

9.4. Interim Analysis

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

9.5. Sample Size Determination

To investigate the safety and effect of sparsentan in participants with IgAN on chronic stable treatment with an SGLT2 inhibitor, approximately 60 participants will be enrolled in the study. The sample size of the study is determined empirically without formal statistical assumptions. A sample size of 60 is sufficient to detect at least one adverse event with probability 95%, assuming an expected adverse event incidence of 5% using the binomial distribution.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Study Contact Information

Medical Monitor (Travere Therapeutics):	[redacted] MD [redacted] Nephrology Clinical Development Travere Therapeutics, Inc. 3611 Valley Centre Drive, Suite 300 San Diego, CA, 92130, USA [redacted]
CRO Medical Monitor (George Clinical):	George Clinical Building 12, Suite 200 10975 Benson Dr Overland Park, KS 66210 USA Phone: See Investigator Site File Email See Investigator Site File
Serious Adverse Event Reporting:	Qinecsa Solutions Email: clinicalsafety.travere@quinecsa.com Fax: See Investigator Site File
Product Handling/Complaints:	Travere Therapeutics, Inc. Tel: +1-888-211-5014 InvestigationalProductComplaints@travere.com

10.1.2. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, IDFU, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.3. Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4. Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. All potential participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.

10.1.5. Recruitment Strategy

Potential patients will be identified using various methods which will include some or all of the following: site database and medical record review, site referral networks, patient advocacy groups and social media/traditional advertisements. Patient privacy will be always maintained, with no identifying information, such as the patient's name, used in communications with the Sponsor or Sponsor representative(s). Recruitment of patients will be from diverse backgrounds.

10.1.6. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, and by inspectors from regulatory authorities.
- The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.7. Dissemination of Clinical Study Data

Sponsor fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and other public registries in accordance with applicable local laws/regulations. In all cases, study results are reported by Sponsor in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted. Clinical trial results are posted on www.clinicaltrials.gov for Sponsor-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by United States (US) law. Clinical trial results are posted on EudraCT for Sponsor-sponsored interventional studies with at least 1 site in the European Union (EU), in accordance with the format and timelines set forth by EU requirements.

In addition, results from clinical trials may be submitted to peer-reviewed journals, scientific congresses, and corporate communications following internal company review for accuracy, fair balance and intellectual property. Travere is committed to data transparency and sharing data

collected in completed and published clinical trials (Phase 3 and some Phase 2), observational trials, and post-marketing studies to further research while ensuring that patient privacy is protected. Pertinent individual patient-level data that underlie the results reported in a manuscript may be made available after deidentification. Relevant information may include redacted study protocol and redacted clinical study report.

Requests for clinical trial data, including language stating its intended use, should be directed to datarequest@travere.com. If approved, the requested information will be provided to the requestor after signing a data access agreement. Requests can be made following completion of the study and full publication of the study data in a peer-reviewed journal for up to 36 months following its publication. Travere reserves the right to decline or recommend modifications to a request if it does not comply with the data sharing policy or if it is determined that the request is made by a biased source.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- Guidance on completion of CRFs will be provided by the Sponsor.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided by the Sponsor.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 2 years after study completion. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

- The Investigator agrees to the unrestricted use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If required, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- For more details about the publication policy, the contract agreement between Sponsor and Investigator should be consulted.

10.2. Appendix 2: Minimum ACEI/ARB Daily Dose Requirements at Screening

Inclusion Criteria 6 requires that patients have been on a stable, MTD of ACEI and/or ARB therapy for at least 12 weeks prior to signing of the informed consent. The criterion also requires the MTD to be at least one half the MLD. The application of inclusion criterion 7 is intended to ensure that only patients with the potential to tolerate the minimum doses of study intervention, 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		

10.3. Appendix 3: Clinical Laboratory Tests

Samples for the tests detailed below (Table 4) will be collected per the timelines provided in the SoA (Section 1.3).

The tests detailed in Table 4 will be performed by a Central Laboratory.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 4: Clinical Safety Laboratory Tests and Quantitative Urinalysis

Clinical Chemistry	**Pregnancy Tests**	**Hematology**	**Quantitative Urinalysis (FMV samples)**
Sodium	Urine pregnancy test	Red blood cells	Albumin Excretion
Potassium	(Serum pregnancy test at screening and for confirmation of positive urine pregnancy test)	Hemoglobin	Protein Excretion
Chloride		Hematocrit	Urea
Bicarbonate	**Other Tests**	MCV, MCH, MCHC	Creatinine
Total protein	NT-proBNP	Platelets	
Albumin		White blood cells	**Routine Urinalysis**
Calcium	**Lipid Panel**	WBC differential (percentage and absolute)	Color
Phosphate	Total cholesterol	Neutrophils	Appearance
Glucose	LDL (direct)	Eosinophils	pH
Cystatin	HDL (direct)	Basophils	Specific gravity
Uric acid	Triglycerides (direct)	Lymphocytes	Protein
Blood urea nitrogen		Monocytes	Glucose
Creatinine, including eGFR			Ketones
Total bilirubin		**Screening Tests**	Bilirubin
Direct bilirubin		Plasma follicle stimulating hormone level (to confirm menopausal status)	Blood
Indirect bilirubin			Urobilinogen
ALT			Leukocyte esterase
AST			
ALP			
GGT			
Creatine kinase			
Amylase			

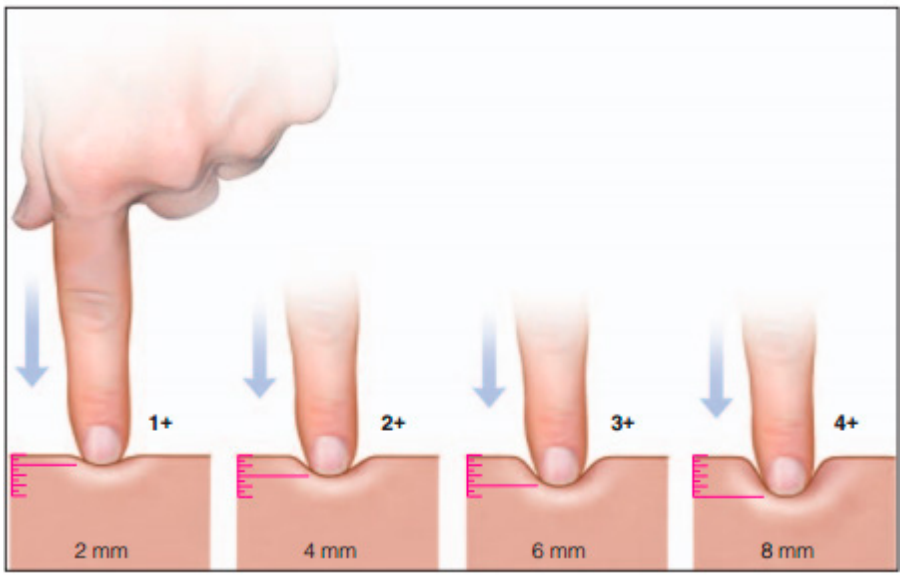
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; FMV = first morning void; GGT = gamma glutamyltransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; WBC = white blood cells.

10.4. Appendix 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 CHF Pathway



10.5. Appendix 5: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.5.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram (ECG), radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.5.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death
b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment or a pre-existing condition that did not worsen from baseline are not considered an SAE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.5.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- 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.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to SAE contact. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to SAE contact.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by SAE contact to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide SAE contact with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to SAE contact within 24 hours of receipt of the information.

10.5.4. Reporting of SAEs

SAE Reporting to SAE Contact Via an Electronic Data Collection Tool

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next Section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next Section) or to the SAE contact by telephone.
- Contacts for SAE reporting will be provided by the Sponsor.

SAE Reporting to SAE Contact Via Paper Data Collection Tool

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 (Section 10.1.1) of this protocol or by fax to the number in the Investigator Site File without undue delay but not later than 24 hours after obtaining knowledge of the events, 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, diagnostic test results) will be provided by email to the SAE contact on the Study Contact Information page (Section 10.1.1) 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 (Section 10.1.1) 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 subject/hospital records, discharge summaries, laboratory/test results, or autopsy reports.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- If at any time after the subject has completed participation in the study, the Investigator or study staff becomes aware of an SAE that they suspect is related to the study medication, the event and any known details will be reported promptly by email

to the SAE contact on the Study Contact Information page (Section 10.1.1) or by fax to the number in the Investigator Site File, following the reporting instructions in this section.

10.6. Appendix 6: Concomitant Medication Considerations

A. While Taking Study Intervention (Starting from Day 1 to Week 24)

1. Prohibited Medications While Taking Study Intervention (Starting from Day 1 to Week 24)
   - Inhibitors of the RAAS.
     - Examples include (not all inclusive) the following: ACEIs, aldosterone blockers, ARBs, ERAs and aliskiren.
   - Inhibitors of the endothelin system (eg, 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 Cytochrome P450 3A (CYP3A) inhibitors. For a detailed list of these medications, see the P450 Drug Interaction table at: http://medicine.iupui.edu/clinpharm/ddis/maintable.
     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 intervention and more intensive patient monitoring is recommended.
   - 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 participant 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 Intervention (Starting from Day 1 to Week 24)

It is recommended that high dose systemic corticosteroid (defined as >10 mg/day prednisone or equivalent) and/or systemic immunosuppressive therapy for the treatment of IgAN be avoided for the duration of participation in the study. If, in the Investigator's opinion, high dose systemic corticosteroid and/or systemic immunosuppressive therapy is warranted, such

intervention may be provided in addition to study intervention at the discretion of the Investigator. Consultation with the Medical Monitor is recommended before starting interventional therapy, when possible.

Similarly, it is recommended to avoid the introduction or change dose of patients receiving low dose systemic corticosteroids (defined as ≤10 mg/day prednisone or equivalent), enteric budesonide and/or mineralocorticoid receptor antagonists (eg. spironolactone, eplerenone, finerenone) for the duration of the study, unless, in the Investigator's opinion, such introduction is warranted, and may be provided in addition to study intervention. Appropriate potassium monitoring should be conducted for patients receiving mineralocorticoid receptor antagonists.

Consultation with the Medical Monitor is recommended before changing/starting interventional therapy, when possible.

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

- Strong P-glycoprotein (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 intervention 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 6.6.
  - 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 intervention.
  - 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.
  - International normalized ratio (INR) monitoring is recommended if warfarin is used concomitantly with study intervention.

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 Intervention (ie, Non-Treatment Period from Week 24 to Week 28)

- 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.
- 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. Participants Who Have Permanently Discontinued Study Intervention Prior to Safety Follow-Up Visit

- 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.

10.7. Appendix 7: Contraceptive and Barrier Guidance

10.7.1. Definitions

Participants in the following categories are considered participants who can become pregnant:

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Participants on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy.
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.7.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency *Failure rate of* <1% per year when used consistently and correctly.

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c].
- IUD.
- Intrauterine hormone-releasing system (IUS)[c].
- Bilateral tubal occlusion.
- Azoospermic partner (vasectomized or due to a to medical cause)

  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant who can become pregnant, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

  Note: documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]

1. oral
2. intravaginal
3. transdermal
4. injectable

Progestogen-only hormone contraception associated with inhibition of ovulation[c]

5. oral
6. injectable

Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

a) Contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c) If hormonal contraception is used, one additional barrier method must also be used during sexual activity, such as a diaphragm or diaphragm with spermicide (preferred), or male condom or male condom with spermicide (preferred), from Day 1/Randomization until 30 days after the last dose of study intervention. Hormonal implants do not require an additional barrier method to be used. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

10.8. Appendix 8: 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. 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 BP 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 BP, eGFR, sodium, and potassium within 1 week after starting the diuretic.
    b. 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 BP permit). Assess the patient's tolerability and measure their BP, 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 intervention by 50%. For long-term prevention of hyperkalemia, consider treatment with patiromer or sodium zirconium cyclosilicate.
4. If hyperkalemia persists or recurs, study intervention must be discontinued permanently.

10.9. Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines

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 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 study period (ie, Day 1) in participants who had elevated values prior to starting study intervention.

In such instances, the following steps should be taken:

1. Temporarily discontinue study intervention.
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 SAE Contact Information page (Section 10.1.1) of this protocol.
   b. Monitor liver enzymes and serum bilirubin 2 or 3 times weekly. The frequency of retesting can decrease to once weekly or less if the abnormalities stabilize and the participant is asymptomatic.
   c. Perform additional testing to evaluate liver function, as appropriate (eg, INR and direct bilirubin).
4. Do not resume study intervention until monitoring indicates abnormalities have resolved or stabilized.

Participants are not allowed to resume study intervention 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 participants 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; nonalcoholic steatohepatitis; biliary tract disease or exposure to hepatotoxic medications or environmental chemical agents). Additionally, participants who demonstrate elevated liver enzymes a second time after re introduction of the study intervention may continue in the clinical study; however, they will not receive study intervention 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 intervention 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).

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