NOVARTIS

Novartis Research and Development

Clinical Trial Protocol

A Randomized, Double-blind, Placebo-controlled, Crossover Study of Atrasentan in Subjects with IgA Nephropathy on Sodium-glucose Cotransporter-2 Inhibitors (SGLT2i) (The ASSIST study)

Synopsis/Clinical Trial Protocol Number: CEXV811A12201

Version Number: v03 Amended Global Protocol Version

Compound: Atrasentan

Brief Title: Randomized, Double-blind, Placebo-controlled, Crossover Study of Atrasentan in Subjects with IgA Nephropathy (The ASSIST study)

Study Phase: II

Study Acronym: ASSIST

Sponsor Name: Novartis Pharma AG or its affiliates outside of the EEA (where applicable)

Sponsor address : Novartis Pharma AG, Lichtstrasse 35, 4056 Basel Town, Switzerland

Regulatory Agency Identifier Number(s): 2023-503828-13-00 (EudraCT number), 151085 (IND number), NCT05834738 (ClinicalTrials.gov)

Content final Date: 16-Jan-2025

DECLARATION OF THE INVESTIGATOR

Title: Randomized, Double-blind, Placebo-controlled, Crossover Study of Atrasentan in Subjects with IgA Nephropathy (The ASSIST study)

Protocol Amendment 02 (v03): 16 Jan 2025

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, data captured in the electronic data capture (EDC) system, Site Initiation Visit (SIV) slides, and any scientific or other information that may be provided to support the study.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to address an immediate hazard to the subjects.

I understand and agree to abide by all the requirements of this protocol.

Principal Investigator

_____ _____

Signature Date

_____

Name (Print)

_____

Title (Print)

_____

Institution (Print)

TABLE OF CONTENTS

List of Tables

List of Figures

1. PROTOCOL SUMMARY

1.1. Synopsis

Study Title

A Randomized, Double-blind, Placebo-controlled, Crossover Study of Atrasentan in Subjects with IgA Nephropathy on Sodium-glucose Cotransporter-2 Inhibitors (SGLT2i) (The ASSIST Study)

Study Rationale

Atrasentan is a potent antagonist of endothelin receptor A (ETA, *Ki* = 0.034 nM) that has been studied extensively as a once-daily treatment for diabetic nephropathy in individuals with type 2 diabetes in addition to optimized doses of renin-angiotensin system (RAS) inhibitors (RASi).

Atrasentan is now being studied in subjects with immunoglobulin A nephropathy (IgAN) at risk of progressive loss of renal function despite treatment with a maximally tolerated and stable dose of a RAS inhibitor. IgAN is a glomerular disease, marked by excessive levels of urinary protein excretion.

Atrasentan previously demonstrated benefit in subjects with diabetic nephropathy in reducing albuminuria and has a well characterized safety profile in > 5300 subjects with diabetic nephropathy. In a global Phase 3 study (SONAR), subjects with an early beneficial response of albuminuria reduction following daily atrasentan treatment experienced a clinically important and statistically significant improvement on the primary composite endpoint of time to doubling of serum creatinine or progression to end stage renal disease (ESRD; log-rank p value, 0.029, hazard ratio 0.65 [95% confidence interval (CI) 0.49 - 0.88]) (Heerspink, 2019). A similarly favorable trend was also observed in a smaller cohort of subjects with lesser or no initial response to atrasentan on albuminuria reduction (log-rank p value, 0.15, hazard ratio 0.75 [95% CI 0.55 - 1.03]). These results were obtained despite the early termination of the study prior to completion of the planned number of renal composite events.

In a Phase 2 study of atrasentan in subjects with proteinuric glomerular diseases (the AFFINITY study), a preliminary analysis of 17 IgAN subjects receiving a maximally tolerated and stable dose of RAS inhibitor; 8 subjects were evaluable for the primary endpoint of urine protein:creatinine ratio (UPCR) change from baseline at Week 12, treatment with atrasentan provided a > 43% geometric mean reduction in UPCR after 12 weeks and was well tolerated, strongly supporting a key role of the endothelin pathway in the pathogenesis of IgAN (Kim, 2022).

The sodium glucose co-transporter 2 (SGLT2) is located in the first segment of the proximal tubule and is the major transporter responsible for glucose reabsorption in the kidney. SGLT2 inhibitors (SGLT2i) are highly selective and reversible inhibitors of this transporter. Various SGLT2i such as dapagliflozin, empagliflozin, and canagliflozin are approved for adults with type 2 diabetes and most recently dapagliflozin and empagliflozin have also been approved for adults with chronic kidney disease at risk of progression, including patients with kidney disease due to IgAN (Wheeler, 2021; EMPA Kidney Collaborative Group, 2023). SGLT2 inhibitors cause direct and insulin independent elimination of glucose by the kidneys, which results in reduced blood glucose levels in type 2 diabetes patients. In addition, dapagliflozin has a diuretic and natriuretic effect which results in a reduction in body weight and blood pressure and increase in hematocrit.

In a post-hoc analysis of the SONAR study (Heerspink, 2021), subjects on a combination of atrasentan and SGLT2i (n=14) resulted in decreased body weight, suggesting reduced fluid retention, and further decreased albuminuria after 6 weeks versus a matched group of subjects on atrasentan and background RASi therapy alone. These data combined with the potential of dapagliflozin becoming an established treatment option for subjects with chronic kidney disease (CKD) (including IgAN) in regions that prescribe SGLT2i, merits the investigation of SGLT2i use in combination with atrasentan in the treatment of IgAN

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with atrasentan are justified by the anticipated benefits that may be afforded to subjects with IgAN.

This study will evaluate the safety and efficacy of atrasentan vs placebo in subjects with IgAN while on background therapy with an SGLT2i.

Objective(s) and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of atrasentan vs placebo while on background therapy with SGLT2i	• The change in proteinuria (UPCR from a 24-hour urine collection) from Baseline to Week 12
Secondary	
• To evaluate the efficacy of atrasentan vs placebo while on background therapy with SGLT2i at 24 weeks of treatment	• In Treatment Period 2, the change in proteinuria (UPCR from a 24-hour urine collection) from Baseline to Week 24
Safety	
• To evaluate the safety of atrasentan vs placebo while on background therapy with SGLT2i	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
Pharmacokinetics	
• To evaluate the steady-state pharmacokinetics (PK) of atrasentan CCI [redacted]	• Atrasentan plasma levels

AE = adverse event; PK = pharmacokinetic; SGLT2i = sodium glucose co-transporter 2; UPCR = urine protein:creatinine ratio

BACKGROUND THERAPY

This study will be conducted using a randomized, double-blind, placebo-controlled, crossover design to compare the efficacy and safety of atrasentan to placebo in subjects with IgAN who are receiving

standard of care treatment with RASi and who are on background therapy with SGLT2i. At study entry, subjects will be:

- On a stable dose of a RAS inhibitor (angiotensin-converting-enzyme inhibitor [ACEi] or angiotensin receptor blockers [ARB]) for at least 12 weeks prior to screening
- On a stable dose of SGLT2i for ≥ 8 weeks with a 24-hour total urine protein of > 0.5 grams/day
  OR
- Willing to undergo a run-in period of 8 weeks with an SGLT2i with a 24-hour total urine protein of > 0.85 grams/day at screening prior to the run-in period and have 24-hour total urine protein of > 0.5 grams/day at the end of the run-in period to be eligible for randomization.

After signing an informed consent for the study, subjects will be screened for study eligibility. Total urine protein eligibility will be determined from a 24-hour urine sample at screening. All subjects must have > 0.5 grams/day total urine protein as measured on a 24-hour urine collection prior to enrollment in the trial.

Subjects are considered to be "enrolled" in the study when they, or their legally acceptable representative, have agreed to participate in the clinical study after they have provided informed consent and have been randomized. Potential subjects who are screened to determine their eligibility but fail screening, or do not meet all of the eligibility criteria, or who withdraw consent prior to randomization, are not considered enrolled.

Subjects who are not on or have not received stable doses of SGLT2i prior to study entry will enter a run-in period during which they will receive SGLT2i treatment for 8 weeks. The choice of SGLT2i will be at the discretion of the principal investigator and per local treatment guidelines. Subjects who participate in the run-in period will be required to meet the criterion of a 24-hour total urine protein of >0.5 grams/day, which will be confirmed at the end of the run-in period. Subjects who do not meet this criterion will be considered run-in failures and will not be randomized into the treatment period.

All eligible subjects (i.e., meeting all eligibility criteria, including participation in the 8-week run-in period as applicable) will be randomized 1:1 to either sequence AB or sequence BA in which they will receive 0.75 mg atrasentan once daily (QD) during one period and matching placebo during the other period as determined by the randomization schema. Following randomization, subjects will remain on their maximally tolerated and stable dose of RASi and stable dose of SGLT2i therapies for the duration of the study.

Randomization will be stratified by SGLT2i status (stable vs run-in). All subjects will enter Treatment Period 1 for 12 weeks. Thereafter, all subjects will enter a 12-week washout period before entering Treatment Period 2 for 24 weeks.

Following the end of treatment, subjects will have follow-up evaluations for safety approximately 4 weeks after the end of treatment.

Subjects who prematurely discontinue study drug should have an End of Treatment (EoT) visit at the time of study drug discontinuation, followed by a safety follow up visit 4 weeks after study drug discontinuation (Section 1.3).

The study schema is presented in Section 1.2.

Brief Summary

The purpose of this study is to evaluate the safety and efficacy of atrasentan vs placebo while on background therapy with SGLT2i in subjects with IgAN. The primary efficacy assessment is the change from baseline in proteinuria (UPCR) at week 12 in both Treatment Period 1 and 2.

Study details include:

- Individual subject participation duration: up to 64 weeks for subjects completing the SGLT2i run-in period and 56 weeks for subjects who do not participate in the run-in period
- Treatment duration: 36 weeks of treatment with investigational product (IP)

Study Population and Main Criteria for Eligibility

The main inclusion criteria for eligibility are:

Age

1. Legal adults (per local and country specifications) ≥ 18 years of age at the time of signing the informed consent form (ICF) prior to initiation of any study specific activities/procedures.

Types of Subjects and Disease Characteristics

2. Biopsy-proven IgAN that, in the opinion of the investigator, is not due to secondary causes.
   - Biopsy could have occurred at any point in time prior to study.
   - A diagnostic report must be available for review by the Sponsor or designee.
3. Receiving a maximally tolerated and stable dose of a RASi for at least 12 weeks prior to screening. Investigator discretion should be used in determining maximally tolerated and optimized dose.
4. Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 at screening based on the 2021 CKD-EPI equation (https://www.kidney.org/professionals/kdoqi/gfr_calculator).

Pregnancy and Contraception

5. Willing to abide with highly effective forms of contraception, as specified in the protocol, throughout the study and for up to at least 1 month after treatment completion and per local regulations. In women of child-bearing potential (WOCBP), use of hormonal contraceptive agents must have been started at least 1 month prior to baseline.

Informed Consent

6. Willing and able to provide written informed consent and comply with all study visits and study procedures.

Inclusion Criteria for SGLT2i Stable Subjects

7. Receiving treatment with SGLT2i that has been at a stable dose for at least 8 weeks

prior to screening.

8. Must have a 24-hour total urine protein of > 0.5 grams/day at screening.

Inclusion Criteria for Run-In Subjects

9. Must have a 24-hour total urine protein of > 0.85 grams/day at screening.
10. Willing to participate in an 8-week run-in period with an SGLT2i.

Additional Inclusion Criteria for Run-in Subjects at the end of Run-In

11. Must have completed the 8-week run-in period on a stable and well tolerated dose of an SGLT2i.
12. Must have a 24-hour total urine protein of > 0.5 grams/day confirmed at the Run-in Week 8 visit.
13. Must have an eGFR of ≥ 30 mL/min/1.73 m^2 based on the CKD-EPI equation at their Run-in Week 8 Visit*.

* Please keep in mind for subjects that go through the run-in period with SGLT2i, there is the potential for an acute eGFR reduction of about 10%, but can be up to 30% in rare cases (Meraz-Muñoz, 2021; Heerspink, 2021a)

Subjects who are unable to fulfill the last three criteria during the run-in period will be considered run-in failures.

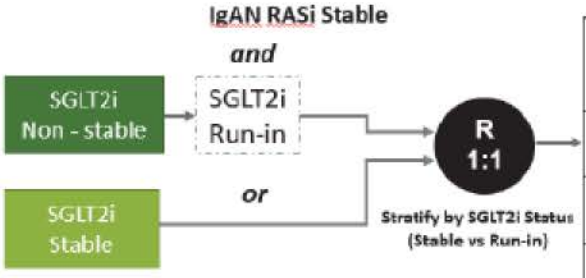
Number of Subjects: Approximately 52 subjects will be enrolled, with approximately 26 subjects per treatment sequence.

Duration of Study Periods

Screening:	up to 6 weeks
SGLT2i Run-in Period[a]:	8 weeks
Treatment Period 1:	12 weeks
Washout Period:	12 weeks
Treatment Period 2:	24 weeks
End of study period	4 weeks

[a] For subjects not on stable doses of SGLT2i

1.2. Study Schema



	Period 1 12 weeks	Wash-out 12 weeks	Period 2 24 weeks (1° EP at wk 12)	EOS (4 weeks)
Sequence AB	A		B	
Sequence BA	B		A	
A = Atrasentan; B = Placebo				

EOS = end of study; EP = endpoint; IgAN = immunoglobulin A nephropathy; R = randomization; RASi = renin-angiotensin system inhibitor; SGLT2i = sodium glucose co-transporter 2

Note: Subjects who have not been on a stable dose of SGLT2i prior to study entry are required to complete the 8-week run-in period. Following randomization, subjects will continue RASi and SGLT2i therapies for the duration of the study.

1.3. Schedule of Activities

1.3.1. Treatment Period 1 for SGLT2i Stable Subjects

Period	Screening [B]	Treatment Period 1						
Day / Week		Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12/EOT[A]
Window	-42 to -1	NA	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d
Phone contact			X		X		X	
In-clinic visits	X	X		X		X		X
Informed Consent	X							
Subject Eligibility	X							
Demographics	X							
Medical History	X							
Prior and Concomitant Therapy Review[J]	←							→
Physical Examination	X	X		X		X		X
12-lead ECG	X	X						
Vital Signs	X	X		X		X		X
Height	X							
Weight	X	X	X	X	X	X	X	X
Pregnancy Test[C]	S	U			U		U	U
Contraception Counseling	X	X	X	X	X	X	X	X
Coagulation Panel	X	X						
Hematology	X	X		X		X		X
HbA1c	X							
Chemistry	X	X		X		X		X
BNP	X	X		X		X		X
FMV for Urinalysis & Urine Chemistry	X	X						
Spot Urine for Urinalysis and Urine Chemistry				X		X		
24-hour urine[I]	X	X[D]						X[E]

Period	Screening [B]	Treatment Period 1						
Day / Week		Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12/EOT[A]
Window	-42 to -1	NA	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d
In-clinic IP Administration		X						
IP dispensing		X[F]						
IP accountability and return								X
IP compliance review			X	X	X	X	X	X
PK (Pre-dose)				X		X		X
CCI								
Randomization		X						
Adverse Events[G]	◄							►

BNP = brain natriuretic peptide; ECG = electrocardiogram; EOT = end of treatment; FMV = first morning void; IP = investigational product; RASi = renin-angiotensin system inhibitor; PD = pharmacodynamic; PK = pharmacokinetic; S = serum; SGLT2i = sodium glucose co-transporter 2 inhibitor; U = urine; Wk = week

[A] For subjects who discontinue the study drug prematurely. These subjects should be followed by a safety follow up visit 4 weeks after study drug discontinuation.

[B] Screening assessments will be conducted within 42 days of Day 1 for SGLT2i stable subjects.

[C] Pregnancy testing for women of childbearing potential will be performed at Screening (serum), Day 1 (urine), Week 4 (urine), Week 8 (urine), Week 12 (urine), and EOT (urine).

[D] Within 7 days prior to Day 1 visit

[E] There will be 2 collections at Week 12. Both collections should be within 7 days prior to study visit.

[F] Subjects will receive study drug for the 12-week treatment period at this visit

[G] All adverse events will be collected between Informed Consent until end of study.

CCI

[I] Provide 24-hour urine collection container for Screening sample, at end of Screening visit for Baseline sample, and at Week 6 for Week 12 samples.

[J] Includes confirmation of maximally tolerated and stable dose of RASi therapy

CCI

1.3.2. Treatment Period 1 for Run-In Subjects

Period	Screening[A]	Run-In			Treatment Period 1						
Day / Week		Day 1	Wk 4	Wk 8	Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12/EOT[B]
Window	-42 to -1		± 3d	±3d	[D]	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d
Phone contact		X				X		X		X	
In-clinic visits	X		X	X	X		X		X		X
Informed Consent	X										
Subject Eligibility	X			X							
Demographics	X										
Medical History	X										
Prior and Concomitant Therapy Review[J]	←										→
Physical Examination	X		X		X		X		X		X
12-lead ECG	X				X						
Vital Signs	X		X	X	X		X		X		X
Height	X										
Weight	X		X		X	X	X	X	X	X	X
Pregnancy Test[C]	S	U	U	U	U			U		U	U
Contraception Counseling	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X				X						
Hematology	X		X		X		X		X		X
HbA1c	X										
Chemistry	X		X	X	X		X		X		X
BNP	X		X		X		X		X		X
FMV for Urinalysis & Urine Chemistry	X			X							

Period	Screening[A]	Run-In			Treatment Period 1						
Day / Week		Day 1	Wk 4	Wk 8	Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12/EOT[B]
Window	-42 to -1		± 3d	±3d	[D]	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d
Spot Urine for Urinalysis and Urine Chemistry			X				X		X		
24-hour urine[D]	X			X[H]	[D]						X[E]
Initiation of SGLT2i		X									
In-clinic IP Administration					X						
IP dispensing					X[F]						
IP accountability and return											X
IP compliance review						X	X	X	X	X	X
PK (Pre-dose)							X		X		X
CCI											
Randomization					X						
Adverse Events[G]	◄										►

BNP = brain natriuretic peptide; d = day; ECG = electrocardiogram; EOT = end of treatment; FMV = first morning void; IP = investigational product; PK = pharmacokinetic; RASi = renin-angiotensin system inhibitor; S = serum; SGLT2i = sodium glucose co-transporter 2 inhibitor; U = urine; Wk = week

[A] Screening assessments will be conducted within 42 days of entering the run-in period for subjects who are not on a stable SGLT2i dose.

[B] For subjects who discontinue the study drug prematurely. These subjects should be followed by a safety follow-up visit 4 weeks after study drug discontinuation.

[C] Pregnancy testing for women of childbearing potential will be performed at Screening (serum), Run-in Day 1 (urine), Run-in Week 4 (urine), and Run-in Week 8 (urine), Baseline Day 1 (urine), Week 4 (urine), Week 8 (urine), Week 12 (urine), and EOT (urine).

[D] Provide 24-hour urine collection container at Run-in Week 4. The 24-hour Urine collected at Run-in Week 8 will qualify as the Run-In subjects' Baseline 24-hour Urine. Baseline Day 1 will occur after eligibility for Treatment Period 1 is confirmed and within 14 days of Run-in Week 8.

[E] There will be 2 collections at Week 12. Both collections should be within 7 days prior to study visit.

[F] Subjects will receive study drug for the 12-week treatment period at this visit.

[G] All adverse events will be collected between Informed Consent until end of study.
[H] Reconfirm eligibility for Run- in subjects.
CCI
[J] Includes confirmation of maximally tolerated and stable dose of RASi therapy. Subjects who complete the run-in period will also be required to be on a stable dose of SGLT2i.
CCI

1.3.3. Washout Period

Period	Washout											
Day / Week	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12[A]
Window	NA	NA	NA	± 3d	NA	± 3d	NA	± 3d	NA	NA	NA	± 3d
In-clinic visits						X						
Phone contact				X				X				X
Concomitant Therapy Review[C]	◄											►
Physical Exam						X						
Vital Signs						X						
Weight				X		X		X				
Pregnancy Test				U		S		U				U
Contraception Counseling				X		X		X				X
Hematology						X						
Chemistry						X						
BNP						X						
FMV for Urinalysis & Urine Chemistry						X						
PK						X						
Distribute 24-hour urine collection jug[B]						X						
Adverse Events	◄											►

BNP = brain natriuretic peptide; d = day; FMV = first morning void; PK = pharmacokinetic; RASi = renin-angiotensin system inhibitor; U = urine; Wk = week
[A] Day 1 of Treatment Period 2 occurs within 7 days after the end of Week 12 of the washout period
[B] Subjects should be instructed to return a 24-hour urine sample on Day 1 of Treatment Period 2
[C] Includes confirmation of maximally tolerated and stable dose of RASi therapy and stable dose of SGLT2i

1.3.4. Treatment Period 2

Period	Treatment Period 2										Follow-up
Day / Week	Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ EOT[B]	Wk 28/EOS
Window	[A]	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 7d	± 7d
Phone contact		X		X		X		X	X		
In-clinic visits	X		X		X		X			X	X
Concomitant Therapy Review[J]	◄										►
Physical Examination	X		X		X		X			X	X
Vital Signs	X		X		X		X			X	X
Weight	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test [C]	U			U		U	U	U	U	U	S
Contraception counseling	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X										
Hematology	X		X		X		X			X	X
Chemistry	X		X		X		X			X	X
BNP	X		X		X		X			X	X
FMV for Urinalysis & Urine Chemistry	X										
Spot Urine for Urinalysis & Urine Chemistry			X		X						
24-hour urine[I]	X[D]						X[E]			X[G]	
PK (pre-dose)			X		X		X			X	

Period	Treatment Period 2										Follow-up
Day / Week	Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ EOT[B]	Wk 28/EOS
Window	[A]	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 7d	± 7d
CCI											
In-clinic IP administration	X										
IP dispensing	X[F]						X[F]				
IP accountability and return							X			X	
IP compliance review		X	X	X	X	X	X	X	X	X	
Adverse Events	◄										►

BNP = brain natriuretic peptide; d = day; EOS = end of study; EOT = end of treatment; FMV = first morning void; IP = investigational product; PK = pharmacokinetic; RASi = renin-angiotensin system inhibitor; SGLT2i = sodium glucose co-transporter 2 inhibitor; Wk = week

A Period 2 Baseline Day 1 will occur within 7 days of Washout Period Week 12

B. For subjects who discontinue the study drug prematurely. These subjects should be followed by a safety follow up visit 4 weeks after study drug discontinuation

C. Pregnancy testing for women of childbearing potential will be performed approximately every 4 weeks at Day 1 (urine), Week 4 (urine), Week 8 (urine), Week 12 (urine), Week 16 (urine), Week 20 (urine), Week 24 (EOT) (urine) and EOS (serum).

D Subjects should return a 24-hour urine sample on Day 1 of Treatment Period 2

E There will be 2 collections at Week 12. Both collections should be within 7 days prior to study visit.

F Subjects will receive study drug at Day 1 and at Week 12. Day 1 dose will be administered at the clinic.

G. There will be 2 collections at Week 24. Both collections should be within 7 days prior to study visit.

CCI

J Includes confirmation of maximally tolerated and stable dose of RASi therapy and stable dose of SGLT2i until end of study

2. INTRODUCTION

2.1. Background

Atrasentan is a potent antagonist of endothelin receptor A (ETA, Ki = 0.034 nM) that has been studied extensively as a once-daily treatment for diabetic nephropathy in individuals with type 2 diabetes in addition to optimized doses of renin-angiotensin system (RAS) inhibitors (RASi). Atrasentan is now being studied in subjects with immunoglobulin A nephropathy (IgAN) at risk of progressive loss of renal function despite treatment with a maximally tolerated and stable dose of a RASi. IgAN is a glomerular disease marked by excessive levels of urinary protein excretion. EXV811 is the Novartis project code for Atrasentan. Atrasentan is referenced throughout the protocol, however, it is the same as EXV811.

The sodium glucose co-transporter 2 (SGLT2) is located in the first segment of the proximal tubule and is the major transporter responsible for glucose reabsorption in the kidney. Sodium glucose co-transporter 2 inhibitors (SGLT2i) are highly selective and reversible inhibitors of this transporter. Various SGLT2i such as dapagliflozin, empagliflozin, and canagliflozin are approved for adults with type 2 diabetes and most recently, dapagliflozin has been approved for adults with chronic kidney disease, at risk of progression, including patients with kidney disease due to IgAN (Wheeler, 2021). SGLT2i cause direct and insulin independent elimination of glucose by the kidneys, which results in reduced blood glucose levels in patients with type 2 diabetes. In addition, dapagliflozin has a diuretic and natriuretic effect which results in a reduction in body weight and blood pressure and increase in hematocrit.

The cardio-renal efficacy and safety of SGLT2i has been established in tewo dedicated kidney outcome trials recruiting more than 4000 subjects in each trial. The first trial demonstrated that in adult subjects with type 2 diabetes and chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] 30–90 mL/min/1.73m^2), the SGLT2i canagliflozin reduced the risk of renal and cardiovascular outcomes. The second trial, DAPA-CKD, was designed to assess the efficacy and safety of dapagliflozin in subjects with CKD with and *without* type 2 diabetes (Heerspink, 2020).

The trial enrolled adult subjects with an estimated glomerular filtration rate between 25 and 75 mL/min/1.73m^2 and a urinary albumin:creatinine ratio between 200 and 5000 mg/g. After a median of 2.4 years follow-up, the trial was terminated early by the independent data monitoring committee for overwhelming efficacy. Dapagliflozin compared to placebo treatment reduced the primary outcome of 50% eGFR decline, end-stage kidney disease, renal or cardiovascular death by 39%. In addition, dapagliflozin reduced the risk of the composite endpoint of heart failure hospitalizations or cardiovascular death by 29% and it reduced the risk of all-cause mortality by 31%. These effects were present both in subjects with and without type 2 diabetes. In participants with type 2 diabetes, the hazard ratio for the comparison of dapagliflozin and placebo for the primary outcome was 0.64 (95% CI, 0.52 to 0.79), as compared with 0.50 (95% CI, 0.35 to 0.72) in participants without type 2 diabetes (Heerspink, 2020). Proposed mechanisms for the beneficial effects of SGLT2 inhibitors include reduced intra-glomerular pressure through an enhanced tubuloglomerular feedback mechanism, reduced glucose and sodium transport by proximal tubular cells, increased natriuresis, and reduced systemic blood pressure.

Atrasentan previously demonstrated benefit in subjects with diabetic nephropathy in reducing albuminuria and has a well characterized safety profile in > 5300 subjects with diabetic nephropathy. In a global Phase 3 study (SONAR), subjects with an early beneficial response of albuminuria reduction following daily atrasentan exposure experienced a clinically important and statistically significant improvement on the primary composite endpoint of time to doubling of serum creatinine or progression to end stage renal disease (ESRD; log-rank p value, 0.029, hazard ratio 0.65 [95% confidence interval (CI) 0.49 - 0.88]). A similarly favorable trend was also observed in a smaller cohort of subjects with lesser or no initial response to atrasentan on albuminuria reduction (log-rank p value, 0.15, hazard ratio 0.75 [95% CI 0.55 - 1.03]). These results were obtained despite the early termination of the study prior to completion of the planned number of renal composite events.

2.1.1. Clinical Development of Atrasentan

To date, atrasentan has been investigated in 51 completed Phase 1, 2, and 3 studies involving approximately 641 healthy volunteers, 2,276 subjects with cancer (primarily prostate cancer), 12 subjects with congestive heart failure, 10 subjects with moderate chronic hepatic impairment, and more than 5,400 subjects with renal diseases: diabetic nephropathy, IgA nephropathy (IgAN), and focal segmental glomerulosclerosis (FSGS).

In multiple Phase 2 randomized placebo-controlled studies in diabetic nephropathy, treatment with atrasentan was shown to reduce urinary albumin:creatinine ratio (UACR) in a rapid and durable fashion. The most common adverse events (AEs) associated with treatment included fluid retention, hemodilution, and vasodilation. These AEs were consistent with the on-target pharmacologic mechanism of atrasentan. Through dose-range finding studies and exposure-response analyses, an optimal daily dose of 0.75 mg was identified and led to marked reduction in UACR with only modest fluid retention. This dose was then used in a large Phase 3 randomized placebo-controlled study in diabetic nephropathy subjects receiving optimized doses of renin angiotensin system (RAS) inhibitors to evaluate the effect of atrasentan on the primary composite endpoint of delaying time to end stage renal disease (ESRD) or doubling of serum creatinine (SONAR). This study was halted prematurely as a result of a lower than predicted annual occurrence of the primary renal outcomes; however, despite the lower number of primary endpoint events, subjects who tolerated atrasentan and demonstrated an early reduction of UACR showed a benefit on reducing poor renal outcomes. No new safety findings were identified, and the risks of fluid retention were shown to be mitigated by careful monitoring and use of diuretics.

Atrasentan is now under evaluation for its potential to reduce proteinuria and slow the progression of kidney function loss in subjects with IgAN (CHK01-01 – the ALIGN study). The study enrolled 340 subjects with IgAN who were not currently receiving SGLT2i therapy and 64 subjects with IgAN who were on a stable dose of SGLT2i. Similar to diabetic nephropathy, IgAN is treated with RAS inhibitors to decrease proteinuria and slow the decline in kidney function. Despite RAS inhibitor treatment, many patients continue to have significant proteinuria and remain at risk for ESKD. As such, patients with IgAN and residual proteinuria > 500 mg/day, despite optimized RAS inhibition, represent a population with an important unmet need for a therapy. IgAN was also chosen based on the known association of endothelin system activation in disease progression as well as the importance of proteinuria in driving disease progression.

A detailed description of the chemistry, pharmacology, efficacy, and safety of atrasentan is provided in the Investigator's Brochure.

2.2. Study Rationale

Current standard of care therapy for IgAN, as outlined by Kidney Disease Improving Global Outcomes (KDIGO) guidelines, is blood pressure control with RASi (angiotensin-converting-enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]) (KDIGO, 2021). However, for patients with persistent proteinuria despite optimal blood pressure control, there are limited second-line treatment options and disease progression can lead to end stage kidney disease (ESKD), resulting in dialysis or kidney transplant. Therefore, there is an unmet medical need for patients with IgAN who do not achieve sufficient benefit from blood pressure control alone.

In view of the current uncertainty over the safety and efficacy of existing immunosuppressive treatment choices and KDIGO glomerular disease guidelines, all patients who remain at high risk of progressive CKD despite maximal supportive care should be offered the opportunity to take part in a clinical trial (KDIGO, 2021).

In addition to the study SONAR results (described in Section 2.1), a post-hoc analysis (Heerspink, 2021) of SONAR subjects revealed that 6 weeks treatment with combined SGLT2i/atrasentan versus atrasentan alone decreased body weight, a surrogate for fluid retention, and further decreased albuminuria. These promising findings support the rationale to investigate long-term efficacy and safety of combined SGLT2i and atrasentan treatment in the ASSIST study.

SGLT2 inhibitors have been used in the treatment of IgAN (Wheeler, 2021). In 2021, FARXIGA® (dapagliflozin) was the first approved SGLT2i by FDA and EMA to reduce the risk of sustained eGFR decline, ESKD, cardiovascular death, and hospitalization for heart failure in adults with non-diabetic CKD at risk of progression. A post-hoc analysis of the SONAR study showed that the combination of atrasentan and an SGLT2i (n=14) resulted in decreased body weight (surrogate for fluid retention) and further decreased albuminuria after 6 weeks versus atrasentan alone (Heerspink, 2021). This data combined with the potential of dapagliflozin becoming an established treatment option for subjects with CKD (including IgAN) in regions that prescribe SGLT2i, merits the investigation of SGLT2i use in combination with atrasentan in the treatment of IgAN.

Thus, this study will evaluate the safety and efficacy of atrasentan versus placebo in subjects with IgAN while on background therapy with an SGLT2i. The study will enroll 2 separate populations:

- subjects who are not on a SGLT2i at enrollment (referred to throughout as SGLT2i run-in stratum) and
- subjects who are on stable dose of SGLT2i (referred to throughout as SGLT2i stable stratum).

Both populations will be on their maximally tolerated stable dose of RASI throughout the study.

2.3. Benefit / Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of atrasentan are provided in the Investigator's Brochure. The most common adverse events associated with treatment (fluid retention, hemodilution, and vasodilation) are consistent with its on-target pharmacologic mechanism of action.

2.3.1. Benefit Assessment

Atrasentan has been studied extensively by a previous sponsor (see Section 2.1.1), first as a potential treatment for advanced prostate cancer, and subsequently as a potential treatment for patients with diabetic kidney disease.

In multiple Phase 2 randomized placebo-controlled studies in diabetic nephropathy, treatment with atrasentan was shown to reduce urinary albumin:creatinine ratio (UACR) in a rapid and durable fashion.

Atrasentan previously demonstrated benefit in subjects with diabetic nephropathy in reducing albuminuria and has a well characterized safety profile in > 5300 subjects with diabetic nephropathy. In a global Phase 3 study (SONAR), subjects with an early beneficial response of albuminuria reduction following daily atrasentan exposure experienced a clinically important and statistically significant improvement on the primary composite endpoint of time to doubling of serum creatinine or progression to ESKD (log-rank p value, 0.029, hazard ratio 0.65 [95% confidence interval (CI) 0.49 - 0.88]). A similarly favorable trend was also observed in a smaller cohort of subjects with lesser or no initial response to atrasentan on albuminuria reduction (log-rank p value, 0.15, hazard ratio 0.75 [95% CI 0.55 - 1.03]). These results were obtained despite the early termination of the study prior to completion of the planned number of renal composite events.

In a Phase 2 study of atrasentan in subjects with proteinuric glomerular diseases (the AFFINITY study), 20 subjects with IgAN who were receiving a maximally tolerated and stable does of RASi were enrolled in Cohort 1 and evaluated for the primary endpoint of UPCR change from baseline at Week 12. As of an October 2022 data cutoff, the LSMean percent change from baseline to Week 12 was -48.3%, strongly supporting a key role of the endothelin pathway in the pathogenesis of IgAN (Kim, 2022). Atrasentan was well tolerated in subjects with IgAN up to 52 weeks of treatment. Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with atrasentan are justified by the anticipated benefits that may be afforded to subjects with IgAN.

2.3.2. Risk Assessment

Table 1 Risks and Mitigation Strategies - Atrasentan

Identified Risk	Rationale / Summary of Data	Mitigation Strategy (ies)
Potentially decreased spermatogenesis	Decreased sperm counts have been observed in some patients taking endothelin antagonists (ambrisentan, bosentan). Following drug discontinuation, recovery was noted. In man, the risk of testicular dysfunction from prolonged exposure to atrasentan is not known.	Subject education regarding potential effects of spermatogenesis
Teratogenicity	Atrasentan embryofetal development studies in both rats and rabbits showed teratologic changes in both species. Similar developmental anomalies have been reported with other ET-receptor antagonists, indicating that teratogenicity is a class effect.	Pregnancy testing and contraception counselling
Fluid retention	Fluid retention is a pharmacological effect of ET-receptor antagonists. Peripheral edema and excessive weight gain secondary to fluid retention have been observed in clinical studies. Fluid retention is considered a class effect.	Close monitoring of fluid status by Investigator and, if needed, prompt initiation of diuretics. In cases where fluid retention cannot be managed by diuretics, in consultation with the Sponsor's Medical Lead (or designee), study drug may be discontinued in subjects with fluid retention that is intolerable to the subject and cannot be adequately managed with diuretics and dietary modifications.
Vasodilation/hypotension	Hypotension through vasodilatation is associated with the suppression of ET-1 effects by ET-receptor antagonists and is a class effect.	Investigators are instructed to contact the Sponsor's Medical Lead to discuss guidance for the management of subjects who experience a volume depletion adverse event (e.g., hypotension, hypovolemia) or a meaningful change in eGFR (such as >30% decline from a prior visit).
Cardiac Failure	Pulmonary edema and CHF are potential effects of ET-receptor antagonists.	Subjects with a known history of heart failure or prior hospital admissions for conditions relating to fluid overload are excluded from the trial. In cases where patients develop de novo cardiac failure immediate treatment per standard of care must be initiated, study drug is to be

	discontinued immediately and Medical Lead notified.

CHF = congestive heart failure; eGFR = estimated glomerular filtration rate; ET = endothelin receptor; SGLT2i = sodium glucose co-transporter 2 inhibitor

As this is the first study with the combination of atrasentan and SGLT2i's, an overlapping risk of both medications is hypotension. Increased monitoring of subjects for the signs and symptoms of hypotension should be done after initiating therapy.

*There may also be additional identified risks associated with the use of specific SGLT2i's used, please refer to the Prescribing Information for the specific SGLT2i used to treat the subject.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Objectives and Endpoints

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of atrasentan vs placebo while on background therapy with SGLT2i	• The change in proteinuria (UPCR from a 24-hour urine collection) from Baseline to Week 12
Secondary	
• To evaluate the efficacy of atrasentan vs placebo while on background therapy with SGLT2i at 24 weeks of treatment	• In Treatment Period 2, the change in proteinuria (UPCR from a 24-hour urine collection) from Baseline to Week 24
Safety	
• To evaluate the safety of atrasentan vs placebo while on background therapy with SGLT2i	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
Pharmacokinetics	
• To evaluate the steady-state pharmacokinetics (PK) of atrasentan CCI [redacted]	• Atrasentan plasma levels
Exploratory	
• To evaluate the effect on eGFR between atrasentan vs placebo while on background therapy with SGLT2i at 24 weeks of treatment	• In Treatment Period 2, the change in eGFR of atrasentan vs placebo using the chronic kidney disease-epidemiology collaboration (CKD-EPI) creatinine equation from Baseline to Week 24
• To evaluate additional safety outcomes	• Incidence, severity, seriousness, and relatedness of adverse events of special interest including events of fluid overload • Clinically significant changes in: ○ Safety laboratory (hematology, complete chemistry and urinalysis) and BNP

Objectives	Endpoints
Exploratory	
CCI	

AE = adverse event(s); BNP = brain natriuretic peptide; CKD-EPI = chronic kidney disease-exocrine pancreatic insufficiency (equation); eGFR = estimated glomerular filtration rate; CCI CCI SGLT2i = sodium-glucose co-transporter 2 inhibitor; UPCR = urine protein:creatinine ratio

3.2 Primary Estimand

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of study drug).

Clinical Question: What will be the expected effect of being assigned atrasentan, compared to placebo, on UPCR reduction at Week 12 for the target population in the absence of investigational or approved products for the treatment of IgAN?

Justification: Treatment effect assessed in real-world clinical practice including the effects of study drug discontinuation, initiation of maintenance dialysis or kidney transplantation, dose modification or discontinuation of background therapies, and initiation of prohibited or restricted concomitant medications in conditions similar to clinical practice, but in the absence of any potential confounding effects of investigational or approved products for the treatment of IgAN.

The primary estimand for the primary endpoint and the handling of intercurrent events are defined below:

- **Population:** Adults with biopsy-proven IgAN at risk of progressive loss of renal function who are receiving background therapy with SGLT2i and RASi.
- **Endpoint:** Change in proteinuria (UPCR from a 24-hour urine collection) from Baseline to Week 12 (across both periods).
- **Treatment of interest:** The randomized treatment of 0.75 mg atrasentan once daily (QD) or placebo in addition to background therapy with SGLT2i and RASi.
- **Handling of intercurrent events:**
  - Study drug discontinuation for any reason: treatment policy strategy.
  - Initiation of maintenance dialysis or kidney transplantation: treatment policy strategy.
  - Dose modification or discontinuation of background therapy (RAS/SGLT2 inhibitors): treatment policy strategy.

- Initiation of prohibited or restricted concomitant medication: treatment policy strategy.
- Initiation of an investigational or approved product for the treatment of IgAN (other than RASi and SGLT2i): hypothetical strategy.

- **Summary measure:** Ratio of geometric means relative to baseline between treatment groups. The summary measure will be converted to a percentage change.

3.3 Secondary Estimand

Clinical Question: What will be the expected effect of being assigned atrasentan, compared to placebo, on UPCR reduction at Week 24 of Treatment Period 2 for the target population in the absence of investigational or approved products for the treatment of IgAN?

Justification: Treatment effect assessed in real-world clinical practice including the effects of study drug discontinuation, initiation of maintenance dialysis or kidney transplantation, dose modification or discontinuation of background therapies, and initiation of prohibited or restricted concomitant medications in conditions similar to clinical practice, but in the absence of any potential confounding effects of investigational or approved products for the treatment of IgAN.

The secondary estimand for the secondary endpoint and the handling of intercurrent events are defined below:

- **Population:** Adults with biopsy-proven IgAN at risk of progressive loss of renal function who are receiving background therapy with SGLT2i and RASi.
- **Endpoint:** Change in proteinuria (UPCR from a 24-hour urine collection) from Baseline to Week 24 of Treatment Period 2.
- **Treatment of interest:** The randomized treatment of 0.75 mg atrasentan once daily (QD) or placebo in addition to background therapy with SGLT2i and RASi.
- **Intercurrent events**
  - Study drug discontinuation for any reason: treatment policy strategy.
  - Initiation of maintenance dialysis or kidney transplantation: treatment policy strategy.
  - Dose modification or discontinuation of background therapy (RAS/SGLT2 inhibitors): treatment policy strategy.
  - Initiation of prohibited or restricted concomitant medication: treatment policy strategy.
  - Initiation of an investigational or approved product for the treatment of IgAN (other than RASi and SGLT2i): hypothetical strategy.
- **Summary measure:** Ratio of geometric means relative to baseline between treatment groups. The summary measure will be converted to a percentage change.

4. STUDY DESIGN

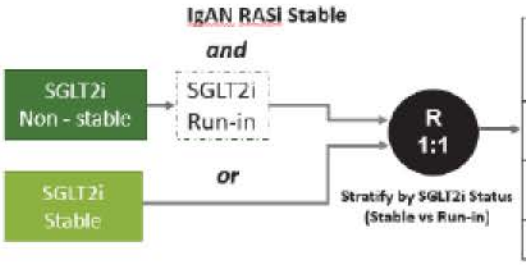
4.1. Overall Design

This study will be conducted using a randomized, double-blind, placebo-controlled, crossover design to compare the efficacy and safety of atrasentan to placebo in subjects with IgAN on background therapy with SGLT2i and RASi. Per KDIGO guidelines on standard of care for IgAN, all subjects are required to be on a maximally tolerated dose of RASi (ACE inhibitors or ARBs) prior to screening (KDIGO, 2021). Subjects eligible for this study may be on a stable dose of SGLT2i prior to screening, may have received SGLT2 inhibitors in the past but not be on a stable dose, or be SGLT2i naïve. Following randomization, subjects will remain on their maximally tolerated and stable dose of RASi and stable dose of SGLT2i therapies for the duration of the study.

Subjects who are not on an SGLT2i (or have not received stable doses prior to study entry) will enter a run-in period, starting on the first day of SGLT2i administration, during which they will receive SGLT2i (choice of SGLT2i per PI's discretion and per local treatment standards) for 8 weeks. Thereafter, all eligible subjects will be randomized 1:1 to either sequence AB or sequence BA in which they will receive 0.75 mg atrasentan once daily (QD) during one period and matching placebo during the other period as determined by the randomization schema. Randomization will be stratified by SGLT2i status (stable vs not stable). All subjects will enter Treatment Period 1 for 12 weeks. Thereafter, all subjects will enter a 12-week washout period before entering Treatment Period 2 for 24 weeks.

The study design is illustrated in Figure 1.

Figure 1. Overall Study Schema



	Period 1 12 weeks	Wash-out 12 weeks	Period 2 24 weeks (1° EP at wk 12)	EOS (4 weeks)
Sequence AB	A		B	
Sequence BA	B		A	
A = Atrasentan; B = Placebo				

EOS = end of study; EP = endpoint; IgAN = immunoglobulin A nephropathy; R = randomization; RASi = renin-angiotensin system inhibitor; SGLT2i = serum glucose co-transporter 2 inhibitor
Note: Subjects who have not been on a stable dose of SGLT2i prior to study entry are required to complete the 8-week run-in period. Following randomization, subjects will remain on RASi and SGLT2i therapies for the duration of the study.

At the end of Week 1 of each study period, subjects will have a telephone contact for safety evaluation. Subsequently and throughout the treatment period, subjects will be evaluated for change in proteinuria and eGFR from baseline.

Pregnancy testing for women of child-bearing potential (WOCBP) and counselling for men and women on study contraception requirements will also occur throughout the study (see Section 8.1.7.8). Subjects will be requested to monitor their weight regularly throughout each study period.

Following the end of treatment, subjects will have follow-up evaluations for safety, approximately 4 weeks after the end of treatment.

Throughout the study, subjects will be assessed through on-site clinic visits, and telephone calls, as specified in the Schedule of Activities (see Section 1.3). Please also refer to Appendix 4 or guidance to address global health emergencies.

4.2. End of Study Definition

A subject will be considered to have completed the study if they have completed all phases of the study (see Section 1.3).

The global end of study is defined as the date of the last visit of the last subject in the study.

5. STUDY POPULATION

Subjects must meet all inclusion criteria and none of the exclusion criteria to be eligible for enrollment into this study. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

All subjects must meet the following inclusion criteria to be enrolled.

Age

1. Legal adults (per local and country specifications) ≥ 18 years of age at the time of signing the informed consent form (ICF) prior to initiation of any study specific activities/procedures.

Types of Subjects and Disease Characteristics

2. Biopsy-proven IgAN that, in the opinion of the investigator, is not due to secondary causes.
    a. Biopsy could have occurred at any point in time prior to study.
    b. A diagnostic report must be available for review by the Sponsor or designee.
3. Receiving a maximally tolerated and stable dose of a renin-angiotensin system inhibitor (RASi) for at least 12 weeks prior to screening. Investigator discretion should be used in determining maximally tolerated and optimized dose.
4. eGFR ≥ 30 mL/min/1.73 m^2 at screening based on the 2021 CKD-EPI equation (https://www.kidney.org/professionals/kdoqi/gfr_calculator).

Pregnancy and Contraception

5. Willing to abide with highly effective forms of contraception, as specified in the protocol, throughout the study and for up to 1 month afterward. In WOCBP, use of hormonal contraceptive agents must have been started at least 1 month prior to baseline.

Informed Consent

6. Willing and able to provide written informed consent and comply with all study visits and study procedures.

Inclusion Criteria for SGLT2i Stable Subjects

7. Receiving treatment with SGLT2i at a stable dose for at least 8 weeks prior to screening.
8. Must have a 24-hour total urine protein of > 0.5 grams/day.

Inclusion Criteria for Run-In Subjects

9. Must have a 24-hour total urine protein of >0.85 grams/day at screening.

10. Willing to participate in an 8-week run-in period with an SGLT2i.

Additional Inclusion Criteria for Run-in Subjects at the end of Run-In

11. Must have completed the 8-week run-in period on a stable and well tolerated dose of an SGLT2i.
12. Must have a 24-hour total urine protein of > 0.5 grams/day confirmed at the Run-in Week 8 visit.
13. Must have an eGFR of ≥ 30 mL/min/1.73 m2 based on the CKD-EPI equation at their Run-in Week 8 visit*.

* Please keep in mind for subjects that go through the run-in period with SGLT2i, there is the potential for an acute eGFR reduction of about 10%, but can be up to 30% in rare cases (Meraz-Muñoz, 2021; Heerspink, 2021a).

Subjects who are unable to fulfill the last 3 criteria during the run-in period will be considered run-in failures.

5.2. Exclusion Criteria

Subjects must meet NONE of the following exclusion criteria to be enrolled.

1. Concurrent diagnosis of another cause of chronic kidney disease including diabetic kidney disease or another primary glomerulopathy.
2. Clinical suspicion of rapidly progressive glomerulonephritis (RPGN) based on KDIGO guidelines or clinical suspicion of Henoch-Schonlein Purpura (IgA vasculitis).
3. Clinical diagnosis of nephrotic syndrome.
4. Diagnosis of Type 1 diabetes.
5. Brain natriuretic peptide (BNP) value of > 200 pg/mL at screening.
6. Platelet count <80,000 per µL at screening.
7. History of organ transplantation (subjects with history of corneal transplant are not excluded).
8. Use of systemic immunosuppressant medications including systemic corticosteroids (e.g., prednisone, prednisolone, budesonide, etc.) mycophenolate, azathioprine, cyclosporine, tacrolimus, etc.; use of herbs such as Tripterygium Wilfordii Hook F, Caulis sinomenii and Sinomenium acutum; for > 2 weeks in the past 3 months. Use of rituximab within the past 6 months.
9. Confirmed blood pressure > 150 mmHg systolic or > 95 mmHg diastolic based on a blood pressure measurement obtained at screening.
10. Known history of heart failure or prior hospital admissions for conditions relating to fluid overload including but not limiting to pulmonary edema, uncontrolled peripheral edema, pleural effusion, ascites that in the opinion of the Investigator or Sponsor's Medical Lead (or designee), might confound the results of the study

or pose additional risk to the subject by their participation in the study.

11. Known history of clinically significant liver disease or transaminase or bilirubin values more than twice the upper limit of normal. Subjects with treated hepatitis C can be considered for inclusion into the study upon consultation with the Sponsor's Medical Lead (or designee).
12. Hemoglobin below 9 g/dL at screening or prior history of blood transfusion for anemia within 3 months of screening.
13. History of malignancy unless cancer free for at least 5 years or nonmelanoma skin cancer that was completely resected. A subject with curatively treated cervical carcinoma in situ is eligible for this study.
14. Pregnancy, breast feeding, or intent to become pregnant during the study period and at least 1 month afterward for females.
15. Intent to father a child or donate sperm during the study period and at least 1 month afterward for males.
16. Have received any investigational agent or approved treatment for IgAN (other than a RAS inhibitor and SGT2i) within 1 month (or 5 half-lives of the agent, whichever is longer) prior to screening. If the investigational agent is a cytotoxic or immunosuppressive agent, then this washout period is 6 months.
17. Concurrent clinically significant, unstable, or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the Investigator or Sponsor's Medical Lead (or designee), might confound the results of the study or pose additional risk to the subject by their participation in the study.
18. History of an alcohol or illicit drug-related disorder within the past 1 year.

5.3. Lifestyle Considerations

The investigator should educate subjects to refrain from high protein meals and to avoid heavy/strenuous activity for 24 hours prior to their scheduled laboratory assessments.

Below are suggested measures to decrease serum creatinine variability prior to the scheduled blood draws required by this protocol.

All subjects should:

- Maintain a stable dietary protein intake and avoid very different or high protein meals the day before each scheduled serum creatinine assessment.
- Maintain a stable exercise routine and avoid very different or heavy physical activity/exercise the day before each scheduled serum creatinine assessment.

Subjects are to refrain from vigorous exercise 48 hours prior to any urine collection.

- Plan to arrive at the same time for each blood-draw and clinic visit to better standardize time of the sample collection throughout the study.
- Some medications may increase serum creatinine levels (e.g., cimetidine, non-steroidal anti-inflammatory drugs [NSAID] medications like aspirin or ibuprofen, chemotherapy drugs, cephalosporin). Subjects should alert the investigator, and any other health-care providers, to take this into consideration when considering changes in their prescribed or over-the-counter medications, and all medication changes should be reported to the investigator.

5.4. Screen Failure & Run-In Failure

A screen failure is defined as a subject who consents to participate in the clinical study, does not enter the run-in period, and is not randomized. A run-in failure is defined as a subject who does not complete the run-in period or is not randomized after the run-in period.

A minimal set of information is required to ensure transparent reporting of screen failure and run-in failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. If a subject is not eligible to enter the study (i.e., is a screen or run-in failure), minimal information should be documented (reference CRF Completion Guidelines for data collection requirements).

Screen failures may be eligible to re-screen once with a new consent and new subject identifier (ID). Additional screening and re-testing may be allowed with Medical Lead approval.

Run-in failures may be eligible to re-screen at the discretion of the investigator and upon discussion with the Medical Lead.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

6.1. Study Interventions

Investigational Product (IP) (or "study drug") includes both atrasentan, and matching placebo.

6.1.1. Investigational Products

Table 3 Pharmaceutical Properties and Formulation

Investigational product name	Atrasentan (Active)	Placebo (Control)
Dose formulation	Film-coated round tablets	Matching placebo film-coated round tablets
Unit dose strength	0.75 mg per tablet	Placebo tablet
Dose regimen	1 tablet QD	1 tablet QD
Route of administration and administration instructions	Oral with or without food at approximately the same time each day. Subjects should not take more than one tablet each day. The tablets should not be crushed or broken and must be administered whole. Subjects will also be instructed that the bottle containing the study drug contains a desiccant, which should be returned to the bottle directly after each tablet removal.	
Sourcing	Study drug will be provided to the site centrally by the Sponsor or designated representative. Where allowed by local regulations, shipment of a three-month (12-week) supply of study drug directly from the site to the subject may also be permitted.	
Packaging	Atrasentan and placebo tablets will be packaged in bottles (20 counts per bottle). Refer to the Pharmacy Binder for additional details.	
Labeling	Label text will at a minimum include the protocol number, lot number, storage conditions, and Sponsor (or designee) name and address. Labels will comply with local regulatory requirements for study drug.	

QD = once daily

6.2. Preparation, Handling, Storage, and Accountability

- Investigational product should only be dispensed or administered to subjects currently enrolled in the study.
- Investigational product must be used only as directed in the Clinical Study Protocol.
- The investigator or delegate will confirm receipt of all shipments of IP in the Interactive Response Technology (IRT) system.
- All supplies of IP must be accounted for throughout the study.

- Records for the delivery of IP to the study site, the inventory at the study site, assignment to each subject, and the destruction or return of IP to Novartis / designee will be maintained by the investigator (or delegate) and/or the IRT system.
- The investigator (or delegate) must provide reasons for any discrepancies in drug accountability.

Further details regarding accountability and destruction of IP are provided in the Site Investigational Medicinal Product (IMP) Manual. Please refer to the IB for further details on the storage and handling requirements of atrasentan

6.3. Randomization and Blinding

6.3.1. Randomization

Eligible subjects will be randomized in a ratio of 1:1 to either sequence AB or sequence BA by means of the IRT. A centralized randomization schedule will be used. The randomization schedule will be stratified by SGLT2i status (stable vs run-in).

6.3.2. Blinding

6.3.2.1. Blinding Method

Investigational site staff, including the investigator(s), will be blinded to treatment allocation. Subjects and Sponsor staff (with the exception of IRT and Clinical Trial Supplies personnel) or designees participating in the conduct of the study will also be blinded to treatment allocation (double-blind).

Study unblinding will take place after the study database has been locked except in the situations as outlined in Sections 6.3.2.2, 6.3.2.3, and 6.3.2.4. Other specified personnel or independent vendors may be unblinded based on their study role. These individuals include those who analyze and manage the pharmacokinetic and/or bioanalytical data, manage study drug inventory, manage expedited reporting of suspected unexpected serious adverse events (SUSARs), manage product complaints, and who conduct unblinded analyses for safety committee review. A firewall will be in place to ensure team members working directly with the sites remain blinded to subject-level treatment assignment.

The preliminary pharmacokinetic (PK) data available during the course of the study will refer to mean data with descriptive statistics and individual data without revealing any individual randomization numbers, subject numbers, or other sensitive information with the potential to lead to unblinding (e.g., dates or times).

6.3.2.2. Breaking the Blind for an Emergency

The randomization code for individual subjects may be unblinded to a site during the study in emergency situations related to subject safety, if knowing the subject's treatment assignment will change the investigator's management of the subject's condition. In case of an emergency situation for the reason of subject safety, the investigator should use the instructions for Emergency Unblinding in the IRT manual to identify the treatment allocation for a subject.

Whenever possible, the investigator should consult with the Sponsor before unblinding the treatment assignment. Any occurrence of unblinding should be reported to the Sponsor within 24 hours. The reason for unblinding the treatment assignment must be fully recorded in the subject's source documents and the investigator must follow the defined procedures provided in the study reference manuals. The subject's treatment allocation should not be recorded in the subject's source document.

6.3.2.3. Planned Unblinding Procedures

The study will not include an interim unblinded analysis. Sponsor personnel will remain blinded to aggregate and subject-level data until the final study database lock. Study personnel working directly with the sites will remain blinded to subject-level treatment assignment until final study database lock.

6.3.2.4. Ad hoc Safety Unblinding

Sponsor's Global Product Safety (GPS) personnel may unblind the randomization code of a subject directly in the IRT at any time during the study due to safety reporting. The purpose of the unblinded data review is to determine if there is a risk to subject safety that would require further action either for the management of an individual study subject or for the ongoing conduct of the study. The need to unblind on an ad hoc basis will be determined by the Sponsor's Safety team senior leadership.

6.4. Investigational Product Compliance

Investigational product will be administered to the subjects at the site on Day 1 for each treatment period directly from the investigator (or delegate), under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents. The dose of IP and the subject's identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the IP.

The IP will be self-administered by subjects at home after the first dose is administered at the study site under medical supervision. Compliance with IP will be assessed at each visit. Compliance will be assessed 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 IP dispensed to and administered by each subject must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for IP delays and/or dose reductions will also be recorded.

6.5. Dose Modifications

6.5.1. Study Drug

No study drug dose reductions are permitted during the study.

6.5.2. Background Therapy

Following randomization, subjects will remain on their maximally tolerated and stable dose of RASi and stable dose of SGLT2i therapies for the duration of the study. All efforts should be made to avoid dose modification or discontinuation of RASi or SGLT2i therapy. Sponsor's Medical Lead (or designee) should be notified of any modification, interruption (defined as ≥ 3 days of interruption) or discontinuation of RASi or SGLT2i therapy. If medically necessary, for example in the setting of an acute illness, dehydration, or similar events, temporary interruption of the RASi or SGLT2i will be allowed. Conversions from one RASi or SGLT2i to another should be avoided, but if required, then efforts should be made to use equivalent doses. The use of more than 1 RASi or more than 1 SGLT2i concomitantly is prohibited.

6.5.3. Auxiliary Medicinal Product Categorization

AxMP (auxiliary medicinal product) is defined as a medicinal product used for the needs of a clinical study, but not an investigational product, as per EU Clinical Trial Regulation 536/2014. In this study, authorized ACEi/ARB, andSGLT2i are AxMPs, as they are used as background therapies in the management of IgAN.

6.6. Overdose

Overdose is defined as the ingestion of any dose (single or cumulative) of a product that is considered excessive. Atrasentan has been dosed orally up to 40 mg daily for 10 days in early dose-escalation studies. The maximum tolerated dose (MTD) was 30 mg since at the 40 mg dose level, 5 of 6 subjects experienced headaches refractory to analgesics.

In the event of an overdose (≥ 2 tablets within 24 hours), the investigator should:

- Contact the Sponsor's Medical Lead immediately.
- Evaluate the subject to determine, in consultation with the Medical Lead, whether the IP should be interrupted or discontinued, or whether the dose should be reduced, if applicable.
- Closely monitor the subject for any AE, serious adverse event (SAE), or clinical laboratory abnormalities.
- Document the quantity of the excess dose of IP and the duration of the overdose.

See Section 10.2.5.4 Overdose for reporting AEs associated with overdose.

6.7. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of the initial Screening visit and throughout the course of the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The Sponsor's Medical Lead (or designee) should be contacted if there are any questions regarding management of concomitant or prior therapy including anti-hypertensive agents and diuretics. The

Medical Lead should be consulted prior to the use of any other herbal or holistic substance that may have immunosuppressive potential.

6.8. Prohibited Medications

The following medications are excluded for use during the study.

- Investigational or approved products for the treatment of IgAN (other than RASi and SGLT2i as they are part of the study)
- Organic anion transporting polypeptide (OATP) inhibitors
- Strong inhibitors and inducers of CYP3A4, with the exception of short-term antiviral treatment, as follows:
    - Short-term use of anti-viral medications containing CYP3A4 inhibitors such as ritonavir, may be used with caution if medically needed and in consultation with the Medical Lead as a temporary interruption of atrasentan dosing may be required.
    - Administration of Paxlovid (nirmatrelvir/ritonavir) for the treatment of COVID is allowed in this study, however, atrasentan treatment should be discontinued for the 5-day treatment course of Paxlovid. Atrasentan treatment can be resumed 3 days following completion of the Paxlovid treatment course to allow CYP3A4 regeneration.
    - The use of more than 1 RASi or more than 1 SGLT2i concomitantly isprohibited.
    - The use of an endothelin receptor antagonist or dual endothelin receptor antagonist (DEARA) other than the investigational product.

Atrasentan exposure may be affected by use of concomitant medications that are OATP1B1 or OATP1B3 inhibitors (e.g., protease inhibitors, cyclosporin, and clarithromycin, among others) as well as by those which are potent inhibitors or inducers of CYP3A4. Given the risk of potential drug interactions, Investigators should review all medications that a subject is taking throughout the study. Concomitant OATP1B1 and OATP1B3 inhibitors and potent CYP3A4 inhibitors and inducers are prohibited. Refer to Appendix 3 for examples of OATP and CYP3A4 prohibited medications.

6.9. Restricted Medications

Restricted medications are defined as medications which should be avoided, if possible; however, they are not necessarily prohibited during this study. Restricted medications may be needed during the course of the study if the principal investigator determines that the subject has clinical progression of kidney disease where it would be unacceptable to withhold restricted medications. This determination should consist of a comprehensive clinical evaluation of the subject including assessment of rate of increase of proteinuria and/or decrease in eGFR where it is not thought to be due to secondary causes that are expected to improve (e.g., acute illness causing acute kidney injury). Unless it is considered a medical emergency, this determination should be discussed with the Sponsor's Medical Lead (or designee) prior to starting therapy with a restricted medication. Any use of restricted medication will be documented in the subject's medical lead and the medication will be recorded in the case report form (CRF).

If subjects receive restricted medications for reasons other than progression of kidney disease (e.g., systemic steroids for treatment of an exacerbation of asthma), this will not be considered a "restricted medication" unless given for a significant amount of time that may impact the integrity of clinical study data. The restricted medications, including timing and duration of treatment are described below:

- Systemic steroids (at doses greater than 20 mg/day of oral prednisone or equivalent for more than 5 days) or for ≥1 days in the 7 days prior to the Week 12 primary endpoint assessment.
- Immunosuppressive therapy including but not limited to mycophenolate, azathioprine, rituximab, and tacrolimus
- Herbs with immunosuppressive qualities such as Wilfordii Hook F, Caulis sinomenii and Sinomenium acutum
- Acute use of NSAIDS within 1 week prior to any 24-hour urine collection (use of aspirin is allowed for cardiovascular prevention use)
- Sensitive P-gp substrates (digoxin, dabigatran etexilate, and fexofenadine) must be delayed at least 4 hours after administration of atrasentan

7. SUBJECT WITHDRAWAL AND DISCONTINUATION OF INVESTIGATIONAL PRODUCT

7.1. Discontinuation of Investigational Product

Subjects may discontinue IP at any time at their own request, or at the discretion of the investigator or the Sponsor for safety, behavioral, or administrative reasons.

Subjects who discontinue IP will have an End of Treatment (EoT) visit at the time of IP discontinuation, followed by an End of Study (EOS) visit 4 weeks after IP discontinuation (see Section 1.3). Subjects discontinuing IP who decline further study procedures / visit participation will be withdrawn from the study (see Section 7.2).

The reasons for study drug discontinuation will be captured in the electronic case report form (eCRF) as follows, including but not limited to:

- Adverse event
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by Sponsor
- Study terminated by Sponsor
- Withdrawal by subject

7.1.1. Temporary Interruption

If, in the investigator's judgement, a subject requires temporary interruption of IP (defined as ≥ 3 days of IP interruption), the investigator should contact the sponsor's medical lead.

7.1.2. Stopping Criteria for Investigational Product

In rare instances, it may be necessary for a subject to permanently discontinue (definitive discontinuation) study drug. Subjects will be required to permanently discontinue study drug for the following reasons:

- Evidence of pregnancy
- Noncompliance with protocol specified contraception or pregnancy monitoring
- Initiation of maintenance dialysis or kidney transplantation
- eGFR of < 15 ml/min/1.73 m^2 for ≥ 30 days

- Other IP stopping criteria may be based on Investigator and subject discretion in discussion with the Sponsor Medical Lead

The study may be terminated by the Sponsor if the outcome of ongoing comprehensive standardized safety review determines it to be in the best interest of the study participants to terminate the study.

7.2. Subject Withdrawal from the Study

Subjects may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator or the Sponsor for safety, behavioral, compliance, or administrative reasons (e.g., AE, protocol deviation, subject noncompliance, or study termination).

The investigator may advise a subject to withdraw from the study if the subject's safety or wellbeing is compromised by further participation in the study. The interests of the subject must always prevail over the interests of the study.

If a subject decides to withdraw from further study participation, the extent of withdrawal should be documented in the subject records along with the reason for withdrawal. Safety-related reasons for withdrawal will be reported to the Sponsor as an AE.

At the time of subject withdrawal, if possible, the EoT activities should be completed and documented (see Schedule of Activities Section 1.3). If the subject is withdrawn from the study after receiving IP, every effort must be made to ensure that the relevant safety assessments are completed. The investigator may ask the subject to complete additional study assessments. If a subject is withdrawn from the study during the washout period, the EOS activities should be completed and documented (see Schedule of Activities Section 1.3).

If a subject withdraws from the study the Sponsor may retain and continue to use any data collected before the subject's withdrawal of consent.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if the subject 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 subject fails to return to the clinic for a required study visit (for exceptions, refer to Appendix 4):

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Subjects should be contacted through all communication means available for up to two consecutive missed visits, ensuring subject safety assessments can be evaluated by the delegated site staff. Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls (at least weekly) and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be

documented in the subject's medical record.

- Should the subject continue to be unreachable after the third consecutive missed visit and ceases to return for visits, the subject will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. All subjects that are unreachable after at least 3 documented attempts will be considered lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures and their timing are summarized in the Schedule of Activities (Section 1.3). Protocol waivers or exemptions are not allowed.

The investigator should discuss any immediate safety concerns with the Sponsor's Medical Lead immediately upon occurrence or when the investigator becomes aware of the safety concern to determine if the subject should continue or discontinue IP.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.

All reasonable attempts should be made to process laboratory samples through the central laboratory. As detailed in Section 10.3.1, exceptions can be made; however, only central laboratory data will be used in the primary, secondary, and exploratory analyses unless otherwise specified in the statistical analysis plan (SAP).

8.1. Scheduled Assessments per Study Visit

8.1.1. Screening (Days -42 to -1)

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.

The following procedures will be conducted within 42 days prior to a subject beginning blinded study drug (for SGLT2i stable subjects) or before the Run-In Period (for run-in subjects):

- Obtain and document informed consent
- Review of medical history including IgAN history
- Evaluate screening eligibility
- Collect demographic information
- Perform a complete physical examination
- Record weight and height
- Record AEs
- Record vital signs (temperature, heart rate, blood pressure)
- Perform a single 12-lead ECG
- Obtain blood, for central laboratory analysis per (Section 1.3)
- Obtain an FMV sample for central laboratory analysis
- Obtain urine for 24-hour collection
- Obtain blood from WOCBP for a serum pregnancy test
- Counsel all fertile men and WOCBP on study contraception requirements

- Record medications including RAS inhibitor dose and duration and SGLT2i dose and duration if applicable. For subjects who are on a stable dose of SGLT2i, provide them with a 24-hour urine collection container plus a first morning void (FMV) urine collection container to be returned at the Baseline (Day 1) Visit.
- Educate subjects to refrain from high protein meals and to avoid heavy/strenuous activity for 24 hours prior to scheduled laboratory assessments.

A subject must meet all eligibility criteria to continue in the study. Subjects who do not meet eligibility criteria will be screen failed.

If a subject who is not on a stable dose of SGLT2i meets all screening eligibility criteria, they will enter the 8-week Run-In Period.

If a subject meets all screening eligibility criteria and is on a stable dose of an SGLT2i, they will be randomized into Treatment Period 1 at the Baseline visit (Day 1). The subject will be provided with a 24-hour urine collection container at the end of their Screening Visit to be returned at the Baseline (Day 1) visit.

8.1.2. Run-in Period

8.1.2.1. Run-in Day 1

Subjects who are not on a stable SGLT2i dose and who meet all screening eligibility criteria will enter an 8-week Run-in Period. This Run-In Day 1 visit will be a phone visit where subjects will begin taking an SGLT2i. The choice of SGLT2i will be at the discretion of the principal investigator and per local treatment standards.

At this phone contact visit, the following procedures will be conducted:

- Subject reports result of urine pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Record concomitant medications and AEs
- Begin SGLT2i treatment

8.1.2.2. Run-in Week 4 (± 3 days)

The following procedures will be conducted at Run-In Week 4, halfway through the run-in period:

- Perform a physical examination
- Record weight
- Record vital signs (temperature, heart rate, blood pressure)
- Obtain blood for central laboratory analysis
- Obtain urine for pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements

- Obtain spot urine for central laboratory analysis
- Provide subject with a 24-hour urine collection container to be returned at the Week 8 Visit
- Record concomitant medications and AEs

8.1.2.3. Run-in Week 8 (± 3 days)

The Run-In Week 8 visit should occur when a run-in subject has reached a stable dose of SGLT2i (for at least 8 weeks). This visit will be used to confirm final eligibility criteria for run-in subjects as specified in Section 5.1. The Run-In Week 8 visit and its associated 24-hour urine collection should occur within 14 days of the Baseline Visit (Day 1) of Treatment Period 1.

The following procedures will be conducted:

- Record vital signs (temperature, heart rate, blood pressure)
- Obtain an FMV sample for central laboratory analysis
- Obtain blood for eGFR calculation
- Obtain urine for pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Obtain 24-hour collection urine collection
- Record concomitant medications and AEs

If the subject meets the criteria in Section 5.1, they will then be randomized at the Baseline Visit (Day 1).

8.1.3. Treatment Period 1

8.1.3.1. Baseline (Day 1)

Baseline Day 1 will occur after eligibility for Treatment Period 1 is confirmed and within 14 days of Run-in Week 8. At this in-clinic visit, the following procedures will be conducted:

- Record vital signs (temperature, heart rate, blood pressure)
- Record weight
- Perform a physical examination
- Perform a single 12-lead ECG
- Obtain blood for central laboratory analysis
- Obtain urine for pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Obtain urine for 24-hour collection (except for Run-In Subjects who will provide their 24-Hr. urine collection at Run-in Week 8)

- Obtain an FMV sample for central laboratory analysis (except for Run-In Subjects who will provide their FMV sample collection at Run-in Week 8)
- Obtain blood and spot urine for exploratory biomarkers

CCI

- Randomization to study drug
- Record concomitant medications and AEs
- Dispense blinded study drug. Day 1 dose to be administered in clinic and subject to remain in clinic for observation for 1-hour post-dose.
- Instruct subjects to take blinded study drug once daily with or without food at approximately the same time each day. Further instruct subjects on days when blood draws are required to wait to take study drug until after the blood draw.

8.1.3.2. Week 1 (± 3 days)

At this phone contact visit, the following procedures will be conducted:

- Record weight
- Counsel all fertile men and WOCBP on study contraception requirements
- Record concomitant medications and AEs
- Review IP compliance

8.1.3.3. Week 2 (± 3 days)

At this in-clinic visit, the following procedures will be conducted:

- Perform a physical examination
- Record vital signs (temperature, heart rate, blood pressure)
- Record weight
- Counsel all fertile men and WOCBP on study contraception requirements
- Obtain blood for central laboratory analysis
- Obtain spot urine for central laboratory analysis
- Obtain blood for PK (predose)
- Review IP compliance
- Record concomitant medications and AEs

8.1.3.4. Week 4 (± 3 days)

At this phone contact visit, the following procedures will be conducted:

- Record weight

- Subject reports result of urine pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Review IP compliance
- Record concomitant medications and AEs

8.1.3.5. Week 6 (± 3 days)

At this in-clinic visit, the following procedures will be conducted:

- Perform a physical examination
- Record vital signs (temperature, heart rate, blood pressure)
- Record weight
- Counsel all fertile men and WOCBP on study contraception requirements
- Obtain blood for central laboratory analysis
- Obtain spot urine for central laboratory analysis
- Obtain blood for PK (predose)
- Obtain blood and spot urine for exploratory biomarkers
- Provide subject with two 24-hour urine collection containers to be returned at the Week 12/EOT Visit
- Review IP compliance
- Record concomitant medications and AEs

8.1.3.6. Week 8 (± 3 days)

At this phone contact visit, the following procedures will be conducted:

- Record weight
- Subject reports result of urine pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Review IP compliance
- Record concomitant medications and AEs

8.1.3.7. Week 12/EOT (± 3 days)

At this in-clinic visit, the following procedures will be conducted:

- Perform a physical examination
- Record vital signs (temperature, heart rate, blood pressure)
- Record weight
- Obtain urine for pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Obtain blood for central laboratory analysis
- Obtain urine for 24-hour collection and ensure two 24-hour collections are obtained within 7 days prior to this study visit
- Obtain blood for PK (predose)
- Obtain blood and spot urine for exploratory biomarkers
- Review subject IP compliance and perform study drug accountability and return
- Record concomitant medications and AEs

8.1.4. Washout Period

The washout period lasts for 12 weeks during which the subject will receive no IP but will continue on their maximally tolerated and stable dose of RASi and stable dose of SGLT2i therapies. Concomitant medications and AEs should be collected as necessary during the period outside of scheduled visits.

8.1.4.1. Week 4 (± 3 days)

At this phone contact visit, the following procedures will be conducted:

- Record weight
- Subject reports result of urine pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Record concomitant medications and AEs

8.1.4.2. Week 6 (± 3 days)

At this in-clinic visit, the following procedures will be conducted:

- Perform a physical examination
- Record vital signs (temperature, heart rate, blood pressure)
- Record weight
- Obtain blood from WOCBP for a serum pregnancy test

- Counsel all fertile men and WOCBP on study contraception requirements
- Obtain blood for central laboratory analysis
- Obtain FMV urine sample for central laboratory analysis
- Obtain blood for PK
- Provide subject with 24-hour urine collection container to be returned at the Baseline (Day1) Visit of Treatment Period
- Record concomitant medications and AEs

8.1.4.3. Week 8 (± 3 days)

At this phone contact visit, the following procedures will be conducted:

- Record weight
- Subject reports result of urine pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Record concomitant medications and AEs

8.1.4.4. Week 12 (± 3 days)

At this phone contact visit, the following procedures will be conducted:

- Subject reports result of urine pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Record concomitant medications and AEs

8.1.5. Treatment Period 2

8.1.5.1. Baseline (Day 1)

The Baseline (Day 1) Visit will occur within 7 days of Week 12 of the Washout Period. At this in-clinic visit, the following procedures will be conducted:

- Perform a complete physical examination
- Record weight
- Record vital signs (temperature, heart rate, blood pressure)
- Obtain urine from WOCBP for pregnancy test
- Counsel all fertile men and WOCBP on study contraception requirements
- Obtain an FMV sample for central laboratory analysis
- Obtain blood for central laboratory analysis
- Obtain blood and spot urine for exploratory biomarkers

- Obtain urine for 24-hour collection
- Record concomitant medications and AEs
- Dispense blinded study drug. Day 1 dose to be administered in clinic and subject to remain in clinic for observation for 1-hour post-dose
- Instruct subjects to take blinded study drug once daily with or without food at approximately the same time each day. Further instruct subjects on days when blood draws are required to wait to take study drug until after the blood draw

8.1.5.2. Week 1 (± 3 days)

At this phone contact visit, the following procedures will be conducted:

- Record weight
- Counsel all fertile men and WOCBP on study contraception requirements
- Review subject IP compliance
- Record concomitant medications and AEs

8.1.5.3. Week 2 (± 3 days)

At these in-clinic visits, the following procedures will be conducted:

- Perform a physical examination
- Record vital signs (temperature, heart rate, blood pressure)
- Record weight
- Obtain blood for central laboratory analysis
- Obtain blood for PK (predose)
- Obtain spot urine for central laboratory analysis
- Counsel all fertile men and WOCBP on study contraception requirements
- Review subject IP compliance
- Record concomitant medications and AEs

8.1.5.4. Week 4 (± 3 days)

At these time points, which are all phone contact visits, the following procedures will be conducted:

- Record weight
- Subject will report results of urine pregnancy testing in WOCBP
- Review subject IP compliance
- Counsel all fertile men and WOCBP on study contraception requirements

- Record concomitant medications and AEs

8.1.5.5. Week 6 (± 3 days)

At these in-clinic visits, the following procedures will be conducted:

- Perform a physical examination
- Record vital signs (temperature, heart rate, blood pressure
- Record weight
- Obtain blood for central laboratory analysis
- Obtain blood for PK (predose)
- Obtain blood and spot urine for exploratory biomarkers
- Provide subjects with two (2) 24-hour urine collection containers to be returned at the Week 12 Visit. Both collections should be completed 7 days prior to the Week 12 Visit.
- Obtain spot urine for central laboratory analysis
- Counsel all fertile men and WOCBP on study contraception requirements
- Review subject IP compliance
- Record concomitant medications and AEs

8.1.5.6. Week 8 (± 3 days)

At these time points, which are all phone contact visits, the following procedures will be conducted:

- Record weight
- Subject will report results of urine pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Review subject IP compliance
- Record concomitant medications and AEs

8.1.5.7. Week 12 (± 3 days)

At this in-clinic visit, the following procedures will be conducted:

- Record vital signs (temperature, heart rate, blood pressure
- Record weight
- Perform a physical examination
- Obtain urine for pregnancy testing in WOCBP
- Obtain blood for central laboratory analysis

- Obtain blood for PK (predose)
- Obtain blood and spot urine for exploratory biomarkers
- Obtain a urine sample for 24-hour collection and ensure two 24-hour collections are obtained within 7 days prior to the study visit
- Provide subjects with two (2) 24-hour urine collection containers to be returned at the Week 24/EOT Visit. Both collections should be completed 7 days prior to the Week 24/EOT Visit
- Counsel all fertile men and WOCBP on study contraception requirements
- Review subject IP compliance and perform study drug accountability and return
- Dispense study drug
- Record concomitant medications and AEs

8.1.5.8. Week 16 (± 3 days)

At these time points, which are all phone contact visits, the following procedures will be conducted:

- Record weight
- Subject will report results of urine pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Review subject IP compliance
- Record concomitant medications and AEs

8.1.5.9. Week 20 (± 3 days)

At these time points, which are all phone contact visits, the following procedures will be conducted:

- Record weight
- Subject will report results of urine pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Review subject IP compliance
- Record concomitant medications and AEs

8.1.5.10. Week 24 (EOT) (± 7 days)

At this in-clinic visit, the following procedures will be conducted:

- Perform a physical examination
- Record vital signs (temperature, heart rate, blood pressure)

- Record weight
- Obtain urine for pregnancy testing in WOCBP
- Obtain blood for central laboratory analysis
- Obtain blood for PK (predose)
- Obtain blood and spot urine for exploratory biomarkers
- Obtain a urine sample for 24-hour collection and ensure two 24-hour collections are obtained within 7 days prior to the study visit
- Counsel all fertile men and WOCBP on study contraception requirements
- Review subject IP compliance and perform study drug accountability and return
- Record concomitant medications and AEs

8.1.6. Week 28 (EOS) (± 7 days)

At this in-clinic visit, the following procedures will be conducted:

- Record vital signs (temperature, heart rate, blood pressure)
- Record weight
- Perform a physical examination
- Obtain blood for a serum pregnancy test in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements
- Obtain blood for central laboratory analysis
- Record concomitant medications and AEs

If a subject is unwilling to attend an in-clinic visit, attempts should be made to collect as many of the required assessments as possible, and for WOCBP, if a serum pregnancy test cannot be collected, attempts should be made to obtain a urine pregnancy test.

8.1.7. Study Procedures

8.1.7.1. Informed Consent

Subjects must provide informed consent before any study-specific procedures are initiated.

8.1.7.2. Medical History

A complete medical history, including history of tobacco, alcohol and illicit drug use will be obtained from each subject during Screening. Worsening of pre-existing conditions after informed consent will be considered AEs.

Any medical condition with onset or diagnosis prior to the first administration of study drug, but after informed consent, will be noted as part of the subject's Baseline medical condition.

8.1.7.3. Physical Examination

A complete physical examination will be performed at Screening. The complete physical examination includes assessment of skin, head, eyes, ears, nose, throat, neck, lungs, heart, abdomen (including liver and spleen), lymph nodes, and extremities. All subsequent physical examinations will be focused on cardiovascular evaluation and the assessment of fluid status.

Subjects will be instructed to contact site personnel if they are experiencing symptoms at home (any significant, unfavorable change from the Screening exam); the Investigator will assess if subjects should attend an unscheduled visit at the clinic for a symptom-directed physical examination.

Any significant, unfavorable change from the Screening exam will be recorded as an AE both in the subject's source documentation and in the CRF.

8.1.7.4. Electrocardiogram

12-lead electrocardiograms (ECGs) will be obtained while the subject is in a supine position at the Screening and Baseline (Day1) visits of Treatment Period 1. Subjects should be resting for at least 2 minutes prior to ECG. The investigator should record in the CRF if the ECG is normal, abnormal (not clinically significant) or abnormal (clinically significant, with description of the findings).

8.1.7.5. Vital Signs

Vital signs (temperature, heart rate, blood pressure) will be measured in a seated or recumbent position after at least 5 minutes of rest, according to the Schedule of Activities. Whenever possible, all vital sign measurements should be taken prior to any blood draws. Body weight (kg) will be measured and recorded at each study visit, preferably using the same device and under the same circumstances (i.e., same time of the day, no shoes or coats during measurement). Height (cm) will be determined at the initial Screening visit.

Subjects will be instructed to weigh themselves at approximately the same time of day on Week 1, Week 4, and Week 8 of Treatment Period 1, Week 4, and Week 8 of the Washout period, and Week 1, Week 4, Week 8, Week 16, and Week 20 of Treatment Period 2, and provide that measurement to the site staff during the phone contact. Scales will be provided to the subjects for home weight collection.

8.1.7.6. Blood Pressure Monitoring and Management

The Investigators agree that the goal for the subject will be to attain BP of less than or equal to 130/80 mmHg and maintain this throughout the study.

Blood pressure will be monitored throughout the study, and efforts to maintain subjects at goals consistent with KDIGO 2021 guidelines) for subjects with chronic proteinuric kidney diseases ($\leq$ 130/80 mm Hg).

The Investigator is encouraged to contact the Sponsor's Medical Lead (or designee) regarding decreases in blood pressure.

8.1.7.7. Fluid Overload and Heart Failure Monitoring and Management

Atrasentan, as well as other endothelin receptor antagonists, are associated with an increased risk of fluid retention. In general, these effects are observed early with treatment and fluid status must be monitored closely by the Investigator. Subjects with fluid retention that is not managed appropriately may be at increased risk of cardiac failure, especially those subjects with lower baseline levels of renal function or those with baseline cardiac risk factors. Consistent with standard of care, subjects should be counselled on maintaining a low-salt diet unless medically inappropriate.

Investigators should advise subjects to watch for signs and symptoms of fluid overload and heart failure. Subjects should be informed to notify their physicians immediately if they experience excessive weight gain, swollen ankles or feet, chest pain, shortness of breath with mild exertion or lying down, or other relevant symptoms. Further evaluation and treatment of subjects who report peripheral edema or other symptoms of fluid overload and heart failure should take place as soon as possible. Appropriate medical management, such as diuretics and/or ACE (angiotensin-converting enzyme) inhibitors, may be instituted. Subjects should be educated not to start or stop taking any medications without first informing their Investigator.

Careful monitoring of all subjects especially during the first month of study drug for symptoms of dyspnea, peripheral edema, excessive weight gain (e.g., > 2 kg in a 2-week period), hemoglobin and hematocrit decrease, increase in BNP levels, and other signs and symptoms of fluid overload and heart failure is recommended. Subjects who experience concurrent medical illnesses leading to fluid retention and/or anemia should also be closely monitored for signs and symptoms of heart failure. Changes in the use of other vasoactive drugs should be monitored closely. Subjects who are taking multiple medications with blood pressure–lowering effects, including beta blockers, alpha blockers, central acting agents, loop diuretics, and nitrates, should be monitored and any dose adjustments of concurrent medications should be made under medical supervision.

Subjects will monitor their own weight as instructed in Section 8.1.7.5. Subjects who experience a > 2 kg weight gain likely due to fluid retention, or symptomatic peripheral edema, should be initiated on a diuretic (Table 4). The Sponsor's Medical Lead (or designee) should be contacted for any reported weight gain of > 2 kg over the initial 2-week period, any instance of fluid retention associated with shortness of breath, BNP > 300 pg/mL, and any instance of severe edema. Adequacy of diuretic dose should be made through clinical assessment of fluid status, symptoms, weight, and laboratory measurements which may include serum electrolytes, creatinine, hemoglobin, and BNP.

Weight will also be measured at all in-clinic study visits.

In consultation with the Sponsor's Medical Lead (or designee), study drug should be discontinued in subjects with fluid retention that is intolerable to the subject and cannot be adequately managed with diuretics and dietary modifications.

Table 4. Diuretics Recommendation Based on eGFR Values

	eGFR < 45 mL/min	eGFR 45 to 60 mL/min, inclusive	eGFR > 60 mL/min
Recommended diuretic and dose	Loop diuretic 20-40 mg QD of furosemide or	Loop diuretic 20mg QD of furosemide or equivalent	Chlorthalidone 12.5 mg QD or equivalent

	equivalent OR Chlorthalidone 25 mg QD or equivalent	OR Chlorthalidone 12.5 to 25 mg QD or equivalent	

eGFR = estimated glomerular filtration rate; QD = once daily

8.1.7.8. Pregnancy Prevention and Counselling on Use of Contraceptives

8.1.7.8.1. Female Subjects

Atrasentan is expected to cause fetal harm if administered to pregnant women; therefore, it is contraindicated in women who are or may become pregnant.

The Investigator must determine the reproductive potential status of every female subject. As part of the informed consent process, the Investigator or designee will clearly explain the potential teratogenic risks associated with atrasentan, the need to adopt a highly effective form of birth control prior to Baseline and for up to 1 month after treatment discontinuation, and the limitations and consequences of pregnancy testing to subjects including potential for false negatives, potential for false positives, requirements to terminate study drug if pregnant, and how pregnancy outcomes would be followed up to 5 years.

WOCBP will have serum pregnancy tests performed at Screening, Wash-out Week 6, and Week 28 (EOS) visits, with urine pregnancy tests performed routinely at different time points (approximately every 4 weeks) throughout the duration of the study to exclude pregnancy.

A negative test result will be reviewed and compliance with contraception requirements will be verified by site personnel or a health care provider prior to the subject being approved for continued dosing. A positive or indeterminate pregnancy test result will lead to immediate hold of study drug and a repeat serum test at the clinical study site within 2 days. Confirmed positive pregnancy results by repeat serum pregnancy test will lead to permanent treatment discontinuation, but continued follow-up of the subject to collect data on atrasentan effects as well as the outcome for both mother and fetus.

Subjects will have an option for monthly urine pregnancy testing at a local point of care facility/laboratory or at-home urine pregnancy testing with a virtual site-visit enabled by video/audio. For subjects completing pregnancy testing at a local laboratory or a virtual site visit in between clinic visits, dispensing of 6 or 12 weeks of study drug will be allowed with negative test results, reviewed by site personnel with the subject and counselling on contraception requirements by phone prior to continued dosing.

8.1.7.8.2. Male Subjects

The risk of fathering an abnormal fetus/child due to exposure to atrasentan in semen is unknown. All fertile male study subjects in a sexual relationship with a WOCBP must use a condom during the trial and for up to one month after last study drug administration.

Atrasentan may impact sperm quantity. As part of the informed consent process, the Investigator or designee will clearly explain the potential spermatogenic risks associated with atrasentan, the requirements for contraception, and the requirements to follow pregnancy outcomes.

8.1.7.8.3. Definition of WOCBP and of fertile men

For the purpose of this protocol, a woman is considered a WOCBP, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. 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 post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this protocol, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy/orchiectomy.

Female subjects of childbearing potential who engage in heterosexual intercourse must select one of the options in Table 5 as a reliable form of birth control. Subjects who attest to abstinence may be allowed to participate in the study if abstinence is the preferred and usual lifestyle of the subject, and the subject refrains from heterosexual intercourse during the entire period of risk associated with the study. If the sexual activity status of the subject changes during the study, subject will be required to inform the Primary Investigator and select one of the options in Table 5.

Table 5 Highly Effective Forms of Contraception for WOCBP

Option 1	Option 2	Option 3
One method from this list: • Standard intrauterine device (Copper T 380A IUD) • Intrauterine system (LNg 20 IUS: progesterone IUS) • Tubal sterilization	One method from this list[1]: • Estrogen and progesterone oral contraceptives ("the pill") • Estrogen and progesterone transdermal patch • Vaginal ring • Progesterone injection • Progesterone implant Plus one method from this list: • Male condom • Diaphragm with spermicide • Cervical cap with spermicide	One method from this list: • Partner's vasectomy[2] Plus one method from this list[1]: • Male condom • Diaphragm with spermicide • Cervical cap with spermicide • Estrogen and progesterone oral contraceptives ("the pill") • Estrogen and progesterone transdermal patch • Vaginal ring • Progesterone injection • Progesterone implant

[1] Hormonal contraception (combined and progestogen-only) must be associated with inhibition of ovulation.

[2] A vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP subject and that the vasectomized partner has received medical assessment of the surgical success.

Abbreviations: IUD = intrauterine device; IUS = intrauterine system: LNg = levonorgestrel

8.1.7.9. Urine Collection

8.1.7.9.1. 24-Hour Urine Collection

A 24-hour urine will be collected at time points specified in the Schedule of Activities (Section 1.3). The Investigator or designee should remind subjects to refrain from a high protein diet approximately 48 hours prior to and during the 24-hour urine collection.

Two 24-hour urine collections are required at Week 12 of Treatment Period 1, Week 12 of Treatment Period 2, and Week 24 of Treatment Period 2. At each of these time points both collections should be within 7 days prior to the study visit. All other time points will be a single 24-hour urine collection.

A 24-hour urine collection is required at Screening and Run-in Week 8 for Run-In subjects and Baseline (Day 1) for SGLT2i stable subjects. Subjects who do not meet screening eligibility criteria based on their total protein excretion may be eligible to re-test for total protein once during the Screening period within 14 days of the Run-in Week 8 visit. Once eligibility based on total protein excretion has been confirmed, another 24-hour urine collection container should be given to the subject for the Baseline collection (Baseline Day 1 visit) if they are in the SGLT2i stable group. The Baseline collection should end by the day of the Baseline (Day 1) Visit. Run-In subjects will receive their second 24-hour urine collection container at the Week 4 Visit during the run-in period and the collection should end by the day of the Run-in Week 8 Visit.

The subject will be provided with urine collection containers prior to each visit where 24-hour urine is required. The central laboratory will provide specific instructions for collection and storage of the specimens.

Subjects will initiate the 24-hour collection within the allowable window prior to the respective visit and single 24-hour urine collections should end on the morning of the subject's study visit. The specimen will be brought to the study visit or may be collected by a courier if applicable and available. All 24-hour urine collections should be initiated on an empty bladder. Each 24-hour urine sample will be analyzed at the central laboratory.

8.1.7.9.2. First Morning Void (FMV) Urine Collection

FMV is defined as the collection of the first urine void after the individual awakes from sleep. FMV urine samples will be collected at time points specified in the Schedule of Activities (Section 1.3). The subject will be provided with urine collection containers prior to each visit where FMV urine collection is required. FMV samples will be collected up to 5 days before the scheduled study visit on a day that does not interfere with the 24-hour urine collection days. The central laboratory will provide specific instructions for collection and storage of the specimens.

8.1.7.9.3. Spot Urine Collection

A spot urine (anytime during the day) will be collected at visits specified in the Schedule of Activities (Section 1.3) The subject will be provided with urine collection containers prior to or during each visit where spot urinalysis is required.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the Schedule of Activities (Section 1.3).

8.3. Safety Assessments

Safety assessments will be performed at the time points specified in the Schedule of Activities (Section 1.3). Details on safety assessments are described in Section 8.1.7.

Table 6 Safety Assessments

Physical Examination	As per the site's standard procedure.	
Vital Signs	• Blood Pressure (systolic and diastolic)	• Pulse rate
	• Weight	• Temperature
	• Height (Screening only)	
12-lead ECG	Interpretation	
Pregnancy Testing	• Serum and/or urine test for Choriogonadotropin Beta (β-hCG), as indicated for women of childbearing potential. • If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.	
Clinical Safety Laboratory Assessments • The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. • Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition. • All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of investigational product should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical lead. o If clinically significant values do not return to normal / baseline within a time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified. o All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3). o If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the subject's source documents.		
Hematology	Hemoglobin	
	Hematocrit	
	Red Blood Cell (RBC)	
	White blood cell (WBC)	
	Neutrophils	
	Lymphocytes	

	Monocytes
	Basophils
	Eosinophils
	Platelet count
Serum Chemistry	Albumin
	Alkaline phosphatase (ALP)
	Alanine aminotransferase (ALT) (SGPT)
	Aspartate aminotransferase (AST) (SGOT)
	Blood urea nitrogen (BUN)
	Calcium
	Potassium
	Chloride
	Cholesterol (non-fasting)
	Creatinine*
	Direct bilirubin
	Glucose (non-fasting)
	Phosphorus
	Sodium
	Bicarbonate
	Total bilirubin
	Total protein
	Uric Acid
	Cystatin C
Analysis of 24 – hr. Urine	Albumin
	Creatinine
	Sodium
	Protein
	Potassium
	Chloride
	UPCR
	UACR
Urinalysis of FMV or Spot Urine	Blood
	Glucose
	pH
	Leukocyte Esterase
	Ketones

	Protein
	Specific Gravity
Urine Chemistry of FMV or Spot Urine	Albumin
	Creatinine
	Sodium
	Protein
	Potassium
	Chloride
	UPCR
	UACR
Additional Blood Tests	BNP
	HbA1c (Screening Only)
Coagulation Tests	PT/INR
	aPTT
	Fibrinogen

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase (SGPT); aPTT = activated partial thromboplastin clotting time; AST = aspartate aminotransferase (SGOT); BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease – Epidemiology Collaboration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FMV = first morning void; HbA1c = Glycated hemoglobin; hCG = human chorionic gonadotropin; INR = international normalized ratio; PK = pharmacokinetics; PT = prothrombin time; RBC = red blood cell; SAE = serious adverse event; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; UACR = urinary albumin:creatinine ratio; UPCR = urine protein:creatinine ratio; WBC = white blood cell
*eGFR will be calculated based on serum creatinine using the CKD-EPI equation (2021)

8.4. Pharmacokinetics

- Whole blood samples of approximately 8 mL (2 x 4 mL K2-EDTA Vacutainer tubes) will be collected for the preparation of plasma samples and the measurement of plasma concentrations of atrasentan at time points/visits specified in the Schedule of Activities (Section 1.3)
- Instructions for the collection and handling of biological samples (preparation of plasma samples from whole blood and storage) will be provided by the Sponsor Lab Manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- Plasma samples will be used to evaluate the steady-state trough PK of atrasentan. Each plasma sample per time point will be transferred to a cryovial (1 sample for primary PK and the second sample for backup PK).
- Concentration information that would unblind the study will not be reported to study sites or blinded personnel until the study is unblinded.

8.5. CCI [redacted]

- Collection of biological samples from all subjects for exploratory biomarker

research is also part of this study. The following samples will be collected from all subjects in this study as specified in the Schedule of Activities (Section 1.3), and may be used for exploratory assessment of biomarkers:

8.5.1. CCI

8.6. CCI

8.7. Immunogenicity Assessments

Immunogenicity will not be evaluated in this study.

8.8. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics will not be evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The final analysis of the primary endpoint will be a test for superiority. The final analysis of the primary endpoint will test the null hypothesis in subjects with IgAN on background therapy with SGLT2i that there is no difference between atrasentan and placebo in the proteinuria reduction at Week 12, as measured by the change in UPCR on 24-hour urine collection from Baseline to Week 12 across both periods, versus the alternative hypothesis that there is a difference.

9.2. Sample Size Determination

Approximately 52 subjects (approximately 26 per treatment sequence) will provide approximately 83% power using a two-sided pairwise test to detect a treatment effect of at least 0.288 in natural log transformed UPCR (25% reduction) from Baseline to Week 12 between atrasentan versus placebo at the 5% significance level, assuming a standard deviation of 0.67 and 5% rate of early withdrawal from the study before Week 12 in Treatment Period 2.

Using the same assumptions as described above, 52 subjects will also provide approximately 80% power using a two-sided two-sample t-test to detect a treatment effect of at least 0.56 in natural log transformed UPCR (43% reduction) over 24 weeks in study Treatment Period 2.

The assumptions used for sample size calculations are supported by the results observed in the previous Phase 3 and Phase 2 studies of atrasentan conducted in subjects with diabetic kidney disease and in Phase 2 studies in IgAN.

9.3. Analysis Sets

9.3.1. Screened Analysis Set

The Screened Analysis Set consists of all subjects who provided written informed consent.

9.3.2. Intention-to-Treat Analysis Set

The Intention-to-Treat (ITT) Analysis Set consists of all subjects randomly assigned to a treatment sequence. Subjects will be analyzed according to the treatment sequence to which they have been randomly assigned.

9.3.3. Run-In Analysis Set

The Run-In Analysis Set is defined as all subjects who took at least one dose of SGLT2i in the run-in period. The Run-In Analysis Set will be used for the run-in period summaries.

9.3.4. Safety Analysis Set

The Safety Analysis Set consists of all subjects randomly assigned to a treatment sequence and who take at least one dose of study drug. Subjects will be analyzed according to the intervention they actually received.

9.3.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set consists of all subjects in the Safety Analysis Set who have at least one non-missing concentration value reported by the bioanalytical laboratory. Subjects will be analyzed according to the intervention they actually received.

9.3.6. CCI

CCI

9.3.7. CCI

CCI

9.4. Statistical Analyses and Methods

The SAP 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.

9.4.1. General Considerations

UPCR will be transformed using natural logarithm before calculating changes.

Only central laboratory data will be used in the primary, secondary, and exploratory analyses unless otherwise specified in the SAP.

All efforts will be made to prevent missing data. Missing data for continuous safety assessments such as laboratory and vital sign data will generally not be imputed unless otherwise specified. The handling of missing date data will be described in the SAP.

Laboratory data that is below the lower limit of quantification (LLOQ) or higher than the upper limit of quantification (ULOQ) will be imputed to one unit less than the LLOQ or one unit more than the ULOQ, respectively. For example, a value of < 11 will be assigned to 10 and a value of < 11.0 will be assigned as 10.9.

9.4.2. Demographics and Baseline Characteristics

Demographic and Baseline measurements will be summarized by treatment sequence using descriptive statistics for continuous variables (n, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum) and using number and percentage of subjects for categorical variables.

Demographic summaries will include gender, race, ethnicity, and age.

Baseline characteristics will include weight, body mass index (BMI), systolic blood pressure, diastolic blood pressure, UPCR, eGFR, and serum creatinine. Other Baseline characteristics may be specified in the SAP.

9.4.3. Efficacy Analyses

9.4.3.1. Analysis of Primary Endpoint

The primary efficacy endpoint is the change in proteinuria (UPCR based on 24-hour urine collection) from Baseline to Week 12 across both periods between atrasentan versus placebo. The final analysis of the primary endpoint will be conducted using the ITT analysis set. The Baseline UPCR value will be defined as the natural log of Day 1 UPCR results from 24-hour urine samples collected within each period. The Week 12 UPCR values will be estimated as the mean of the natural log of two separate samples collected within 7 days prior to Week 12 assessments within each period. Subjects missing Baseline UPCR or with no post-Baseline UPCR measurements will be excluded from the primary efficacy analyses.

The final of the primary efficacy endpoint will be conducted on the ITT analysis set using a mixed-effects model. The model will include change from Baseline of natural log UPCR at Week 12 within each period as outcomes. The model will also include the fixed effects of sequence, period, and treatment treatment, a random effect of subjects nested within sequences, and covariates of Baseline natural log UPCR and the stratification factor of SGLT2i status (stable vs run-in). The covariance structure is assumed to be unstructured. If the analysis fails to converge, the following covariance structures will be tested: first-order autoregressive with heterogenous variances followed by first-order autoregressive with homogenous variances. The between group geometric mean change in 24-hour UPCR will be derived as 100*(exp[least square mean change]-1), and the same transformation will be applied to the 95% confidence limits. Significance testing will be done at the 2-sided 0.05 level.

Subgroup analyses for clinically relevant demographic and baseline disease characteristics may be performed as specified in the SAP.

The following intercurrent events will be handled using treatment policy strategy: study drug discontinuation, initiation of maintenance dialysis or kidney transplantation, dose modification or discontinuation of background therapy (RAS/SGLT2 inhibitors), and initiation of a prohibited or restricted concomitant medication (excluding investigational or approved products for the treatment of IgAN). All data collected after these intercurrent events will be included in the analysis.

The intercurrent event of initiation of an investigational or approved product for the treatment of IgAN will be handled using hypothetical strategy, and data collected following the onset of this intercurrent event will be excluded from analysis (set to "missing"). The "jump-to-reference" ("J2R") imputation approach will be used to impute values after the occurrence of this intercurrent event for subjects in the atrasentan arm. Values for the placebo group will be handled under the missing-at-random (MAR) assumption. Additional details are specified in the SAP.

Missing data due to intercurrent events (e.g., study treatment discontinuation, prohibited

medications) will be imputed to indicate a worsening in condition (i.e., the "jump-to-reference" ("J2R") imputation approach for subjects in the atrasentan arm and under MAR for the placebo group). Missing data not due to intercurrent events (e.g., administrative reasons such as unavailability of a sample or a missed visit) will be handled using missing at random for both treatment arms.

9.4.3.1.1. Sensitivity Analysis

Supplementary analyses of the primary endpoint may be conducted to assess the robustness of the results of the primary analysis and the impact of intercurrent events. Two supplementary analyses are planned:

- A treatment policy strategy will be used to handle all intercurrent events (including investigational or approved products for the treatment of IgAN). All data collected after the occurrence of intercurrent events will be included in the analysis.
- A hypothetical strategy will be used to handle the intercurrent events of maintenance dialysis or kidney transplantation, prohibited/restricted medication use, or use of an investigational or approved product for the treatment of IgAN to assess the treatment effect of atrasentan, compared to placebo, in the absence of these intercurrent events. Values after the above intercurrent events for the treatment of atrasentan and placebo arms of IgAN will be excluded from analysis (set to "missing"). The "jump-to-reference" ("J2R") imputation approach will be used to impute values after the occurrence of these intercurrent events for subjects in the atrasentan arm. Values for the placebo group will be handled under the missing-at-random (MAR) assumption. Additional details are specified in the SAP.

9.4.3.2. Analysis of Secondary Endpoint

The secondary efficacy endpoint is the change in proteinuria (UPCR based on 24-hour urine collection) from Baseline to Week 24 in Treatment Period 2 between atrasentan versus placebo while on background therapy with SGLT2i. The analysis will be conducted using the ITT analysis set. The Baseline UPCR value will be defined as the natural log of Day 1 UPCR results from 24-hour urine samples collected in Treatment Period 2. Subjects missing Treatment Period 2 Baseline UPCR or with no post-Baseline UPCR measurements will be excluded from the secondary efficacy analyses.

The analysis of the secondary efficacy endpoint will be conducted on the ITT analysis set using mixed model repeated measures (MMRM). The MMRM model will include change from Treatment Period 2 Baseline of natural log UPCR at each post-Baseline measurement through Week 24 in Treatment Period 2 as outcomes. The model will also include the fixed effects of treatment, visit, and treatment-by-visit interaction, with covariates of Baseline natural log UPCR and the stratification factor of SGLT2i status (stable vs run-in). The covariance structure is assumed to be unstructured. If the analysis fails to converge, the following covariance structures will be tested: first-order autoregressive with heterogenous variances followed by first-order autoregressive with homogenous variances. The between group geometric mean change in 24-hour UPCR will be derived as 100*(exp[least square mean change]-1), and the same transformation will be applied to the 95% confidence limits. Significance testing will be done at the 2-sided 0.05

level. The same strategies for the analysis of the primary endpoint will be employed for the handling of missing data related to and not related to intercurrent events for the secondary endpoint.

9.4.3.2.1. Sensitivity Analysis of Secondary Endpoint

A supportive analysis of the secondary efficacy endpoint will be conducted to assess the robustness of the data by analyzing change from Baseline to Week 24 in Treatment Period 2. This sensitivity analysis will be conducted using analysis of covariance (ANCOVA) with the Week 24 change from Baseline in natural log UPCR as an outcome variable and fixed effect factors of Treatment Period 2 Baseline natural log UPCR treatment, and SGLT2i status (stable vs. run-in).

9.4.4. Safety Analyses

All safety analyses will be performed using the Safety analysis set. Safety data collected from the first dose up to 30 days after last dose will be included in the safety analyses, unless otherwise specified in the SAP document. No formal statistical testing of treatment difference is planned.

Continuous safety data will be summarized with descriptive statistics (arithmetic mean, standard deviation [SD], median, minimum, and maximum) by treatment group. Categorical safety data will be summarized with frequency counts and percentages by treatment group.

9.4.4.1. Study Drug Exposure and Compliance

The number of days on study drug will be summarized by period, treatment group and overall. The number and percentage of subjects with at least 70% compliance with study drug will be summarized by period, treatment group and overall.

9.4.4.2. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AE (TEAE) will be defined in the SAP. The TEAEs will be analyzed according to the last treatment a subject received prior to the occurrence of the AE. TEAEs will be summarized by the period and treatment group in descending order of overall frequency by MedDRA preferred term, as well as by system organ class (SOC) and MedDRA preferred term. The incidence rates of TEAEs for period and treatment group will be summarized. Additionally, the TEAEs will also be summarized by the relationship to study drug. The AEs reported as reasons for discontinuation will be summarized by period and treatment group. Serious AEs (SAEs) will be evaluated in a similar manner. Specifically, AEs will be summarized by period and treatment group as described below:

- An overview of the number and percentage of subjects with TEAEs.
- A summary of the number and percentage of subjects with TEAEs by primary MedDRA system organ class and preferred term.
- A summary of the number and percentage of subjects with treatment-emergent SAEs by primary MedDRA system organ class and preferred term.
- A summary of the number and percentage of subjects with TEAEs leading to

discontinuation of study drug by primary MedDRA system organ class and preferred term.

- A summary of the number and percentage of subjects with drug-related TEAEs by primary MedDRA system organ class and preferred term.
- A summary of the number and percentage of subjects with Adverse Events of Special Interest.

9.4.5. Pharmacokinetics Analyses

Descriptive statistics for atrasentan plasma concentration values will be summarized for each scheduled sampling visit in Treatment Periods 1 and 2 and in the Washout Period. Additional information on the analyses of PK parameters will be provided in the SAP.

Additional analyses may be performed if useful and appropriate (e.g., comparison of exposure-response, population PK/pharmacodynamic [PD] analysis).

9.4.6. CCI

CCI

9.4.7. CCI

CCI

CCI [redacted]

9.5. Planned Analyses

9.5.1. Final Analysis

The unblinded final full efficacy will be performed after all subjects have completed or withdrawn from the study, outstanding data queries have been resolved (or adjudicated as unresolvable), and the data have been cleaned and finalized for the final analysis.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethics Considerations

This study will be conducted in accordance with the Clinical Study Protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki.
- Applicable International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The Clinical Study Protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) / Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB / IEC before the study is initiated.

Any amendments to the Clinical Study 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 subjects.

Clinical study protocols and any substantial amendments to the Clinical Study Protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- 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 CFR, ICH guidelines, the IRB / IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. 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.

10.1.3. Informed Consent Process

The investigator or delegate will explain the nature of the study to the subject or their legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign and date a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, and/or EU General Data Protection Regulations requirements, as applicable, and the IRB / IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject 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, and, if applicable, Consent Documents. What constitutes Consent Documents can be found in the Clinical Trial Research Agreement.

Subjects must be re-consented 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 subject or their legally authorized representative.

10.1.4. Data Protection

Measures used to protect individual subject data include the following:

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred except for: activities in the scope of on-site monitoring, inspections, audits, patient safety and applicable regulatory and/or legal compliance requirements, and as permitted by the ICF.
- The subject must be informed that their personal study-related data will be used by the Sponsor in accordance with all applicable data protection laws and as permitted by the ICF. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent form.
- The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.1.5. Additional Data Protection Under EU General Data Protection Regulation (GDPR 679/2016)

The Sponsor, as Data Controller, will ensure that all processing activities involving personal data performed in the scope of this study are compliant with, but not limited to, the requirements set by

EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on Data Protection, recommendations, and guidelines as applicable.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and processed personal data, the Sponsor will implement and maintain the following measures:

- restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel, and approved visitors.
- appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial.
- effective pseudonymization of personal data in compliance with the European Data Protection Board's Recommendations 01/2020 (V2.0 adopted 18 June 2021).
- encryption of personal data, where appropriate.
- ability to ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services.
- network, application, and database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures and response to such attacks.
- means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident.
- logging of security events/incidents in information systems.
- procedures that cover reporting, analysis, monitoring and resolution of security incidents.
- ensuring that information systems, computers and software involved in the performance of the services provided in the study are backed up.
- a process for regularly testing, assessing, and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing.
- procedures to detect within reasonable timely manner if a personal data breach has occurred.
- procedures and practices for destruction of paper documents containing personal data.
- business continuity procedures ensuring that the Sponsor can continue to provide services through operational interruption.

All locations, personnel and information systems that are used to perform services for the study will be covered.

Sponsor will ensure the technical and organizational security measures described above, are regularly reviewed, and updated to consider the technological developments.

The Sponsor may apply additional specific statutory requirements, where required by national laws, and will implement the necessary security measures even if they are not expressly listed above.

Besides the already above-mentioned technical and organizational measures, the Sponsor, by means of internal measures and imposed contractual clauses to the selected vendors and partners (in their role of processors), will ensure the confidentiality of records and personal data of the subjects.

With exception of the activities in the scope of the on-site monitoring, inspections, audits, patient safety, and applicable regulatory and/or legal compliance requirements, the name of the patient will neither be asked for, nor recorded by the Sponsor. An identification number will be allocated to each patient registered in the Study. This number will identify the patient and will be included in all Case Report Forms and corresponding material and data associated with the patient.

Monitors acting on behalf of the Sponsor will have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for the source data verification mandatory under clinical trial framework, including the ICH-GCP obligations applicable to the conduct of the study. Staff involved in the performance of this task will be bound by additional stricter confidentiality clauses imposed upon them, as compared to other staff members.

The Sponsor will ensure a functional process for reporting of any data breach occurring at Sponsor's or its vendor's and partner's (in their role of processor) facilities and premises. In case of the occurrence of any data breach, the Sponsor will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, considering its source, underlying intentions, possibilities of recovery, etc. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to the relevant supervisory data protection authority within 72 hours of Sponsor becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, data subjects will be informed by the Sponsor (via investigation site).

10.1.6. Dissemination of Clinical Study Information and Data

- The Sponsor will provide the relevant clinical study protocol information in public database(s) before or at commencement of the study. The Sponsor may also provide study information for inclusion in national registries according to local regulatory requirements.
- Results of this study will be disclosed according to the relevant regulatory requirements including, if applicable, those listed in Section 10.1.5 and as permitted by the ICF. All publications in peer-reviewed medical journals resulting from this study will be listed in the original Clinical Study Protocol registration record.
- This Clinical Study Protocol will be made public following study completion with results posting in any applicable public registry (e.g., ClinicalTrials.gov). Company Confidential Information within the Clinical Study Protocol and Personal Protected

Data may be redacted as defined by regulatory authorities.

10.1.7. Data Quality Assurance

All subject data relating to the study will be recorded in an Electronic Data Capture (EDC) system or on printed CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided to the sites.

The investigator must permit study-related monitoring, audits, IRB / IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checks of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the timeline outlined in the Clinical Trial Research Agreement.

Quality tolerance limits, where appropriate, will be predefined in the Quality Risk Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the quality tolerance limits and remedial actions taken may be summarized in the clinical study report.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk-Based Quality Management), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and Quality Risk Management Plan.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- The definition of what constitutes source data can be found in the Clinical Trial Research Agreement.
- Data reported in the EDC system on CRFs that are transcribed from source documents must be consistent with the source documents. If there are data discrepancies, the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must also be available.
- The investigator must maintain accurate documentation (source data) to support the information entered in the CRF.

Study monitors will perform ongoing source data verification 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 subjects are being protected; and that the study is being conducted in accordance with the currently approved Clinical Study Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

10.1.9.1. Definition of Start of the Clinical Study

The study start date is the date on which the first subject is enrolled in the study.

10.1.9.2. 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 reason for early study termination may include but is not limited to discontinuation of investigational product development for any reason.

Reasons for early closure of a study site include, but are not limited to:

- Failure of the investigator to comply with the Clinical Study Protocol, the requirements of the IRB / IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment (evaluated after a reasonable amount of time) of subjects by the investigator
- Enrollment target achieved earlier than expected
    - If the study is prematurely terminated or suspended, the Sponsor will promptly notify the investigators, the IECs / IRBs, the regulatory authorities, and any contract research organization(s) (CROs) used in the study and provide the reason for suspension or early termination, as specified by the applicable regulatory requirements. The investigator will promptly inform the subject and should ensure that they are properly transitioned out of the study.

10.1.10. Publication Policy

The rights and obligations of investigators and the Sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Research Agreement for the study.

10.2. Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definitions

10.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered an investigational product and that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

The period of observation for reporting AEs extends from the time that the subject provides written informed consent until EOS. Section 10.2.5 provides further details.

Adverse events may include:

- Exacerbation (i.e., an increase in the frequency or severity) of a pre-existing condition. Pre-existing conditions should be recorded in the Medical History CRF and only reported as an AE if there is an increase in the frequency or severity of the condition during the study.
- A clinical event occurring after consent but before IP administration.
- Intercurrent illnesses with an onset after administration of IP.

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered by the investigator as clinically significant must be recorded in the CRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters may be recorded in the CRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at screening, unless a further increase / decrease can be considered an exacerbation of a pre-existing condition.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (e.g., in vitro hemolysis) and flagged as such by the laboratory in the laboratory report.
- Abnormal parameters that are obviously biologically implausible (e.g., values that are incompatible with life or outside the measuring range).
- An abnormal laboratory value that cannot be confirmed after repeat analysis, preferably in the same laboratory (i.e., the previous result could be marked as not valid and should not necessarily be reported as an AE).

10.2.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

Results in death – The event must be the cause of death for the SAE to meet this serious criterion.

Is life-threatening – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.

Requires in-patient hospitalization or prolongation of existing hospitalization – Hospital admissions for planned surgery or for normal disease management procedures (e.g., chemotherapy) are not considered as defining criteria for SAEs.

Results in persistent or significant disability or incapacity.

Is a congenital anomaly or birth defect.

Is medically important – A medically important event is defined as an event that does not necessarily meet any of the SAE criteria, but which is considered by the investigator to potentially jeopardize the subject or to require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.

Adverse events that do not fall into the above categories are defined as nonserious AEs.

10.2.2. Assessment of Severity

The severity of each AE (i.e., nonserious and serious AEs) is to be assessed by the investigator as follows:

Table 7 Definitions of Adverse Event Severity

Severity	Definition
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 subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

AE = adverse event.
Source: CDISC SDTM Severity Intensity Scale for Adverse Event Terminology.

10.2.3. Assessment of Causality

The causal relationship of an AE to IP, AxMP must always be assessed by the investigator. All AEs will be classified as either related or not related to IP, and AxMP. If a causality assessment is not provided for an AE (including an SAE), that AE will be considered related to IP until clarified with the site.

The degree of certainty with which an AE is attributed to IP or an alternative cause (e.g., natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of the IP.
- Clinically and/or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products or reported in the literature for similar products as being product related (e.g., headache, facial flushing, pallor).
- Plausibility supported by the temporal relationship (e.g., the event being related by time to administration or termination of treatment with IP, drug withdrawal, or reproduced on rechallenge).

10.2.4. Follow-up of Adverse Events

Every effort should be made to follow AEs until resolution or stabilization. Ongoing, nonserious AEs that have not resolved or stabilized will be followed until the subject completes the study. Serious adverse events will be followed until the AE resolves, stabilizes, or the subject is lost to follow-up.

10.2.5. Adverse Event Reporting

The reporting of AEs for an individual subject will start after informed consent has been obtained and will continue until EOS.

10.2.5.1. Adverse Events

At each study visit, the investigator (or delegate) will determine whether any AEs have occurred. If AEs have occurred, they are to be recorded in the CRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs, laboratory findings, and/or symptoms. The investigator must follow the course of an AE until the event resolves or stabilizes. If an AE is ongoing at the End of Study Visit, the AE will continue to be followed until resolution or stabilization, or until the subject is lost to follow-up.

If, during the study, a subject presents with a pre-existing condition that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History CRF.

The most appropriate diagnosis or if a diagnosis cannot be established, the abnormal laboratory values must be recorded on the Adverse Event CRF.

10.2.5.2. Serious Adverse Events

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Guideline E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of the investigator becoming aware of the event. The Investigator will also submit any updated SAE data to the Sponsor within 24 hours of it being available.

Detailed instructions regarding how to report to Sponsor or designee within 24 hours are to be found in the document provided to each site.

Any SAE that occurs after the End of Study Visit that is considered to be causally related to IP must be reported immediately (i.e., within 24 hours of the investigator becoming aware of the event) to the Sponsor or Sponsor designee. Such events are not entered into the CRF.

The minimum requirements for the reporting of SAEs are:

- Subject identification number.
- Suspected medicinal product and/or procedure.
- Event term.
- Identity of reporting source (i.e., subject, caregiver, treating physician, investigator).
    - If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event.

In addition, the investigator must:

- Report all SAEs to the relevant IRB / IEC within the timeframe specified by the IRB / IEC.
- If the subject is an active subject in the study:
- Enter Follow-up information in the CRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
- Ensure that the causality assessment for all SAEs is entered in the CRF
    - If the subject is no longer participating in the study, report the follow-up information to the Sponsor or the Sponsor's designee.
- In cases of death, the investigator should supply the Sponsor and the IEC / IRB (as applicable) with any additional information as it becomes available (e.g., autopsy reports and detailed medical reports).

Any potential Hy's Law case will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity, and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Reporting of AEs related to AxMP(s)

All AEs related to any authorized AxMP used in this study must be reported to Novartis within

7 calendar days.

In assessing causality, the investigators will use the points above in Section 10.2.3

If a suspicion that medical occurrence could be related to study treatment (and/or interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

Reporting of SAEs related to AxMP(s)

All SAEs related to any AxMP (whether authorized or not) used in this study must be reported to Novartis within 24 hours of the site becoming aware of it. In assessing causality, the investigators will use the points above. If a suspicion that the medical occurrence could be related to study treatment (or and interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

10.2.5.3. Adverse Events of Special Interest

AESIs include the following:

Fluid retention

Fluid retention is a pharmacological effect of ET-receptor antagonists. Peripheral edema and excessive weight gain secondary to fluid retention have been observed in clinical studies. Fluid retention is considered a class effect.

Dilutional anemia

There is no evidence of a decrease in erythropoiesis in subjects participating in atrasentan clinical studies; however, since anemia has been associated with an increased risk of both cardiovascular and renal events in CKD subjects, the frequency and severity of anemia will be closely monitored.

Vasodilation/ Hypotension

Hypotension through vasodilatation is associated with the suppression of ET-1 effects by ET-receptor antagonists and is a class effects.

Contact the Sponsor's Medical Lead (or designee) to discuss guidance for the management of subjects who experience a volume depletion adverse event (e.g., hypotension, hypovolemia) or a meaningful change in eGFR (such as > 30% decline from a prior visit).

Cardiac Failure

Pulmonary edema and congestive heart failure (CHF) are pharmacological effects of ET-receptor antagonists.

10.2.5.4. Overdose

Any overdose that occurs in association with an adverse sign or symptom must be entered into the CRF as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 10.2.5.2).

The details of an overdose of the IP (defined in Section 6.6) must be recorded in the appropriate CRF. Details of an overdose of any concomitant therapy must be recorded in the Concomitant Medication CRF.

10.2.5.5. Pregnancy and Breastfeeding

A female subject or female partner of a male subject who becomes pregnant while participating in the study, or up to and including 5 times the half-life of the IP after the last dose of IP, must notify the investigator within 24 hours of a positive pregnancy result.

If a female subject becomes pregnant, she must discontinue treatment with atrasentan but may continue other study procedures at the discretion of the investigator. If the female subject is in the active treatment period of the study, their participation will be discontinued and the procedure for discontinuation of a subject will be followed, as described in Section 7).

The investigator must notify the Sponsor within 24 hours of becoming aware of the pregnancy by completing the applicable Pregnancy Form.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Whenever possible, a pregnancy in a subject or in a female partner of a male subject exposed to atrasentan should be followed to term to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination of pregnancy or the status of the mother and child after delivery, should be reported by the investigator to the Sponsor using a Pregnancy Reporting / Outcome Form.

Subjects should not breastfeed during the study and for 1 month after the last dose of study treatment.

All abnormal pregnancies and neonatal outcomes (e.g., spontaneous abortion, stillbirth, neonatal death or congenital anomaly) will meet the criteria for SAE classification. The investigator should follow the procedure for reporting these events as SAEs (see Section 10.2.5.2).

10.2.5.6. Clinical Outcomes of Interest and/or Disease-related Events

Some subjects will experience a progression of their CKD over the course of this study as part of the natural course of the disease. In addition, the study population is prone to experience acute, transient loss of kidney function of different etiologies, sometimes concomitantly complicated by progression of CKD.

Clinical outcomes of interest include eGFR less than 15 mL/min/1.73 m2 (based on the CKD-EPI equation) or reduction of eGFR by 30% or reduction of eGFR by 40%. In addition, progression to chronic dialysis and kidney transplantation will also be considered clinical outcomes of interest. In alignment with the International Consensus definitions, chronic dialysis has been defined as renal replacement therapy for ≥ 30 days (Levin 2020).

To ensure consistent reporting of kidney events, the following guidelines are to be used when reporting a kidney-related AE:

- The following situations should always be reported as SAEs with seriousness criteria "medically important," if no other seriousness criterion is met (see Section 10.2.1):
- Progression of CKD leading to chronic dialysis: Subjects who undergo transition to chronic maintenance dialysis should be reported. The term "chronic dialysis" should

also be captured on the Procedures CRF

- Any medical event requiring transient acute dialysis: For subjects who undergo transient acute dialysis, the verbatim SAE term should record the condition for which the dialysis is required. Examples of AE terms include: "hyperkalemia requiring transient acute dialysis," "volume overload requiring acute dialysis" and, "acute kidney injury requiring acute dialysis." The "acute dialysis" should also be captured on the Procedures CRF
- Kidney transplantation: Subjects receiving a kidney transplant should be reported. The term "kidney transplant" should also be captured on the Procedures CRF.
- The following situations will be reported as SAEs if they meet seriousness criteria (see Section 10.2.1); otherwise, they should be reported as AEs:
- Acute kidney injury not requiring dialysis – The reported AE term should reflect the etiology for the impairment of the kidney function. Non-specific AE terms such as "Decreased eGFR" or "Increased creatinine" should be avoided whenever the underlying etiology is known.
- Examples of AE terms for prerenal impairment include: hypovolemia, hepatorenal syndrome, and heart failure
- Examples of AE terms for intrarenal impairment include: acute tubular necrosis, acute interstitial nephritis, and glomerulonephritis
- Examples of AE terms for postrenal impairment include: hydronephrosis, pelvicaliectasis, and urinary tract obstruction

- Progression of CKD not requiring dialysis – If permanent loss of kidney function due to underlying CKD has occurred, the reported AE term should reflect the underlying etiology. Non-specific terms such as "Decreased eGFR," "Increased creatinine," or "Worsening CKD" should be avoided whenever the underlying etiology is known. Examples of AE terms include: worsening lupus nephritis, worsening diabetic kidney disease, and worsening glomerulonephritis.
- Medical conditions related to CKD that occur without acute kidney injury or progression of CKD – If there is no decline in kidney function, the medical complication of CKD itself should be reported. AE terms such as "Progression of CKD" or "Acute Kidney Injury," should be avoided when there is no decline in kidney function. Examples of AE terms include: edema and hyperkalemia.

10.2.6. IRB / IEC Reporting Requirements

The time frame within which an IRB / IEC must be notified of deaths and investigational product-related unexpected SAEs is stipulated by each IRB / IEC. It is the investigator's responsibility to comply with the requirements for IRB / IEC notification.

10.3. Study Assessment and Procedure Considerations

10.3.1. Optional, On-demand Alternate Visit Modalities

In the event of a state of emergency, public health threat resulting in travel restrictions that prevent a subject from returning to the study site for the required study assessments or procedures, or in the event the central laboratory samples are not able to be assessed the following may be implemented with Sponsor approval as per the Schedule of Activities (Section 1.3): phone or video conference calls at home for safety follow-up, including assessment of AEs and concomitant therapies, and collection of hematology, biochemistry, urine tests, and pregnancy blood sampling at a local laboratory, if needed. In the event that study endpoints are not able to be analyzed at the central laboratory (e.g., event of state of emergency), local labs could be utilized to analyze lab data.

Telemedicine or virtual study visits may be performed by qualified, designated study site personnel.

Home health visits may be performed by a qualified medical provider selected by the Sponsor.

Please refer to Appendix 4 for Guidance to Address Global Pandemic, including alternatives to in-clinic visits.

10.4. Country-specific Requirements

Refer to Section 10.1.5 for data protection requirements in the EU.

11. REFERENCE

Canney M, Barbour SJ, Zheng Y, et al. Quantifying Duration of Proteinuria Remission and Association with Clinical Outcome in IgA Nephropathy. *J Am Soc Nephrol.* 2021;32(2):436-447.

EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2023; 388:117-127.

Heerspink HJL, Kohan DE, de Zeeuw D. New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction. *Kidney Int.* 2021;99(2):346-349.

Heerspink HJ, Cherney DZI. Clinical implications of an acute dip in eGFR after SGLT2 inhibitor initiation. Clin J Am Soc Nephrol. 2021a;16(8):1278-1280. Accessed at: https://kidney360.asnjournals.org/content/2/6/1042

Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, et al. Dapagliflozin in patients with chronic kidney disease N Engl J Med. 2020;383:1436-1446.

Heerspink HJL, Parving H-H, Andress DL, Bakris G, Correa-Rotter R, Hou F-F, et al. Atrasentan and renal events in subjects with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomized, placebo-controlled trial. Lancet. 2019;393(10184):1937-1947.

KDIGO. Clinical Practive Guidelines for the Management of Glomerular Diseases. Chapter 10: Immunoglobulin A nephropathy. Kidney Int Suppl 2021;100(4S).

Kim, S.-G., Vo, N., Lee, S.-H., Ranganathan, D., Inker, L., El-Shahawy, M., Spinelli, T., Sheth, K., Devries, T., Camargo, M., King, A., Glicklich, A., & Wong, M. (2022). FC052: Atrasentan for the Treatment of IGA Nephropathy: Interim Results from the Affinity Study. *Nephrology Dialysis Transplantation*, 37 (Supplement_3), gfac107.004

Levin A, Agarwal R, Herrington WG, Heerspink HL, Mann JFE, Shahinfar S, Tuttle KR, Donner JA, Jha V, Nangaku M, de Zeeuw D, Jardine MJ, Mahaffey KW, Thompson AM, Beaucage M, Chong K, Roberts GV, Sunwold D, Vorster H, Warren M, Damster S, Malik C, Perkovic V; participant authors of the International Society of Nephrology's 1st International Consensus Meeting on Defining Kidney Failure in Clinical Trials. International consensus definitions of clinical trial outcomes for kidney failure: 2020. Kidney Int. 2020 Oct;98(4):849-859.

Meraz-Muñoz AY, Weinstein J, Wald R. eGFR decline after SGLT2 inhibitor initiation: the tortoise and

the hare reimagined. Kidney360 2021;2(6):1042-1047.

Wheeler, David C., et al. "A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy." Kidney international 100.1 (2021): 215-224.

Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med.* 2013;368(25):2402-2414.

12. APPENDICES

Appendix 1. Abbreviations

Term	Definition
ACE	angiotensin converting enzyme
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AxMP	auxiliary medicinal product
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease/exocrine pancreatic insufficiency
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
DEARA	dual endothelin receptor antagonist
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EoS	end of study
EoT	end of treatment
ESKD	end stage kidney disease
ESRD	end stage renal disease
ETA	endothelin receptor A
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
Hb	hemoglobin
HbA1c	glycated hemoglobin
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgAN	Immunoglobulin A nephropathy
IMP	Investigational Medicinal Product
IND	Investigational New Drug

IP	Investigation Product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
KDIGO	Kidney Disease Improving Global Outcomes
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NSAID	Nonsteroidal anti-inflammatory drug
PD	pharmacodynamics
CCI	
PK	pharmacokinetics
QD	once daily
RAS	renin-angiotensin system
RASi	renin-angiotensin system inhibitor
RBC	red blood cell (count)
RPGN	Rapidly progressing glomerulonephritis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGLT2	sodium glucose co-transporter 2
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SOC	system organ class
SUSAR	suspected unexpected serious adverse event
TEAE	treatment-emergent AE
UACR	urinary albumin:creatinine ratio
ULOQ	upper limit of quantification
UPCR	urine protein:creatinine ratio
US	United States
WBC	white blood cell (count)
WOCBP	women of child-bearing potential
βhCG	Choriogonadotropin Beta

Appendix 2. Clinical Study Protocol Amendment History

Amendment	Reasons for Amendment
CCI	

Appendix 3. Prohibited OATP and CYP3A4 Medication List

OATP Inhibitors

Generic Drug Name	Brand Name	OATP
Atazanavir	Reyataz®	OATP1B1, OATP1B3
Clarithromycin	Biaxin®	OATP1B1, OATP1B3
Cobicistat	Part of Stribild®	OATP1B1, OATP1B3
Cyclosporine	Neoral®, Gengraf®, Sandimmune®	OATP1B1, OATP1B3
Daclatasvir	Daklinza®	OATP1B1, OATP1B3
Eltrombopag	Promacta®	OATP1B1
Erythromycin	E-mycin®	OATP1B1, OATP1B3
Gemfibrozil	Lopid®	OATP1B1
Glecaprevir	Mavyret™	OATP1B1, OATP1B3
Lopinavir/Ritonavir	Kaletra®	OATP1B1, OATP1B3
Letermovir	Prevymis®	OATP1B1, OATP1B3
Paritaprevir	Viekira Pak™, Technivie™	OATP1B1, OATP1B3
Pibrentasvir	Mavyret™	OATP1B1, OATP1B3
Sacubitril	Entresto®	OATP1B1, OATP1B3 (*in vitro*)
Saquinavir	Invirase®	OATP1B1, OATP1B3
Simeprevir	Olysio®	OATP1B1, OATP1B3
Telithromycin	Ketek®	OATP1B1, OATP1B3
Teriflunomide	Aubagio®	OATP1B1, OATP1B3
Tipranavir	Aptivus®	OATP1B1
Rifampin	--	OATP1B1, OATP1B3
Velpatasvir	Epclusa®, Vosevi™	OATP1B1, OATP1B3, OATP2B1
Voxilaprevir	Vosevi™	OATP1B1, OATP1B3

Potent CYP3A4 Inhibitors and Inducers

Generic Drug Name	Brand Name
Inhibitors	
Grapefruit juice	--
Nefazodone	Serzone®
Cobicistat	Tybost®
Idelalisib	Zydelig®
Macrolide Antibiotics	
Clarithromycin	Biaxin®
Telithromycin	Ketek®
Azole Antifungals	
Itraconazole	Sporanox®
Posaconazole	Noxafil®

Ketoconazole (systemic)	--
Voriconazole	Vfend®
HIV Antivirals	
Ritonavir	Norvir®
Indinavir	Crixivan®
Lopinavir	Kaletra® (Lopinavir/Ritonavir)
Nelfinavir	Viracept®
Atazanavir	Reyataz®
Saquinavir	Invirase®
Telaprevir	Incivek®
Boceprevir	Victrelis®
Danoprevir	Ganovo®
Paritaprevir	--
Elvitegravir	Vitekta®
Inducers	
Carbamazepine	Tegretol®
Phenytoin	Dilantin®
Apalutamide	Erleada®
Rifampin	Rifadin®
St. John's Wort	--
Enzalutamide	Xtandi®
Mitotane	Lysodren®

Source: FDA Guidance for Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (March 2020)

Appendix 4. Guidance to address Global Health Emergencies and Potential Impact on the Clinical Study

As of 12 March 2020, a coronavirus disease 2019 (COVID-19) pandemic has been declared by the World Health Organization, leading to implementation of extensive measures by healthcare systems globally to limit viral spread, with potential impact on conduct of clinical studies (because subjects/healthcare workers are in self-isolation/quarantine, there is limited access to public places, including hospitals, and health care professionals are committed to critical tasks).

Based on guidelines issued by global regulatory authorities, the actions listed below are being implemented in this protocol to address potential disruptions to study conduct secondary to COVID-19 infection or control measures. These actions are to assure the safety of subjects, maintain compliance with good GCP, and minimize the risks to study integrity. Member states within the National Competent Authorities or countries in other regions may issue their own guidance requiring country specific recommendations to be followed.

To the extent feasible, the Sponsor should ensure that the methods and conduct of remote assessments are consistent across sites, subjects, and visits.

Informed Consent

- If written consent by the study subject is not possible (for example because of physical isolation due to COVID-19 infection), consent could be given verbally by the study subject. Site to record date and time of discussion.
- Subjects in the study and the person obtaining consent could sign and date separate informed consent forms
- In case a written informed consent cannot be obtained at the clinical site, the consent form may be sent to the subject or the subject's legally authorized representative by facsimile or e-mail, and the consent interview may then be conducted by telephone when the subject or subject's legally authorized representative can read the consent form during the discussion.
- If re-consent is necessary for the implementation of new urgent changes in study conduct (mainly expected for reasons related to COVID-19 or important safety issues for other trials), alternative ways of obtaining may include contacting the study subject via phone or video-calls and obtaining verbal consents, to be documented in the study subjects' medical records, supplemented with e-mail confirmation.
- The informed consent procedure will remain compliant with the study protocol as well as local regulatory requirements. All relevant records should be archived in the Investigator's site master file. A signed and dated informed consent form should be obtained from the study subjects later, as soon as possible.

Study Visits and Procedures

COVID-19 screening procedures that may be mandated by the health care system in which a clinical study is being conducted do not need to be reported as an amendment to the protocol even if done during clinical study visits. The Investigator in consultation with the Sponsor will decide if it is in the best interest of COVID positive subjects to remain in the study.

To maintain the integrity of the study, alternative methods of collecting study procedures may be considered where possible and in certain situations, with Sponsor approval:

- Where allowed, remote visits have been incorporated as part of the study, in addition to clinic visits and phone visits. During remote visits, subject's privacy would be maintained, as would be done for a clinic visit.
  The following approaches to enable study visits will be supported:
- In-clinic at the Investigational site
- Site- to-subject delivery/return of:
  - 24-hour urine collection
    - In the case of missed visits due to COVID-19 (or other health pandemic) related reasons:
      - The site should make every effort to contact the study subject to confirm and document the reason for the missed visit, and at minimum evaluate AEs/SAEs, and concomitant medications in order to assess subject safety.

Study drug Supply

1. Alternative methods of supplying and disposing of study drug to enrolled study subjects, e.g., direct-to-subject shipment (delivery/return of blinded study drug) from site may be considered where possible.
2. Study drug may be shipped to the subject's home from the investigative site, as required by regulations. In this case, appropriate controls will be used to ensure that the drug is received by the subject.
3. Additional study drug will not be released to the subject without an evaluation of subject safety, including protocol-required laboratory results (at a minimum hematology, clinical chemistries, vital signs and pregnancy testing for WOCBP), and clearance communicated to the subject.

Monitoring and Audits

- Certain Sponsor oversight responsibilities, such as monitoring and quality assurance activities need to be re-assessed and temporarily, alternative proportionate mechanisms of oversight may be required. On-site audits will be avoided or postponed, and if permitted under local regulations, social distancing restrictions should apply.
- Cancelling or postponing of on-site monitoring visits and extending of the period between monitoring visits will be allowed.
- To the extent on-site monitoring remains feasible, it should take into account national, local and/or organizational social distancing restrictions.
- Centralized monitoring can be considered for data acquired by electronic data capture systems (e.g. CRFs, central laboratory or vital signs, ePROs etc.) that are in place or could be put in place provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner.
- Off-site monitoring can be conducted and may include phone calls, video visits, e-mails or other online tools in order to discuss the study with the Investigator and site staff. Remote monitoring will be focused on review of critical study site documentation and source data. These activities may be used to get information on the clinical study progress, to exchange

information on the resolution of problems, review of procedures, study subject status as well as to facilitate remote site selection and Investigator training for critical study procedures.

Risk Benefit Assessment

- The Sponsor will continually assess whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to study subjects, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.
- IgAN is a disease with a large unmet need and no approved therapies that primarily affects individuals in their second and third decade of life. Among subjects who develop >1gram/day proteinuria and/or an elevated serum creatinine concentration, progression to end-stage renal disease is approximately 15 to 25 percent at 10 years and 20 to 30 percent at 20 years (Wyatt, 2013). Additionally, a recent large multicenter cohort of subjects with biopsy proven IgA nephropathy, showed that each 3 months that subjects stay in remission of proteinuria is associated with 9% reduction in the risks of disease progression, highlighting the importance of prompt treatment for subjects who are at high risk of renal disease progression (Canney, 2021).
- Data from all subjects treated in the large, Phase 3, placebo-controlled SONAR trial did not show a clinically meaningful difference between atrasentan and placebo cohorts with respect to fluid retention (37.7% [689/1829) vs. 32.7% [599/1830)], any cardiac failure (5.8% [106/1829] vs. 3.7% [67/1830]) or any vasodilation (9.2% [168/1829] vs. 9.5% [174/1830] in a patient population with diabetic kidney disease and concurrent medical comorbidities. The CEXV811A12201 excludes subjects with CHF or clinically significant fluid overload and those with BNP >200 (Protocol Section 5.2, Exclusion Criteria). Subjects enrolled in the CEXV811A12201 trial will be closely monitored during the duration of the trial for fluid accumulation by having frequent weights measured (standardized scale will be provided to subjects), and any weight gain greater than 2 kg is to be reported to the primary Investigator and the Medical Lead so that prompt mitigating such as use of diuretics could be instituted.
- There are no data or biological reason to suspect that atrasentan would have any negative effect on immune response or interfere with potential COVID-19 inoculation.
- The CEXV811A12201 trial has been designed to minimize any unnecessary potential viral exposure by allowing most of the study visits to be conducted remotely, and in addition, bloodwork and required laboratory tests can be collected from the subject in their home (Protocol Section 8, Study Assessments and Procedures).
- Additionally, given the heterogeneity of disease course in subjects infected with COVID-19, should a subject become infected during the study, further participation in the study will be discussed by the subject's physician and the Medical Lead keeping the subject's safety as the only priority. If there is any remote indication of a possible untoward effect from continuing to participate in the study, the subject will be discontinued from study drug.

Benefit-Risk Conclusion

- IgAN is rare, serious disease with no approved therapies or safe and effective treatment options for subjects who continue to experience proteinuria despite optimal treatment with RAS inhibitors. There is an underlying and important unmet medical need to develop

therapies for subjects with IgAN who remain at risk for progressive renal failure.

- In light of the current COVID-19 pandemic, and with the comprehensive mitigation and safety monitoring procedures to be followed above, it can be concluded that this study can proceed for the benefit of subjects with IgAN.