CLINICAL STUDY PROTOCOL

A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO EVALUATE EFFICACY AND SAFETY OF NEFECON IN PATIENTS WITH PRIMARY IGA NEPHROPATHY AT RISK OF PROGRESSING TO END-STAGE RENAL DISEASE (NefIgArd)

Investigational Product: Nefecon (budesonide modified-release capsules)
Protocol Number: Nef-301
EudraCT Number: 2017-004902-16
IND Number: 107950
NCT Number: 03643965

Sponsor:
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Date: 14 January 2021

SIGNATURE PAGE

STUDY TITLE: A Randomized, Double-Blind, Placebo Controlled Study to Evaluate Efficacy and Safety of Nefecon in Patients with Primary IgA Nephropathy at Risk of Progressing to End-Stage Renal Disease (NefIgArd)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
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INTERNATIONAL COORDINATING INVESTIGATOR SIGNATURE PAGE

STUDY TITLE: A Randomized, Double-Blind, Placebo Controlled Study to Evaluate Efficacy and Safety of Nefecon in Patients with Primary IgA Nephropathy at Risk of Progressing to End-Stage Renal Disease (NefIgArd)

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date

_____ _____

[redacted]

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Calliditas Therapeutics AB to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Calliditas Therapeutics AB and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by Calliditas Therapeutics AB, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with International Council for Harmonisation for Good Clinical Practice, the Declaration of Helsinki as amended, and all other applicable regulatory requirements.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Randomized, Double-Blind, Placebo Controlled Study to Evaluate Efficacy and Safety of Nefecon in Patients with Primary IgA Nephropathy at Risk of Progressing to End-Stage Renal Disease (NefIgArd)

PROTOCOL NUMBER: Nef-301

EudraCT NUMBER: 2017-004902-16

INVESTIGATIONAL PRODUCT: Nefecon (budesonide modified-release capsules)

PHASE: 3

INDICATION: Treatment of primary immunoglobulin A nephropathy (IgAN)

OBJECTIVES:

The overall aim of the study is to evaluate the efficacy, safety, and tolerability of Nefecon 16 mg per day in the treatment of patients with primary IgAN at risk of progressing to end-stage renal disease (ESRD), despite maximum tolerated treatment with renin-angiotensin system (RAS) blockade using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II type I receptor blockers (ARBs).

Primary Objectives:

Part A

The primary objective of Part A is to assess the effect of Nefecon 16 mg treatment on urine protein to creatinine ratio (UPCR) over 9 months compared to placebo.

Part B

The primary objective of Part B is to assess the effect of the Nefecon 16 mg treatment given in Part A on clinical consequences of any proteinuria reduction as measured by estimated glomerular filtration rate (eGFR) recorded over 2 years compared to placebo.

Secondary Objectives:

Part A

The secondary objectives of Part A are:

- To assess the effect of Nefecon 16 mg treatment on eGFR at 9 and 12 months compared to placebo, and
- To evaluate additional aspects of renal function, and safety and tolerability of Nefecon 16 mg treatment over 9 months compared to placebo.

Part B

The secondary objectives of Part B are to assess the effects of the Nefecon 16 mg treatment given in Part A on different aspects of renal function and safety compared to placebo over 2 years.

POPULATION:

The population for this study is patients ≥18 years of age, diagnosed with IgAN with biopsy verification within the 10 years prior to screening, on a stable dose of RAS inhibitor therapy for the 3 months prior to randomization, eGFR ≥35 mL/min per 1.73 m^2 and ≤90 mL/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, and proteinuria based on 2 consecutive measurements separated by at least 2 weeks and calculated by the central laboratory showing either ≥1 g per day (≥1000 mg per day) in 2 consecutive measurements or UPCR ≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements. Patients will be excluded from the study if they have undergone a kidney transplant; have liver cirrhosis, as assessed by the Investigator; have poorly controlled type 1 or type 2 diabetes mellitus; have history of unstable angina, class III or IV congestive heart failure, and/or clinically significant arrhythmia, as judged by the Investigator; have unacceptable blood pressure control; have known osteoporosis in medium- or high-risk category; have known glaucoma, known cataract(s), and/or history of cataract surgery, unless the surgery was performed on both eyes; have been treated with systemic immunosuppressive medications, other than glucocorticoids (GCSs), within the 12 months before randomization; have been treated with any systemic GCSs within the 3 months before randomization; have been treated with any systemic GCSs within the 12 months before randomization except for a maximum of 3 periods of 2 weeks with the equivalent of 0.5 mg/kg/day prednisolone or less for non-IgAN indications; or are taking potent inhibitors of cytochrome P450 3A4.

STUDY DESIGN AND DURATION:

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of oral Nefecon compared to matching placebo in patients with primary IgAN on a background of optimized RAS inhibitor therapy. Approximately 360 patients will be randomized at approximately 160 sites in Europe, North America, South America, Asia Pacific, and China. The study will consist of 2 parts, Part A and Part B. Part A will include a Screening Period (up to 35 days) followed by a 9-month blinded Treatment Period, and a 3-month Follow-up Period (including a 2-week Tapering Period). The total duration of Part A is up to 13.5 months.

Part B will consist of a 12-month (+14 to 35 days) observational Follow-up Period after Part A has ended. Each patient randomized will be followed for 25 months after the first dose (or, if the patient randomized does not receive any study drug, 25 months after the patient is randomized). The total duration of the study is up to 26.5 months (including the Screening Period and a final visit for replicate eGFR sampling at 2 years). Part A will be blinded, and the blinding will remain in place throughout Part B. No study drug will be administered during Part B. The primary analysis in Part B will occur 25 months after the 360th/last patient is dosed (or, if the 360th/last patient randomized does not receive any study drug, 25 months after the 360th/last patient is randomized).

Part A

In order to be eligible for randomization, patients must be on a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed dose or maximum tolerated dose according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for at least 3 months prior to randomization. A stable dose is defined as doses within 25% of the dose at randomization. Patients should remain on their regimens of RAS inhibitors for the whole duration of the study (Part A and Part B). It is recommended that patients achieve a target systolic blood pressure <125 mmHg and target diastolic blood pressure <75 mmHg according to the 2012 KDIGO guidelines. The use of additional antihypertensive therapy will be permitted as needed. Investigators should ensure that patients are informed at screening of potentially beneficial lifestyle choices including weight normalization, smoking cessation, physical activity, and diet (low salt and low protein). Patients must, after informed consent, have proteinuria based on 2 consecutive measurements (24-hour urine sampling) after informed consent, separated by at least 2 weeks and calculated by the central laboratory (baseline will be the geometric mean of these 2 measurements).

Both samples of the same parameter must show either of the following:

- Proteinuria ≥1 g per day (≥1000 mg per day) in 2 consecutive measurements, or
- UPCR ≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements.

Additionally, all other eligibility criteria must be met in order to be eligible for randomization.

After confirming all eligibility criteria, patients will be randomized in a 1:1 ratio to Nefecon 16 mg or placebo within 35 days of Study Visit 1 (screening). The study will be double-blinded, and randomization will be stratified according to baseline proteinuria, eGFR, and geographic region. Randomized patients will receive either Nefecon 16 mg (four 4 mg budesonide modified-release capsules once per day [QD]) or placebo (4 matching capsules QD) for a 9-month Treatment Period.

Following completion of the Treatment Period, patients will enter the 3-month Part A Follow-up Period. The first 2 weeks of this Follow-up Period will consist of a 2-week Tapering Period to reduce the risk of insufficiency of the adrenal glands. During the 2-week Tapering Period, the study drug dose will be reduced from 4 capsules QD (Nefecon 16 mg or placebo) to 2 capsules QD (Nefecon 8 mg or placebo).

Patients will discontinue study drug at the end of the Tapering Period and then complete the remainder of the Part A Follow-up Period before entering Part B.

Patients who prematurely discontinue study drug during the Treatment Period should complete the 2-week Tapering Period, if feasible, to prevent insufficiency of the adrenal glands. All patients who prematurely discontinue study drug should have eGFR, proteinuria, and creatinine measured at each scheduled visit; it is of particular importance for the 9- and 12-month study visits (Study Visits 11 and 13). All patients who prematurely discontinue study drug should also subsequently enter Part B of the study and continue to have eGFR, proteinuria, and creatinine measured unless they have withdrawn their consent to any kind of follow-up. In the case of patients who are randomized but do not receive any study drug, they should have eGFR, proteinuria, and creatinine measured at each scheduled visit; it is of particular importance for the 9- and 12-month study visits (Study Visits 11 and 13). They should also subsequently enter Part B of the study and continue to

have eGFR, proteinuria, and creatinine measured unless they have withdrawn their consent to any kind of follow-up.

Part B

Part B of the study will consist of a 12-month (+14 to 35 days) observational Follow-up Period; no study drug will be administered during Part B. Each patient randomized will be followed for 25 months after the first dose (or, if the patient randomized does not receive any study drug, 25 months after the patient is randomized). Following completion of Part A, patients will remain on their optimized RAS inhibitor/antihypertensive therapy and continue into Part B of the study. During Part B, the Investigator may consider that rescue medication (steroids and/or immunosuppressive treatment) may be needed. Such treatment can be initiated by the Investigator; however, patients should have a proteinuria level at least above 1 g per 24 hours, as suggested in the 2012 KDIGO guidelines, and the Medical Monitor should be consulted for advice.

During Part B of the study, patients will complete onsite study visits at 18 and 24 months, including a final visit for replicate eGFR sampling at 14 to 35 days after the 24-month visit. Telephone contacts will be performed between the onsite study visits at 15 and 21 months. The measurements of eGFR, proteinuria, and creatinine will continue in Part B. Additional telephone contacts and/or unscheduled study visits can be made as needed.

Part B will continue until 25 months after the 360th/last patient is dosed (or, if the 360th/last patient randomized does not receive any study drug, 25 months after the 360th/last patient is randomized). Patients who receive rescue medication should continue in the study and complete all study procedures as indicated in the Schedule of Procedures table. Patients will be followed until initiation of dialysis, undergoing renal transplantation, death, or study completion (i.e., maximum of 25.5 months after the first dose [or, if the patient randomized does not receive any study drug, 25.5 months after the patient is randomized]), whichever occurs first.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Nefecon 16 mg (four 4 mg budesonide modified-release capsules QD) or placebo (4 matching capsules QD) will be administered orally for 9 months (or up to 10 months, when applicable, due to the Coronavirus Disease 2019 [Covid-19] pandemic) during the Treatment Period in Part A.

Patients must take the first dose of study drug (Nefecon 16 mg or placebo) in the presence of site staff during Study Visit 4 within 10 days after their randomization. As a result, the first dose of study drug may be administered at any time of day and without regard to the timing of meals. Patients may self-dose for all other doses of study drug and should take study drug in the morning approximately 1 hour before breakfast.

The daily dose of double-blinded study drug may be reduced from 4 capsules QD (Nefecon 16 mg or placebo) to 2 capsules QD (Nefecon 8 mg or placebo) if clinically relevant adverse events (AEs) develop that the Investigator considers related to the study drug and that mandate dose reduction. The Medical Monitor should preferably be consulted prior to reducing the daily dose of study drug during the first 9 months (or up to 10 months, when applicable, due to the Covid-19 pandemic) of treatment (Treatment Period in Part A). If a dose reduction is made during this time, then the dose should not be increased back to 4 capsules QD (Nefecon 16 mg or placebo).

After completing 9 months (or up to 10 months, when applicable, due to the Covid-19 pandemic) of study drug treatment, the daily dose of study drug will be reduced from 4 capsules QD

(Nefecon 16 mg or placebo) to 2 capsules QD (Nefecon 8 mg or placebo) for 2 weeks to prevent insufficiency of the adrenal glands (Tapering Period in Part A). Patients who have their daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg or placebo) due to safety and/or tolerability reasons during the first 9 months (or up to 10 months, when applicable, due to the Covid-19 pandemic) of treatment (Treatment Period in Part A), will remain on this dose of study drug for an additional 2 weeks after completing 9 months (or up to 10 months, when applicable, due to the Covid-19 pandemic) of study drug treatment (during the Tapering Period in Part A). Patients who prematurely discontinue study drug treatment while taking 4 capsules QD (Nefecon 16 mg or placebo), should have the daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg or placebo) for 2 weeks, if feasible, to prevent insufficiency of the adrenal glands.

EFFICACY VARIABLES:

Part A Analysis

The data cut-off for the Part A analysis will occur once the first 201 patients randomized have had the opportunity to complete their 9-month visit. Therefore, it is expected the data cut-off will occur at the latest 9.5 months after the 201st patient randomized is dosed.

The dataset extracted from the database, and cleaned for analysis, will include all safety data from all patients randomized at the data cut-off date and all efficacy data up to and including the 12-month visit from all patients randomized at the data cut-off date. Therefore, any efficacy data recorded after 12 months will not be extracted from the database.

Part A Analysis Primary Efficacy Endpoint

The primary efficacy endpoint for the Part A analysis is defined as the ratio of UPCR (based on 24-hour urine collections) at 9 months following the first dose of study drug compared to baseline.

Part A Analysis Secondary Efficacy Endpoints

The secondary efficacy endpoints for the Part A analysis are:

- Ratio of eGFR at 9 and 12 months compared to baseline calculated using the CKD-EPI formula, and

  Note: A supportive analysis of 1-year eGFR slope will also be performed.

- Ratio of urine albumin to creatinine ratio (UACR) at 9 months compared to baseline.

Supportive analyses of the above endpoints will also be performed at all time points up to 12 months to describe the time course of effect.

Part B Analysis

The Part B analysis will be performed when the 360th/last patient randomized has had the opportunity to complete Visit 17b, which can occur up to 35 days after Visit 17a (the 24-month visit).

Part B Analysis Primary Efficacy Endpoint

The primary efficacy endpoint for the Part B analysis is an area under the curve (AUC)-based endpoint of eGFR calculated as a time-weighted average of eGFR recordings observed at each time point over 2 years. The eGFR (CKD-EPI) at 2 years (which must be repeated to provide a second value obtained within 14 to 35 days) will be the geometric mean of the 2 assessments. A supportive analysis of 2-year eGFR slope will also be performed.

Part B Analysis Secondary Efficacy Endpoints

The secondary efficacy endpoints for the Part B analysis are:

- Time to 30% reduction from baseline in eGFR (CKD-EPI) confirmed by a second value, with ≥4 weeks of separation between the 2 sampling time points;
- Time from the first dose of study drug until receiving rescue medication;
- Ratio of UPCR, UACR, and eGFR (CKD-EPI) compared to baseline averaged over time points between 12 and 24 months, inclusive, following the first dose of study drug;
- Proportion of patients without microhematuria in at least 2 of the following time points: 12, 18, and 24 months following the first dose of study drug;
- Proportion of patients receiving rescue treatment; and
- Short Form 36 (SF-36) quality of life assessment at 9 and 24 months.

Part B Analysis Exploratory Efficacy Endpoints

Exploratory analyses may be performed on blood and urine to explore potential changes between the treatment groups that may add to the understanding of the disease mechanism and how the treatment influences these mechanisms. In addition, already existing kidney biopsy samples will be collected for exploratory analyses at a central reading unit. Participation and sample shipment for exploratory analyses will be optional.

SAFETY VARIABLES:

The safety variables will include the following:

- Treatment-emergent AEs, defined as AEs that occur for the first time after dosing with study drug, or exist before but worsen in severity or relationship to study drug after dosing;
- AEs of special interest (AESIs) (severe infections requiring hospitalization, new onset of diabetes mellitus, confirmed fracture, new osteonecrosis, gastrointestinal bleeding that requires hospitalization, reported occurrence of cataract formation, and reported onset of glaucoma); and
- Vital signs, body weight, clinical laboratory variables, and physical examination findings.

STATISTICAL ANALYSES:

The primary efficacy analyses will be based on the Full Analysis Set (FAS), which will include all randomized patients, regardless of whether the patient received study drug. For Part A, the FAS will include the first 201 patients randomized. The data cut-off for the Part A analysis will occur once the first 201 patients randomized have had the opportunity to complete their 9-month visit.

Therefore, it is expected the data cut-off will occur at the latest 9.5 months after the 201st patient randomized is dosed. Two patients are excluded from the Part A FAS due to errors in randomization; this decision was pre-defined in the Statistical Analysis Plan prior to unblinding.

Baseline proteinuria, eGFR, UPCR, and UACR will be the geometric mean of the 2 consecutive measurements prior to randomization.

The protocol requires that all randomized patients continue to have assessments performed at each scheduled visit regardless of whether they prematurely discontinue study drug or even if they are randomized but do not receive any study drug. However, any data recorded after a patient receives rescue medication will be excluded from the primary efficacy analyses in Parts A and B so that the underlying effect of Nefecon can be estimated free from the confounding effects of rescue medication.

The primary efficacy endpoint for the Part B analysis is an AUC-based endpoint calculated as a time-weighted average of eGFR (CKD-EPI) measurements recorded over 2 years, where each time point is given a weight in proportion to the time elapsing from the previous recording. Therefore, recordings made at 18 and 24 months receive twice as much weight as those made at 3, 6, 9, and 12 months. The weights will sum to one so that the treatment effect can be interpreted as the average effect of Nefecon over 2 years.

The eGFR data will be log-transformed prior to analysis. Data included at baseline and 24 months will be the log of the geometric mean of the 2 replicate values recorded at each time point, respectively. Previous eGFR data from Nefecon trials suggest it is possible there will be a small sub-population of patients with extreme outlying data resulting from very rapid progression of disease. Therefore, the primary analysis will be based on a Robust Regression of each patient's AUC having multiply imputed missing data.

The primary efficacy endpoint for the Part A analysis, the ratio of UPCR at 9 months to baseline, will be log-transformed prior to analysis, as will data from the other time points used in the analysis model. The primary analysis of the log-transformed baseline ratios in UPCR will be analyzed using a Mixed Model Repeated Measures analysis based on the FAS and incorporating UPCR data from baseline, 3 months, 6 months, 9 months, and 12 months.

A multiplicity strategy will be used to control type I error amongst the primary and key secondary efficacy endpoints across both Part A and Part B.

The Safety Analysis Set will include all patients who receive at least 1 dose of study drug. For both Part A and Part B, AEs will be coded using the Medical Dictionary for Regulatory Activities and will include all safety data from patients who have received at least 1 dose of study drug at the time of the analysis. The incidence of treatment-emergent AEs and AESIs will be summarized by body system and organ class.

SAMPLE SIZE DETERMINATION:

Part A Analysis

The Nefecon Phase 2b study (Nef-202) gave an estimated standard deviation of 0.59 for the change in the log of UPCR from baseline after 9 months of treatment. Based on this assumption, 200 patients in Part A will provide >90% power to demonstrate statistical significance at a 1-sided

alpha level of 0.025 given a true 25% relative reduction in UPCR with Nefecon treatment compared to placebo.

Part B Analysis

A 28% reduction in UPCR, relative to placebo, was observed with the 16 mg dose of Nefecon in the Phase 2b study. Based on an analysis of the relationship between treatment effects on proteinuria at 1 year and the 2-year eGFR slope using aggregate data for trials in IgAN presented at the March 2018 NKF/FDA/EMA workshop Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of Chronic Kidney Disease, a 28% reduction in UPCR is predicted to translate into a treatment effect of 1.12 mL/min/1.73 m^2/year on 2-year eGFR slope, and hence, a 2.24 mL/min/1.73 m^2 treatment effect for the difference in mean eGFR at 2 years. If 360 patients are recruited and followed for 2 years, and replicate values of eGFR are recorded both at baseline and at 2 years, Part B will have 90% power to detect a statistically significant difference in eGFR at 2 years, using a 2-sided alpha of 5%, if the true effect of Nefecon is 2.24 mL/min/1.73 m^2.

The power for the primary efficacy endpoint for Part B, 2-year eGFR AUC, is >90% for the expected mean eGFR profiles for Nefecon and placebo over 2 years, if the treatment effect increases linearly over the first year to a maximum of at least 3 mL/min/1.73 m^2 and decreases linearly thereafter to a minimum of at least 2.24 mL/min/1.73 m^2.

A total of 360 randomized patients are planned to be evaluable for the final primary efficacy analysis for the study.

It is estimated that approximately 900 patients will be screened.

SITES:

It is anticipated that there will be approximately 160 sites in Europe, North America, South America, Asia Pacific, and China.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACEI	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
ARB	Angiotensin II type I receptor blocker
AUC	Area under the curve
CEC	Central Ethics Committee
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Covid-19	Coronavirus Disease 2019
CRA	Clinical research associate
CTA	Clinical trial authorization
CYP3A4	Cytochrome P450 3A4
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCS	Glucocorticoid
Gd-IgA1	Galactose-deficient polymeric immunoglobulin A1
GFR	Glomerular filtration rate
HbA1c	Hemoglobin A1c
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
IRB	Institutional Review Board
IRT	Interactive Response Technology
KDIGO	Kidney Disease: Improving Global Outcomes
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MTD	Maximum tolerated dose
OSTA	Osteoporosis Self-Assessment Tool for Asians

Abbreviation	Definition
QD	Once per day
RAS	Renin-angiotensin system
RSI	Reference Safety Information
SAE	Serious adverse event
SF-36	Short Form 36
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
UACR	Urine albumin to creatinine ratio
UPCR	Urine protein to creatinine ratio
WOCBP	Women of childbearing potential

1 INTRODUCTION AND BACKGROUND INFORMATION

Immunoglobulin A (IgA) nephropathy (IgAN), also known as Berger's disease, is the most common cause of glomerulonephritis worldwide, with prevalence estimates varying from 5% to more than 40% of patients with glomerular disease.[1] It is characterized by the deposition of IgA-containing immune complexes in the glomerular mesangium, leading to inflammation. Primary IgAN may present in different forms. One form is characterized by recurrent episodes of hematuria, often associated with viral infections, but no or minimal proteinuria and long-term stable renal function. Another form is characterized by persistent proteinuria and frequently hypertension and/or reduced glomerular filtration rate (GFR). Patients with this more severe form are at risk of progressing to end-stage renal disease (ESRD) and require treatment.

Primary IgAN can occur at any age, but the clinical onset is commonly during the second or third decades of life.[2] Immunoglobulin A nephropathy progresses to ESRD in 15% to 20% of patients within 10 years and in 30% to 40% within 20 years from disease onset.[3,4,5] It is the main cause of ESRD in patients with primary glomerular disease who require renal-replacement therapy.[6] It is estimated that IgAN accounts for 10% of renal transplants among patients with primary glomerulonephritis in the United States, and between 7% to 20% of patients in Europe and Australia in long-term dialysis and renal transplantation programs.[6,7]

Risk factors for disease progression include persistent proteinuria, elevated serum creatinine, microhematuria, and specific histological lesions.[8,9,10] Other risk factors for progressive renal failure include hypertension, reduced GFR, and to a lesser extent, hyperlipidemia.[11,12,13]

Clinical and nonclinical evidence suggests a pivotal role for the mucosal immune system in the pathogenesis of IgAN.[14,15,16,17] In IgAN patients, mucosal B-cells located in Peyer's patches are primed to produce aberrantly glycosylated, galactose-deficient polymeric immunoglobulin A1 (Gd-IgA1), which in circulation can form large immune complexes with anti-glycan immunoglobulin G antibodies.[14,18,19,20] These complexes bind to glomerular mesangial cells and stimulate cell proliferation, release of inflammatory mediators that promote proteinuria, and fibrotic remodeling, ultimately leading to loss of renal function.[14,18] This pathogenesis suggests that local immunosuppression of mucosal B-cell activation and proliferation in Peyer's patches, which reside in high density in the distal ileum, could attenuate Gd-IgA1 production and leakage to the systemic circulation, thereby reducing subsequent pathophysiological changes in the kidneys.

In March 2020, the Coronavirus Disease 2019 (Covid-19), caused by infection with the newly discovered coronavirus, was characterized as a pandemic by the World Health Organization. The Covid-19 pandemic impacted clinical studies worldwide due to quarantines, site closures, travel limitations, diversion of resources, and/or general interruptions in study-related procedures. Due to the Covid-19 pandemic, contingency procedures were implemented during this study in the US and Europe to manage possible disruptions due to the Covid-19-risk-of-infection-associated control measures. The contingency procedures will be applicable only for patients impacted by the Covid-19 control measures and will no longer be necessary once the Covid-19 pandemic resolves. Contingency procedures described herein are to prevent treatment disruption for patients who are not able to visit the sites for the scheduled end of treatment Visit 11 when the study primary endpoint is to be evaluated and, therefore, maintain the study integrity. It is also to ensure the study drug tapering bottle is dispensed in a timely manner, which otherwise may raise an important safety concern.

1.1 Rationale

There is currently no optimal management strategy for IgAN. Treatment recommendations have been provided in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[21] Rigorous blood pressure control with angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II type I receptor blockers (ARBs) to achieve blood pressure targets of <130/80 mmHg is the cornerstone of therapy. For patients with proteinuria despite rigorous blood pressure control by renin-angiotensin system (RAS) inhibition, immunosuppressive agents such as corticosteroids or cyclophosphamide may be added. Corticosteroids may lower the risk of kidney disease progression and the need for dialysis and transplantation, but the use is limited by well-known adverse effects.[4]

Budesonide is a glucocorticoid (GCS) with potent GCS and weak mineralocorticoid activities. Immunosuppressive and anti-inflammatory properties have led to the approval of budesonide formulations for use in respiratory indications since 1981 and for inflammatory bowel diseases including Crohn's disease and ulcerative colitis.[22,23] Budesonide has a high first-pass metabolism with formation of metabolites with very low GCS activity, reducing the degree of systemic effects.

Nefecon is an oral, modified-release capsule formulation of budesonide that is designed to deliver its active ingredient to the ileum where the target immune tissues, Peyer's patches, reside in high density and for a sufficient length of time to provide the local therapeutic effect. By targeting local administration of budesonide to this area, Nefecon treatment may suppress local B-cell activation and proliferation, and the subsequent production of Gd-IgA1 and leakage to the systemic circulation, thereby decreasing glomerular mesangial deposition and consequential nephritis and loss of renal function. Nefecon is under investigation for the treatment of patients with primary IgAN at risk of developing ESRD. From the results in Phase 1 and 2 studies in healthy volunteers and in patients with primary IgAN, Nefecon is indicated to be a safe and well-tolerated steroid formulation for adjunctive therapy to ACEIs and/or ARB treatment in IgAN patients at risk of progressing to ESRD.

Further details regarding the nonclinical studies of Nefecon and the clinical development program can be found in the Investigator's Brochure.[24]

The current study is a Phase 3 study to evaluate the efficacy, safety, and tolerability of Nefecon 16 mg per day in the treatment of patients with primary IgAN at risk of progressing to ESRD, despite maximum tolerated treatment with RAS blockade using ACEIs or ARBs.

1.2 Benefit/Risk

The active ingredient in Nefecon is budesonide, a potent steroid with a high first pass liver metabolism, which makes it well suited for local treatment, where feasible. The advantage of local application of budesonide has been demonstrated in several marketed products, such as for the treatment of asthma, where the inhaled budesonide products can provide a high concentration of steroid to the airway tissue with only limited systemic exposure due to the low bioavailability. In this way, high exposure of the steroid can be achieved to the target tissue with only limited systemic exposure and risk for steroid-related adverse effects.

Budesonide is a well-characterized glucocorticosteroid that, apart from treatment of asthma, also has been developed for local treatment of inflammatory conditions such as Crohn's disease and ulcerative colitis. These products have been on the market for up to 25 years. Budesonide has been studied extensively in nonclinical and clinical development programs that have supported the

approval of several medicinal products (e.g., Pulmicort Respules®, Pulmicort Flexhaler®, Entocort®, Uceris®).[22,23,25,26] A vast amount of safety information from previous human experience with budesonide, both from inhaled and oral administered products is available.

Nefecon is a unique optimized formulation which combines a delayed capsule disintegration with a concentrated short, but sustained release of the active substance budesonide, ensuring delivery of budesonide to the ileum, and a release profile providing exposure through the passage of the distal part of the small bowel where the Payer's patches are located.

Thereby a high local concentration of budesonide can be delivered to the mucosa in a restricted part of the gut. When the budesonide is absorbed it will undergo a high first pass metabolism in the liver, resulting in only limited systemic exposure. The Nefecon formulation of budesonide has been tested in patients with IgAN at a daily dose of 8 mg or 16 mg for up to 9 months. Nefecon was found to be safe and well tolerated, and the treatment-provided evidence that local exposure of budesonide to a restricted area of the gut, where the Peyer's patches are located, results in significant reduction in proteinuria and improvement in renal function parameters.

There are currently no treatments approved for patients with IgAN at risk of progressing to ESRD. However, the current standard of care includes rigorous blood pressure control using ACEIs and/or ARB to target <130/80 mmHg to reduce hemodynamic stress and proteinuria.[12,13,27] For those patients with proteinuria despite rigorous blood pressure control by RAS inhibition, a 6-month treatment course of high-dose systemic corticosteroids can be considered; however, there is not consensus for this treatment regimen, mainly due to the increased level of severe side effects.[21,28]

Based on experience from the treatment of patients suffering from IgAN with Nefecon and the already documented safety profile of budesonide, it is judged that the benefit/risk of Nefecon treatment for patients with IgAN at risk of progressing to ESRD, who have persistent proteinuria despite rigorous blood pressure control with ACEI and/or ARB, will be favorable.

2 STUDY OBJECTIVES

The overall aim of the study is to evaluate the efficacy, safety, and tolerability of Nefecon 16 mg per day in the treatment of patients with primary IgAN at risk of progressing to ESRD, despite maximum tolerated treatment with RAS blockade using ACEIs or ARBs.

2.1 Primary Objectives

2.1.1 Part A Primary Objective

The primary objective of Part A is to assess the effect of Nefecon 16 mg treatment on urine protein to creatinine ratio (UPCR) over 9 months compared to placebo.

2.1.2 Part B Primary Objective

The primary objective of Part B is to assess the effect of the Nefecon 16 mg treatment given in Part A on clinical consequences of any proteinuria reduction as measured by estimated glomerular filtration rate (eGFR) recorded over 2 years compared to placebo.

2.2 Secondary Objectives

2.2.1 Part A Secondary Objectives

The secondary objectives of Part A are:

- To assess the effect of Nefecon 16 mg treatment on eGFR at 9 and 12 months compared to placebo, and
- To evaluate additional aspects of renal function, and safety and tolerability of Nefecon 16 mg treatment over 9 months compared to placebo.

2.2.2 Part B Secondary Objectives

The secondary objectives of Part B are to assess the effects of the Nefecon 16 mg treatment given in Part A on different aspects of renal function and safety compared to placebo over 2 years.

3 STUDY DESCRIPTION

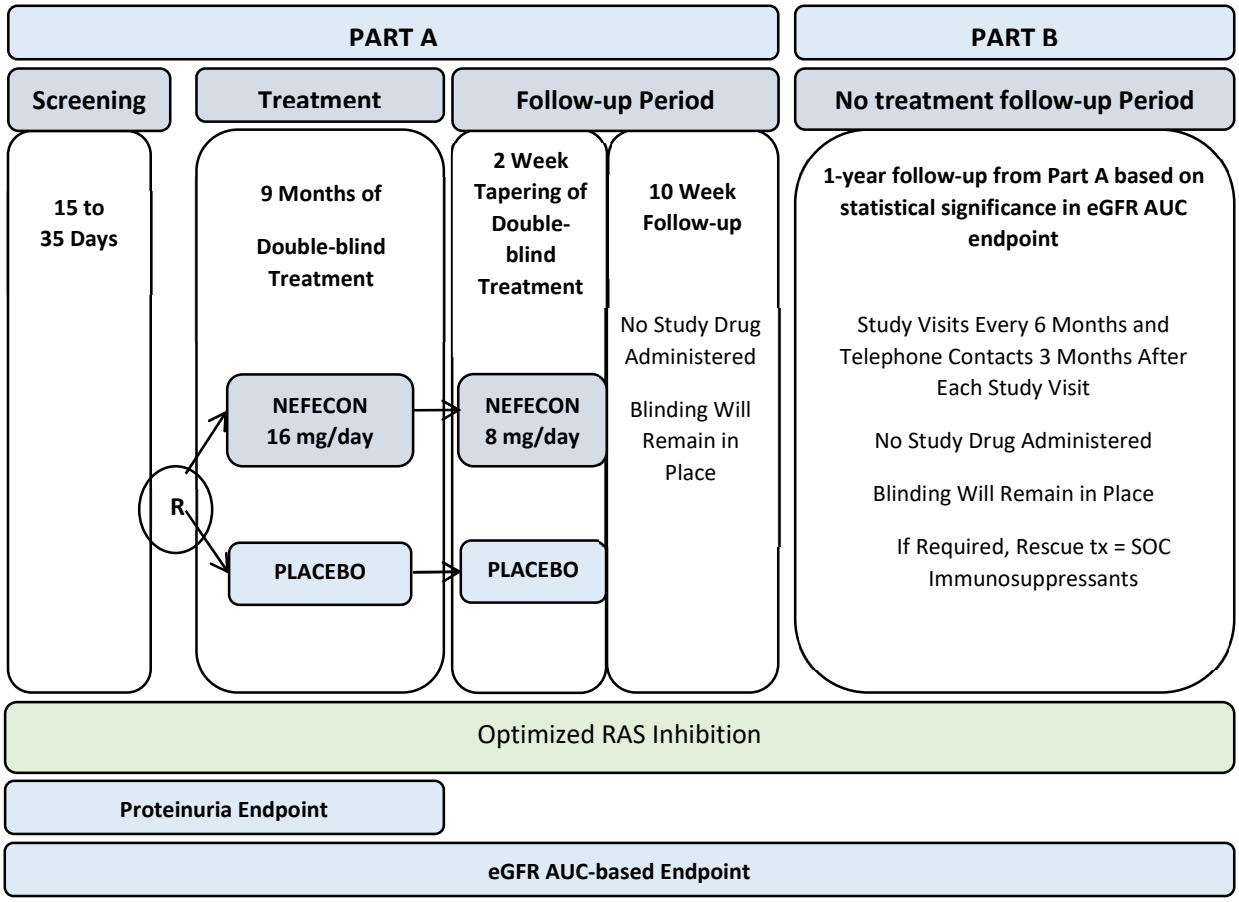
3.1 Summary of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of oral Nefecon compared to matching placebo in patients with primary IgAN on a background of optimized RAS inhibitor therapy. Approximately 360 patients will be randomized at approximately 160 sites in Europe, North America, South America, Asia Pacific, and China. The study will consist of 2 parts, Part A and Part B. Part A will include a Screening Period (up to 35 days) followed by a 9-month blinded Treatment Period, and a 3-month Follow-up Period (including a 2-week Tapering Period). The total duration of Part A is up to 13.5 months.

Part B will consist of a 12-month (+14 to 35 days) observational Follow-up Period after Part A has ended. Each patient randomized will be followed for 25 months after the first dose (or, if the patient randomized does not receive any study drug, 25 months after the patient is randomized). The total duration of the study is up to 26.5 months (including the Screening Period and a final visit for replicate eGFR sampling at 2 years). Part A will be blinded, and the blinding will remain in place throughout Part B. No study drug will be administered during Part B. The primary analysis in Part B will occur 25 months after the 360th/last patient is dosed (or, if the 360th/last patient randomized does not receive any study drug, 25 months after the 360th/last patient is randomized).

Figure 1 provides a summary of the study design.

Figure 1. Summary of Study Design



AUC = area under the curve; eGFR = estimated glomerular filtration rate; R = randomization; RAS = renin-angiotensin system; SOC = standard of care; tx = treatment.

3.1.1 Part A

In order to be eligible for randomization, patients must be on a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed dose or maximum tolerated dose (MTD) according to the 2012 KDIGO guidelines for at least 3 months prior to randomization. A stable dose is defined as doses within 25% of the dose at randomization. Patients should remain on their regimens of RAS inhibitors for the whole duration of the study (Part A and Part B). It is recommended that patients achieve a target systolic blood pressure <125 mmHg and target diastolic blood pressure <75 mmHg according to the 2012 KDIGO guidelines. The use of additional antihypertensive therapy will be permitted as needed. Investigators should ensure that patients are informed at screening of potentially beneficial lifestyle choices including weight normalization, smoking cessation, physical activity, and diet (low salt and low protein). Patients must, after informed consent, have proteinuria based on 2 consecutive measurements (24-hour urine sampling) after informed consent, separated by at least 2 weeks and calculated by the central laboratory (baseline will be the geometric mean of these 2 measurements).

Both samples of the same parameter must show either of the following:

- Proteinuria ≥1 g per day (≥1000 mg per day) in 2 consecutive measurements, or
- UPCR ≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements.

Additionally, all other eligibility criteria must be met in order to be eligible for randomization.

After confirming all eligibility criteria, patients will be randomized in a 1:1 ratio to Nefecon 16 mg or placebo within 35 days of Study Visit 1 (screening). The study will be double-blinded, and randomization will be stratified according to baseline proteinuria, eGFR, and geographic region. Randomized patients will receive either Nefecon 16 mg (four 4 mg budesonide modified-release capsules once per day [QD]) or placebo (4 matching capsules QD) for a 9-month Treatment Period.

Following completion of the Treatment Period, patients will enter the 3-month Part A Follow-up Period. The first 2 weeks of this Follow-up Period will consist of a 2-week Tapering Period to reduce the risk of insufficiency of the adrenal glands. During the 2-week Tapering Period, the study drug dose will be reduced from 4 capsules QD (Nefecon 16 mg or placebo) to 2 capsules QD (Nefecon 8 mg or placebo).

Patients will discontinue study drug at the end of the Tapering Period and then complete the remainder of the Part A Follow-up Period before entering Part B.

Patients who prematurely discontinue study drug during the Treatment Period should complete the 2-week Tapering Period, if feasible, to prevent insufficiency of the adrenal glands. All patients who prematurely discontinue study drug should have eGFR, proteinuria, and creatinine measured at each scheduled visit; it is of particular importance for the 9- and 12-month study visits (Study Visits 11 and 13). All patients who prematurely discontinue study drug should also subsequently enter Part B of the study and continue to have eGFR, proteinuria, and creatinine measured unless they have withdrawn their consent to any kind of follow-up. In the case of patients who are randomized but do not receive any study drug, they should have eGFR, proteinuria, and creatinine measured at each scheduled visit; it is of particular importance for the 9- and 12-month study visits (Study Visits 11 and 13). They should also subsequently enter Part B of the study and continue to have eGFR, proteinuria, and creatinine measured unless they have withdrawn their consent to any kind of follow-up.

Figure 3 (Appendix C) provides a schematic summary of Part A.

3.1.2 Part B

Part B of the study will consist of a 12-month (+14 to 35 days) observational Follow-up Period; no study drug will be administered during Part B. Each patient randomized will be followed for 25 months after the first dose (or, if the patient randomized does not receive any study drug, 25 months after the patient is randomized). Following completion of Part A, patients will remain on their optimized RAS inhibitor/antihypertensive therapy and continue into Part B of the study. During Part B, the Investigator may consider that rescue medication (steroids and/or immunosuppressive treatment) may be needed. Such treatment can be initiated by the Investigator; however, patients should have a proteinuria level at least above 1 g per 24 hours, as suggested in the 2012 KDIGO guidelines, and the Medical Monitor should be consulted for advice (see Section 5.6.2.2).

During Part B of the study, patients will complete onsite study visits at 18 and 24 months, including a final visit for replicate eGFR sampling at 14 to 35 days after the 24-month visit. Telephone contacts will be performed between the onsite study visits at 15 and 21 months. The measurements of eGFR, proteinuria, and creatinine will continue in Part B. Additional telephone contacts and/or unscheduled study visits can be made as needed.

Part B will continue until 25 months after the 360th/last patient is dosed (or, if the 360th/last patient randomized does not receive any study drug, 25 months after the 360th/last patient is randomized). Patients who receive rescue medication should continue in the study and complete all study procedures as indicated in the Schedule of Procedures table (see Appendix A). Patients will be followed until initiation of dialysis, undergoing renal transplantation, death, or study completion (i.e., maximum of 25.5 months after the first dose [or, if the patient randomized does not receive any study drug, 25.5 months after the patient is randomized]), whichever occurs first.

Figure 4 (Appendix C) provides a schematic summary of Part B.

4 SELECTION AND WITHDRAWAL OF PATIENTS

All inclusion and exclusion criteria must be assessed at screening and must be reassessed before randomization to confirm that the patient is still eligible. The confirmation of patient eligibility at screening and prior to randomization will be documented in the source documents and the electronic case report forms (eCRFs).

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria at screening to be eligible for admission into the study:

1. Female or male patients ≥18 years of age;
2. Diagnosed IgAN with biopsy verification within the past 10 years;
3. On a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) at the maximum allowed dose or MTD according to the 2012 KDIGO guidelines for the 3 months prior to randomization (see Appendix D). In this instance, a stable dose is defined as doses within 25% of the dose at randomization. Patients on a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) below the maximum allowed dose or MTD according to the 2012 KDIGO guidelines will be permitted into the study if an attempt to reach the maximum allowed dose or MTD has been performed[21] or if such attempt is deemed unsafe for the patient by the Investigator; and

   Note: It is recommended that patients achieve a target systolic blood pressure <125 mmHg and target diastolic blood pressure <75 mmHg according to the 2012 KDIGO guidelines.
4. Willing and able to provide written informed consent at screening.

In addition, patients must meet the following inclusion criteria before randomization into the study:

5. Proteinuria based on 2 consecutive measurements (24-hour urine sampling) after informed consent, separated by at least 2 weeks and calculated by the central laboratory. **Both samples of the same parameter** must show either of the following:
   - Proteinuria ≥1 g per day (≥1000 mg per day) in 2 consecutive measurements, or
   - UPCR ≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements; and
6. eGFR ≥35 mL/min per 1.73 m^2 and ≤90 mL/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, confirmed by the central laboratory at Study Visit 1 **or** Study Visit 3.

4.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria at screening will not be eligible for admission into the study:

1. Systemic diseases that may cause mesangial IgA deposition including, but not limited to, Henoch Schönlein purpura, systemic lupus erythematosus, dermatitis herpetiformis, and ankylosing spondylitis;
2. Patients who have undergone a kidney transplant;

3. Patients with presence of other glomerulopathies (e.g., C3 glomerulopathy and/or diabetes nephropathy) and with nephrotic syndrome (i.e., proteinuria >3.5 g per day and with serum albumin <3.0 g/dL, with or without edema);
4. Patients with acute, chronic, or latent infectious disease including hepatitis, tuberculosis (TB), human immunodeficiency virus (HIV), and chronic urinary tract infections;
5. Patients with liver cirrhosis, as assessed by the Investigator;
6. Patients with a diagnosis of type 1 or type 2 diabetes mellitus which is poorly controlled (defined as hemoglobin A1c [HbA1c] >8% [64 mmol/mol]);
7. Patients with history of unstable angina, class III or IV congestive heart failure, and/or clinically significant arrhythmia, as judged by the Investigator;
8. Patients with unacceptable blood pressure control defined as a blood pressure consistently above national guidelines for proteinuric renal disease, as assessed by the Investigator. Patients with ≥140 mmHg systolic blood pressure or ≥90 mmHg diastolic blood pressure are not eligible. At least one blood pressure measurement at either Study Visit 1 or Study Visit 3 should be within these limits (based on up to 3 measurements, measured 1 minute apart, after resting in the supine position for at least 5 minutes);
9. Patients with diagnosed malignancy within the past 5 years, except for treated basal cell carcinoma of the skin, curatively resected squamous cell carcinoma of the skin, colon polyps, or cervical carcinoma in situ;
10. Patients with known osteoporosis in medium- or high-risk category according to the 2010 American College of Rheumatology recommendations (see Appendix E). For patients in China, the medium- or high-risk category is defined according to the Osteoporosis Self-Assessment Tool for Asians (OSTA) index (see Appendix E);
11. Patients with known glaucoma, known cataract(s), and/or history of cataract surgery, unless the surgery was performed on both eyes;
12. Gastrointestinal disorders (e.g., peptic ulcer disease, inflammatory bowel disease, and chronic diarrhea) that may interfere with the effects or release of the study drug;
13. Patients with hypersensitivity to budesonide or any component of the study drug formulation;
14. Patients with previous severe adverse reactions to steroids, at the discretion of the Investigator, including psychotic symptoms;
15. Patients who have been treated with systemic immunosuppressive medications, other than GCSs, within the 12 months before randomization. See Appendix F for more information on immunosuppressive medications;
16. Patients who have been treated with any systemic GCSs within the 3 months before randomization;
17. Patients who have been treated with any systemic GCSs within the 12 months before randomization except for a maximum of 3 periods of 2 weeks with the equivalent of 0.5 mg/kg/day prednisolone or less for non-IgAN indications;
18. Patients taking potent inhibitors of cytochrome P450 3A4 (CYP3A4);

19. Current or prior (within the past 2 years) alcohol or drug abuse;
20. Intake of an investigational drug within 30 days and at least 5 half-lives before randomization;
21. Patients unwilling or unable to meet the requirements of the protocol;
22. Other medical or social reasons for exclusion at the discretion of the Investigator;
23. Life expectancy <5 years;
24. Females who are pregnant, breastfeeding, or unwilling to use highly-effective contraception during the Treatment Period and the 3-month Follow-up Period in Part A of the study (contraception only required for women of childbearing potential [WOCBP]);
    - Highly-effective methods of contraception are defined as those that achieve a low failure rate (<1% per year) when used consistently and correctly. Such methods include the use of combined (estrogen and progesterone) hormonal contraceptives (oral, intravaginal, or transdermal), progesterone-only hormonal contraceptives (oral, injectable, or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence;
    - WOCBP are defined as women who are not surgically or chemically sterilized, including hysterectomy or bilateral oophorectomy (tubal ligation is not acceptable), and who are between menarche and 1 year post-menopause; and
    - Postmenopausal is defined as amenorrhoeic for at least 1 year AND, if aged under 60 years have a serum follicle-stimulating hormone (FSH) level of at least 30 IU/L. Women who are taking hormone replacement therapy (HRT) do not have to have FSH assessments, but the amenorrhea (before starting HRT) must have been naturally (spontaneously) occurring and have been accompanied by an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms); or
25. Staff involved in the conduct of the study.

4.3 Withdrawal Criteria

A distinction must be made between patients who prematurely discontinue study drug treatment and those who withdraw consent to any follow-up in the study. If a patient is withdrawn from study drug treatment, they are still to continue their participation in the study. The reason for premature discontinuation of study drug or patient withdrawal for any follow-up in the study must be documented in the eCRF.

See Section 6.7 for additional information on the Early Termination Visit, End of Study Visit, and withdrawal procedures.

4.3.1 Withdrawal From the Study

Participation of a patient may be permanently discontinued if the patient requests discontinuation and withdraws consent from the study for any follow-up.

If a patient withdraws prematurely from the study due to the below criteria or any other reason, study staff should make every effort to complete an Early Termination Visit (see Section 6.7) if the patient discontinues prior to completion of Study Visit 11, or an End of Study Visit (see

Section 6.7) if the patient discontinues after completion of Study Visit 11 but prior to completion of Part B.

Withdrawn patients will not be replaced.

4.3.2 Premature Discontinuation of Study Drug

Patients who prematurely discontinue study drug treatment should complete the remaining study visits (especially those required for key efficacy assessments, i.e., 9 and 12 months and 2 years [Study Visits 11, 13, and 17a/b]) despite discontinuation of study drug and should have the daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg or placebo) for 2 weeks, if feasible, to prevent insufficiency of the adrenal glands (see Section 5.5.3).

The following do not fulfil the criteria for withdrawal from the study, but do require discontinuation of study drug:

- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any serious adverse event (SAE), clinically significant adverse event (AE), severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Pregnancy;
- Requirement of prohibited concomitant medication; or
- Patient failure to comply with protocol requirements or study-related procedures.

If one of the above criteria are met, every effort should be made to keep the patient in the study and continue follow-up after study drug discontinuation.

If a patient requires treatment with other interventional therapies this does not require early withdrawal from the study unless the patient withdraws consent to any follow-up; however, this will require discontinuation from study drug treatment with continued patient follow-up (i.e., continuation in the study).

4.3.3 Lost to Follow-Up

The Investigator will make reasonable effort to contact patients who fail to return for scheduled study visits. These actions might include, but are not limited to, the following:

- Contact all telephone numbers for the patient and his/her listed contacts (to be collected in the source documents at the patient's entry into the study), as applicable. This includes making phone calls after normal business hours or on holidays or weekends;
- Contact the patient's primary care physician, referring specialist, pharmacist, or other healthcare professional, as applicable;
- Send e-mails, text messages, and postal mail with certified letters to all of the patient's addresses and contacts, as applicable, and document all attempted contacts;
- Review available medical records/notes for details of hospitalizations, clinic visits, or other procedures that may indicate the status of the patient, as applicable;

- Utilize the internet to search for additional contact information, as applicable; and
- Check local, regional, and national public records to locate the patient or search for mortality status as allowed by law, as applicable.

Once all of these actions have been exhausted and documented, then Calliditas Therapeutics AB (hereinafter Calliditas) or their designee should be contacted for additional guidance.

4.4 Patient Re-Screening Procedures

Patients who do not meet all of the eligibility requirements defined in Sections 4.1 and 4.2 may be re-screened for the study. If the patient will be re-screened more than once, this must be discussed and agreed upon with the Medical Monitor. All re-screened patients must be re-consented and sign a new Informed Consent Form (ICF) prior to completion of any re-screening study procedures. Re-screened patients will be assigned a new patient number at the time of re-screening and all screening assessments must be repeated except hepatitis B and C, HIV, and TB screenings if done as part of the study within the last 12 months. The re-screened patient's new eCRF casebook will contain a reference to the patient's previous identification number(s).

If a re-screened patient agrees to participate in the exploratory kidney biopsy and/or biomarker analyses and signed the specific ICF for the previous screening, then this patient must be re-consented and the biomarker samples must be repeated (except for the already existing kidney biopsy samples).

5 STUDY TREATMENTS

5.1 Treatment Groups

During Part A, patients will be randomized to receive either Nefecon 16 mg (four 4 mg budesonide modified-release capsules QD) or placebo (4 matching capsules QD) orally for 9 months (Treatment Period). After completing 9 months (or up to 10 months, when applicable, due to the Covid-19 pandemic) of study drug treatment, the daily dose of study drug will be reduced from 4 capsules QD (Nefecon 16 mg or placebo) to 2 capsules QD (Nefecon 8 mg or placebo) for 2 weeks to prevent insufficiency of the adrenal glands (Tapering Period).

Part B of the study will consist of a 12-month (+14 to 35 days) observational Follow-up Period; no study drug will be administered during Part B.

5.2 Rationale for Dosing

Budesonide, which is the active drug substance in Nefecon, is a well-documented compound with extensive experience from clinical use in the treatment of asthma and inflammatory bowel disease. Nefecon is a modified-release oral formulation, designed specifically to release budesonide in the ileum where Peyer's patches reside at high density, thus providing a potent immunosuppressive effect to reduce local B-cell activation and proliferation and the subsequent production of Gd-IgA1. Based on safety and efficacy data from the Phase 2b study, where doses of placebo, 8 mg and 16 mg Nefecon doses, given daily for 9 months, were studied, the Nefecon 16 mg dose was selected for Phase 3. Nefecon treatment at doses of up to 16 mg daily for 9 months in IgAN patients at risk of developing ESRD despite optimized RAS blockade, has demonstrated promising efficacy results on proteinuria reduction and eGFR stabilization, with no safety concerns.[24]

5.3 Randomization and Blinding

After confirming all eligibility criteria, patients will be randomized in a 1:1 ratio to Nefecon 16 mg or placebo using an Interactive Response Technology (IRT) system. Randomization will be stratified according to baseline proteinuria, eGFR, and geographic region.

Part A will be blinded, and the blinding will remain in place throughout Part B. The patients, Investigators, and site staff conducting study procedures, evaluating patients, entering study data, and/or evaluating study data will be blinded to treatment assignment. The only exception would be if an emergency situation involving a patient requires unblinding of the treatment assignment.

The Part A analysis is specified in Section 9.2.3. An unblinded team will be assembled, including an unblinded independent biostatistician, a medical monitor, and other individuals from Calliditas or their designee. This unblinded team will be independent from the study team and will not be involved with study conduction other than submission preparation. Calliditas will be unblinded to the results on a group level. In addition, a limited number of named Sponsor personnel will be unblinded on an individual patient level. Further details are provided in the Blinding Plan and Blinding Charter.

A Data and Safety Monitoring Board (DSMB) will be established to review and discuss the available study data as patients are randomized and followed throughout the study. The DSMB will meet periodically throughout the course of the study to review unblinded safety data.

Both Nefecon and placebo will be provided in modified-release capsules. The capsules and their ingredients will be carefully matched in appearance, smell, and taste to ensure maintenance of treatment masking.

5.4 Breaking the Blind

In an emergency, when knowledge of the patient's treatment assignment is essential for the clinical management or welfare of the patient, the Investigator (or his/her designee) can unblind the study treatment. If useful and when times allows, the investigator is recommended to discuss the rationale for breaking the blind with the Medical Monitor, although the decision lies solely with the Investigator.

The Investigator (or his/her designee) must then contact IRT to unblind an individual patient's treatment assignment. If the blind is broken for any reason, the Investigator must record the date and reason for breaking the blind on the appropriate eCRF and source documents, and the patient should remain in the study.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

Nefecon is a modified-release capsule containing 4 mg of the active substance budesonide. The capsule is white to off-white, of size 1, and is coated with an enteric coating layer that delivers the capsule intact until it reaches the distal part of the small intestine. The capsule contains triple coated beads that have a sugar sphere as the core. The inner coating layer contains the active substance, and the outer polymer coating layer is a prolonged-release coating that controls the rate of release of the active substance once the capsule has dissolved. A seal layer is also included between the budesonide and the polymer coating layer.

The placebo formulation consists of the same enteric coated capsule as for the active capsules, but is only filled with sugar spheres, without any coating layers.

Nefecon and placebo capsules will be packaged in high-density polyethylene bottles and should be stored between 15°C to 25°C in their original container with the cap tightly sealed. Nefecon and placebo will be packaged and labeled according to the requirements of local law and legislation, as well as current Good Manufacturing Practices and Good Clinical Practice (GCP) guidelines. Proof labels, detailing actual label text, will be available in the study files.

5.5.2 Study Drug Preparation and Dispensing

According to the IRT system, the Investigator (or his/her designee) will dispense the assigned study drug to the patient. The IRT randomization will trigger the first shipment of study drug to the site for the patient (on-demand shipment). Patients must take the first dose of study drug in the presence of site staff during Study Visit 4.

Following initial shipment, there will be an automatic resupply of study drug to the site for dispensing to the patient at Study Visits 7, 9, and 11 (for the Tapering Period). If the patient will be treated for up to 10 months (due to the Covid-19 pandemic), then the replacement resupply bottle will be provided to the patient for the extended treatment period.

The Investigator (or his/her designee) must record the patient number, the identification number of the study drug dispensed, the date dispensed, and the amount dispensed in the source documents.

The disposition of study drug delivered to an Investigator will be recorded on a per-patient basis. Dispensation logs will be completed for all patients at each site documenting dispensed and returned study drug throughout the course of the study. Patients will be reminded at each scheduled study visit to return all empty bottles and unused study drug. The dispensation logs will be monitored by Medpace on an ongoing basis.

5.5.2.1 Direct to patient shipment

Direct to patient shipments of study drug will originate from the site and are considered as only a Covid-19 pandemic-related measure to ensure uninterrupted patient treatment when no other option is available. Direct to patient shipments must be approved by the Sponsor or representative.

The Investigator or designee will request Sponsor approval of a direct to patient shipment. The Investigator or designee must ensure that informed consent is obtained for direct to patient shipment. In emergency situations, at minimum, this should be obtained verbally with proper documentation in the medical records. At the earliest time point, written confirmation will be required. The Investigator or designee must ensure study drug accountability and reconciliation as well as documentation is maintained in site files.

The Sponsor or representative will assist direct to patient shipments for sites that do not have this process pre-established as part of their internal policy or standard operating procedures.

5.5.3 Study Drug Administration

Nefecon 16 mg (four 4 mg budesonide modified-release capsules QD) or placebo (4 matching capsules QD) will be administered orally for 9 months (or up to 10 months, when applicable, due to the Covid-19 pandemic) during the Treatment Period in Part A.

Patients must take the first dose of study drug (Nefecon 16 mg or placebo) in the presence of site staff during Study Visit 4 within 10 days after their randomization. As a result, the first dose of study drug may be administered at any time of day and without regard to the timing of meals. Patients may self-dose for all other doses of study drug and should take study drug in the morning approximately 1 hour before breakfast.

The daily dose of double-blinded study drug may be reduced from 4 capsules QD (Nefecon 16 mg or placebo) to 2 capsules QD (Nefecon 8 mg or placebo) if clinically relevant AEs develop that the Investigator considers related to the study drug and that mandate dose reduction. The Medical Monitor should preferably be consulted prior to reducing the daily dose of study drug during the first 9 months (or up to 10 months, when applicable, due to the Covid-19 pandemic) of treatment (Treatment Period in Part A). If a dose reduction is made during this time, then the dose should not be increased back to 4 capsules QD (Nefecon 16 mg or placebo).

After completing 9 months (or up to 10 months, when applicable, due to the Covid-19 pandemic) of study drug treatment, the daily dose of study drug will be reduced from 4 capsules QD (Nefecon 16 mg or placebo) to 2 capsules QD (Nefecon 8 mg or placebo) for 2 weeks to prevent insufficiency of the adrenal glands (Tapering Period in Part A). Patients who have their daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg or placebo) due to safety and/or tolerability reasons during the first 9 months (or up to 10 months, when applicable, due to the Covid-19 pandemic) of treatment (Treatment Period in Part A), will remain on this dose of study drug for an additional 2 weeks after completing 9 months (or up to 10 months, when applicable, due to the Covid-19 pandemic) of study drug treatment (during the Tapering Period in Part A). Patients who

prematurely discontinue study drug treatment while taking 4 capsules QD (Nefecon 16 mg or placebo), should have the daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg or placebo) for 2 weeks, if feasible, to prevent insufficiency of the adrenal glands.

5.5.4 Treatment Compliance

Patients will be instructed to return all empty bottles and unused study drug to the site at the next study visit. Accountability of the used and unused study drug will be recorded. Compliance with the study drug regimen will be evaluated by counting unused capsules. During the Treatment Period, if compliance is not between 80% and 120%, inclusive, the patient will be counseled about the importance of compliance with the study drug regimen.

5.5.5 Storage and Accountability

Study drug must be stored in a pharmacy or a locked and secure storage facility, accessible only to those individuals authorized by the Investigator to dispense the drug, between 15°C to 25°C in the original container with the cap tightly sealed. The Investigator or his/her designee will maintain accurate records of all study drug received, dispensed, or returned/disposed, as well as a temperature log to document temperature conditions during storage.

Temperature excursions up to 30°C will be allowed. Details regarding allowed excursions will be available in the pharmacy manual.

Return and destruction of study drug will be described in the pharmacy manual. The Investigator agrees to only distribute study drug to patients participating in the study.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Patients must not receive other investigational drugs during the study.

Systemic immunosuppressive drugs (including GCSs), except when used as rescue medications, are prohibited during the study. However, over the entirety of the study (Parts A and B), patients will be allowed up to 3 courses of treatment with GCSs in any 2-year period for non-IgAN indications, provided no treatment course is greater than 2 weeks and the GCS dose does not exceed the equivalent of 0.5 mg/kg/day prednisolone. Such short-term treatment will not require change or stop of study drug treatment in Part A. For both Part A and Part B, study visits that include collection of 24-hour urine samples for efficacy assessments (see Appendix A) must not be performed within 4 weeks of such short-term GCS treatment. A 24-hour urine collection can be repeated if the Investigator suspects that the sampling is insufficient. Study visits are to be postponed as needed. Herbs for medicinal use, including Chinese herbs and Chinese traditional medicines, with a known effect on the immune system (e.g., *Tripterygium wilfordii*) or with a known effect on decreasing proteinuria and creatinine, are not allowed during the study. Patients should be encouraged to not use herbs for medicinal use, including Chinese herbs and Chinese traditional medicines, during the study; however, if used, they should be recorded as concomitant medications. Topical or inhalation products containing GCS or immunosuppressants are allowed. See Appendix F for additional information on immunosuppressive drugs.

Potent inhibitors of CYP3A4 (e.g., ketoconazole) are prohibited during treatment with study drug in Part A. During this time, patients should also be instructed to avoid grapefruit and grapefruit juice.

All randomized patients will be followed for the entire duration of the study regardless of initiation of other interventional therapies for IgAN.

5.6.2 Restricted Medications and/or Procedures

5.6.2.1 Part A restricted medications and/or procedures

Patients should avoid starting new medications and making changes to existing medications. However, if needed, the introduction of new medications or changes to existing medications are permitted at the discretion of the Investigator.

If a patient requires treatment with other interventional therapies, including immunosuppressants, this does not require early withdrawal from the study unless the patient withdraws consent to any follow-up; however, this will require discontinuation from study drug treatment (see Section 6.7 for study drug withdrawal procedures) with continued patient follow-up (i.e., continuation in the study). See Appendix F for additional information on immunosuppressive drugs.

5.6.2.2 Part B restricted medications and/or procedures

The Investigator may consider that rescue medication (steroids and/or immunosuppressive treatment) may be needed. Such treatment can be initiated by the Investigator; however, patients should have a proteinuria level at least above 1 g per 24 hours, as suggested in the 2012 KDIGO guidelines, in order for rescue medication to be relevant.[21] Although the Investigator is responsible for the decision to implement new treatment, the Medical Monitor should be consulted for advice. If the Investigator determines that rescue medication is necessary, the Investigator can initiate standard of care treatment according to local treatment policies, preferably in accordance with the 2012 KDIGO guidelines.[21] In regions where Nefecon is made commercially available prior to the end of Part B, the Investigator may initiate treatment with Nefecon according to the given label. See Appendix F for additional information on immunosuppressive drugs.

All randomized patients will be followed for the entire duration of the study regardless of initiation of other interventional therapies for IgAN.

5.6.3 Documentation of Prior and Concomitant Medication Use

Medications taken within 3 months prior to Study Visit 1 (screening) and concomitant medications and therapies will be recorded in the eCRFs. All concomitant medications and changes in concomitant medications will be recorded throughout the course of the study in the eCRFs.

Herbs for medicinal use, including Chinese herbs and Chinese traditional medicines, should be recorded as concomitant medications.

Patients are required to be on a stable dose of RAS inhibitor therapies (ACEIs and/or ARBs) at the maximum allowed dose or MTD according to the 2012 KDIGO guidelines for the 3 months prior to randomization.[21] Therefore, all RAS inhibitor therapies (ACEIs and/or ARBs) taken within the 3 months prior to Study Visit 1 must be recorded. If the patient is on a stable dose of RAS inhibitor therapy that is below the maximum allowed dose or MTD of RAS inhibitor therapy, then the site

must have documentation that an attempt to reach the maximum allowed dose or MTD has been performed or if such attempt is deemed unsafe for the patient by the Investigator.

5.6.4 Dietary and Lifestyle Recommendations

The following lifestyle choices should be recommended to the patient at the Study Visit 1 (screening):

- Weight normalization,
- Smoking cessation,
- Physical activity, and
- Diet (low salt and low protein).

Patients should be encouraged to maintain stable lifestyle choices while participating in the study.

6 STUDY PROCEDURES

Study visit schedules in tabular format are provided in Table 3 and Table 4 for Part A and Part B, respectively, in Appendix A.

A detailed list of procedures to be conducted at each study visit is also described below.

6.1 Informed Consent

Prior to conducting any study-related activities, written informed consent must be signed and dated by the patient. See Section 11.4 for more information.

The ICF will include Part A and Part B of the study. The estimated duration of individual patient participation in Part A will be approximately 1 year and the estimated median duration of individual patient participation in Part B will be approximately 1 year (maximum of 26.5 months of individual patient participation in the study). As part of the informed consent process, only patients who fully understand and agree to full participation and follow-up should be consented to participate. All re-screened patients must be re-consented and sign a new ICF prior to completion of any re-screening study procedures.

At Study Visit 1 (screening), patients will be given the option to participate in the exploratory kidney biopsy and biomarker analyses and to provide a genetic sample for exploratory, limited candidate gene analyses; participation will require signing of separate ICFs, one for the biomarker analyses, one for the kidney biopsy analyses, and one for the genetic analyses. The kidney biopsy samples will be already existing biopsies collected from local hospital pathology units, where allowed and agreed to by the patient, pathology unit, and biobanks, as applicable.

Patients who are not allowed to visit the site for the scheduled Visit 11 (9-month Visit) due to the Covid-19 pandemic, and who will be treated for up to 10 months, will be asked to give consent by phone, which will be documented in their medical records. Patients will sign the Covid-19 pandemic-related ICF addendum when they are able to visit the site.

6.2 Part A – Screening Period (Study Visits 1 to 3)

Patients will undergo a Screening Period lasting up to 35 days (prior to randomization). Study Visit 3 must occur at least 2 weeks after Study Visit 2 in order to collect 2 proteinuria measurements separated by at least 2 weeks to determine eligibility.

6.2.1 Study Visit 1 (Within 35 Days Prior to Randomization, Inclusive)

Written informed consent is to be obtained prior to screening procedures. If informed consent has been obtained, SAEs have been assessed, and the patient has been supplied with container(s) for the next 24-hour urine collection, the remaining Study Visit 1 procedures may, at the discretion of the Investigator, be performed at Study Visit 2 (indicated with *).

The following procedures will be performed at Study Visit 1:

- Record demographic information and medical/surgical history*;
- Record prior and concomitant medications and procedures (including all medications taken within the past 3 months)*;

- Confirm that the kidney biopsy report(s) verifies IgAN diagnosis and that the kidney biopsy slide(s), or equivalent, can be obtained for central reading*;
- Conduct eligibility assessment based on inclusion and exclusion criteria*;
- Obtain vital sign measurements (systolic and diastolic blood pressure and heart rate [up to 3 measurements, measured 1 minute apart, after resting in the supine position for at least 5 minutes])*;
- Obtain height and body weight (see Section 8.11)*;
- Perform a complete physical examination (see Section 8.10)*;
- Collect blood samples for the following assessments*:
  - Hematology (including HbA1c) and serum chemistry (including eGFR [CKD-EPI]);
  - FSH (postmenopausal women only); and
  - Hepatitis B and C, HIV, and TB screening;
- Collect fresh urine sample for the following assessments*:
  - Urinalysis; and
  - Urine drug and alcohol screen;
- Provide the following dietary and lifestyle recommendations: weight normalization, smoking cessation, physical activity, and diet (low salt and low protein). Patients should be encouraged to maintain stable lifestyle choices while participating in the study*;
- Supply the patient with the container(s) for the next 24-hour urine collection; and
- Assess SAEs.

* = may be performed at Study Visit 2.

6.2.2 Study Visit 2

The Study Visit 1 procedures indicated with * may be performed at Study Visit 2.

The following procedures will be performed at Study Visit 2:

- Obtain the 24-hour urine sample (sample collected by the patient during the 24-hour period prior to the scheduled study visit); and
- Supply the patient with the container(s) for the next 24-hour urine collection (if not supplied at Study Visit 1).

6.2.3 Study Visit 3 (At Least 2 Weeks After Study Visit 2)

Study Visit 3 must occur at least 2 weeks after Study Visit 2 in order to collect 2 proteinuria measurements separated by at least 2 weeks to determine eligibility.

Patients will be required to fast for at least 10 hours prior to Study Visit 3.

The following procedures will be performed at Study Visit 3:

- Update medical/surgical history;

- Assess concomitant medications and procedures;
- Conduct eligibility reassessment based on inclusion and exclusion criteria. For patients with proteinuria in the nephrotic range, it is recommended to discuss the case with the Medical Monitor prior to inclusion in the study;
- Obtain vital sign measurements (systolic and diastolic blood pressure and heart rate [up to 3 measurements, measured 1 minute apart, after resting in the supine position for at least 5 minutes]);
- Collect blood samples for the following assessments:
  - Hematology (including HbA1c), serum chemistry (including eGFR [CKD-EPI] and fasting blood glucose), and fasting lipid panel;
  - Serum pregnancy test (WOCBP only); and
  - Exploratory biomarker analyses (optional);
- Collect fresh urine sample for the following:
  - Urinalysis; and
  - Exploratory biomarker analyses (optional);
- Complete the Short Form 36 (SF-36) quality of life assessment;
- Obtain the 24-hour urine sample (sample collected by the patient during the 24-hour period prior to the scheduled study visit); and
- Assess SAEs.

6.3 Randomization (Within 35 Days After Study Visit 1, Inclusive)

After confirming all eligibility criteria (laboratory values from Study Visits 1, 2, 3, etc.) (eGFR values from Study Visits 1 or 3 must be within the limits defined by the inclusion criteria for the patient to be eligible [see Section 4.1]), randomization will be performed through IRT, which will trigger the first shipment of study drug to the site for the patient. Following initial shipment, there will be an automatic resupply of study drug to the site for dispensing to the patient at Study Visits 7, 9, and 11 (for the Tapering Period). Patients will be randomized in a 1:1 ratio to Nefecon 16 mg or placebo.

Patients must take the first dose of study drug in the presence of site staff during Study Visit 4.

6.4 Part A – Treatment Period (Study Visits 4 to 11 – Study Day 1 to Study Month 9 [or Month 10, When Applicable, due to the Covid-19 Pandemic])

6.4.1 Study Visit 4 (Study Day 1)

Study Visit 4 should occur within 10 days after randomization.

The following procedures will be performed at Study Visit 4:

- Update medical/surgical history;
- Assess concomitant medications and procedures;

- Obtain vital sign measurements (systolic and diastolic blood pressure and heart rate [measured after resting in the supine position for at least 5 minutes]);
- Obtain body weight;
- Perform a pregnancy test via a local urine assessment (WOCBP only);
- Supply the patient with the container for the next 24-hour urine collection;
- Dispense study drug and instruct patient on study drug administration;
- Administer the first dose of study drug;
- Assess AEs (occurring after administration of the first dose of study drug), including adverse events of special interest (AESIs) and SAEs; and
- Assess the occurrence of one of the following study endpoints:
  - Initiation of maintenance dialysis for at least 1 month;
  - Kidney transplantation; or
  - Any death.

6.4.2 Telephone Study Visits 5 (Study Week 3 [±7 Days]), 6 (Study Week 6 [±7 Days]), 8 (Study Month 4.5 [±7 Days]), and 10 (Study Month 7.5 [±7 Days])

The following procedures will be performed at Study Visits 5, 6, 8, and 10, which will be conducted with the patient by telephone:

- Assess AEs, including AESIs and SAEs; concomitant medications and procedures; and treatment compliance; and
- Assess the occurrence of one of the following study endpoints:
  - Initiation of maintenance dialysis for at least 1 month;
  - Kidney transplantation; or
  - Any death.

6.4.3 Study Visits 7 (Study Month 3 [±7 Days]) and 9 (Study Month 6 [±7 Days])

The following procedures will be performed at Study Visits 7 and 9:

- Assess AEs, including AESIs and SAEs, and concomitant medications and procedures;
- Obtain vital sign measurements (systolic and diastolic blood pressure and heart rate [measured after resting in the supine position for at least 5 minutes]);
- Obtain body weight;
- Collect blood samples for the following assessments:
  - Hematology (including HbA1c) and serum chemistry (including eGFR [CKD-EPI]);
  - Exploratory biomarker analyses (optional); and
  - Genetic sample (Study Visit 7 only) (optional);

- Collect fresh urine sample for the following assessments:
  - Urinalysis;
  - Exploratory biomarker analyses (optional); and
  - Pregnancy test via a local urine assessment (WOCBP only);
- Obtain the 24-hour urine sample (sample collected by the patient during the 24-hour period prior to the scheduled study visit);
- Supply the patient with the container for the next 24-hour urine collection;
- Collect study drug from previous visit, assess for treatment compliance, and perform drug accountability;
- Dispense study drug and instruct patient on study drug administration; and
- Assess the occurrence of one of the following study endpoints:
  - Initiation of maintenance dialysis for at least 1 month;
  - Kidney transplantation; or
  - Any death.

6.4.4 Study Visit 11 (Study Month 9 [or Month 10, When Applicable, due to the Covid-19 Pandemic] [-7 to +28 Days])/Early Termination Visit

The following procedures will be performed at Study Visit 11/Early Termination Visit:

- Assess AEs, including AESIs and SAEs, and concomitant medications and procedures;
- Obtain vital sign measurements (systolic and diastolic blood pressure and heart rate [measured after resting in the supine position for at least 5 minutes]);
- Obtain body weight;
- Perform a complete physical examination;
- Collect blood samples for the following assessments:
  - Hematology (including HbA1c) and serum chemistry (including eGFR [CKD-EPI]); and
  - Exploratory biomarker analyses (optional);
- Collect fresh urine sample for the following assessments:
  - Urinalysis;
  - Exploratory biomarker analyses (optional); and
  - Pregnancy test via a local urine assessment (WOCBP only);
- Complete the SF-36 quality of life assessment;
- Obtain the 24-hour urine sample (sample collected by the patient during the 24-hour period prior to the scheduled study visit);
- Supply the patient with the container for the next 24-hour urine collection;

- Collect study drug from previous visit, assess for treatment compliance, and perform drug accountability;
- Dispense study drug and instruct patient on study drug administration. Study drug dispensed at Study Visit 11 will be for the Tapering Period; and
- Assess the occurrence of one of the following study endpoints:
  - Initiation of maintenance dialysis for at least 1 month;
  - Kidney transplantation; or
  - Any death.

6.5 Part A Follow-up Period (Study Visits 12 and 13 – Study Months 9 to 12)

Following completion of the Treatment Period, patients will enter the 3-month Part A Follow-up Period. The first 2 weeks of this Follow-up Period will consist of a 2-week Tapering Period to reduce the risk of insufficiency of the adrenal glands. Study drug will be dispensed for the Tapering Period at Study Visit 11 and patients will return unused study drug at the next onsite study visit (Study Visit 13) (see Sections 6.4.4 and 6.5.2).

6.5.1 Telephone Study Visit 12 (Study Month 10.5 [±7 Days])

The following procedures will be performed at Study Visit 12, which will be conducted with the patient by telephone:

- Assess AEs, including AESIs and SAEs; concomitant medications and procedures; and treatment compliance; and
- Assess the occurrence of one of the following study endpoints:
  - Initiation of maintenance dialysis for at least 1 month;
  - Kidney transplantation; or
  - Any death.

6.5.2 Study Visit 13 (Study Month 12 [±7 Days])

The following procedures will be performed at Study Visit 13:

- Assess AEs, including AESIs and SAEs, and concomitant medications and procedures;
- Assess the occurrence of one of the following study endpoints:
  - Initiation of maintenance dialysis for at least 1 month;
  - Kidney transplantation; or
  - Any death;
- Obtain vital sign measurements (systolic and diastolic blood pressure and heart rate [measured after resting in the supine position for at least 5 minutes]);
- Obtain body weight;
- Perform a complete physical examination;

- Collect blood samples for the following assessments:
  - Hematology (including HbA1c) and serum chemistry (including eGFR [CKD-EPI]); and
  - Exploratory biomarker analyses (optional);
- Collect fresh urine sample for the following assessments:
  - Urinalysis;
  - Exploratory biomarker analyses (optional); and
  - Pregnancy test via a local urine assessment (WOCBP only);
- Obtain the 24-hour urine sample (sample collected by the patient during the 24-hour period prior to the scheduled study visit);
- Supply the patient with the container for the next 24-hour urine collection; and
- Collect study drug from previous visit, assess for treatment compliance, and perform drug accountability.

6.6 Part B – Follow-up Period (Study Visits 14 to 17b – Study Years 1 and 2)

Part B will consist of a 12-month (+14 to 35 days) observational Follow-up Period after Part A has ended. Each patient randomized will be followed for 25 months after the first dose (or, if the patient randomized does not receive any study drug, 25 months after the patient is randomized) or until initiation of dialysis, undergoing renal transplantation, or death, whichever comes first.

6.6.1 Telephone Study Visits 14 (Study Year 1 and 3 Months [±7 Days]) and 16 (Study Year 1 and 9 Months [±7 Days])

The following procedures will be performed at Study Visits 14 and 16, which will be conducted with the patient by telephone and will occur between onsite study visits:

- Assess AEs, including AESIs and SAEs;
- Assess concomitant medications and procedures; and
- Assess the occurrence of one of the following study endpoints:
  - Initiation of maintenance dialysis for at least 1 month;
  - Kidney transplantation; or
  - Any death.

6.6.2 Study Visits 15 (Study Year 1 and 6 Months [±30 Days]) and 17a (Study Year 2 [±30 Days])

The following procedures will be performed at Study Visits 15 and 17a (End of Study Visit):

- Assess AEs, including AESIs and SAEs;
- Assess concomitant medications and procedures;

- Assess the occurrence of one of the following study endpoints:
  - Initiation of maintenance dialysis for at least 1 month;
  - Kidney transplantation; or
  - Any death;
- Obtain vital sign measurements (systolic and diastolic blood pressure and heart rate [measured after resting in the supine position for at least 5 minutes]);
- Obtain body weight;
- Perform a complete physical examination (Study Visit 17a only);
- Collect blood samples for the following assessments:
  - Hematology (including HbA1c) and serum chemistry (including eGFR [CKD-EPI]); and
  - Exploratory biomarker analyses (optional) (Study Visit 15 only);
- Collect fresh urine sample for the following assessments:
  - Urinalysis; and
  - Exploratory biomarker analyses (optional) (Study Visit 15 only);
- Obtain the 24-hour urine sample (sample collected by the patient during the 24-hour period prior to the scheduled study visit);
- Supply the patient with the container for the next 24-hour urine collection (Study Visit 15 only); and
- Complete the SF-36 quality of life assessment (Study Visit 17a only).

6.6.3 Study Visit 17b (14 to 35 Days After Study Visit 17a) (For Replicate eGFR Sample)

The following procedures will be performed at Study Visit 17b (14 to 35 days after Study Visit 17a) (for replicate eGFR sample) (End of Study Visit):

- Assess AEs, including AESIs and SAEs;
- Assess concomitant medications and procedures; and
- Collect blood samples for serum creatinine (eGFR [CKD-EPI]) assessments.

6.7 Early Termination Visit, End of Study Visit, and Withdrawal Procedures

It is of the utmost importance to encourage patients to remain in the study until completion. If a patient requires treatment with other interventional therapies, this does not require early withdrawal from the study unless the patient withdraws consent to any follow-up; however, this will require discontinuation from study drug treatment with continued patient follow-up (i.e., continuation in the study). Patients who prematurely discontinue study drug treatment should complete the remaining study visits (especially those required for key efficacy assessments, i.e., 9 and 12 months and 2 years [Study Visits 11, 13, and 17a/b]) (see Section 4.3.2).

In all cases of impending study drug discontinuation or patient requests for withdrawal from study visits, Investigators should discuss with the patient his/her options for continuing in the study. At

a minimum, Investigators should encourage patients to continue follow-up with Investigators (or his/her designee) in order to collect the patient's eGFR at 2 years (eGFR assessed twice separated by 14 to 35 days) and vital status until study completion. The Investigator should ensure he/she understands the reasons for a patient's desire to prematurely discontinue study drug or withdraw from the study prior to completion and document these reasons in the eCRF.

6.7.1 Early Termination Visit

For patients who are withdrawn from the study prior to completion of Study Visit 11, the Early Termination Visit procedures will be completed, if possible, at the time the decision is made to withdraw the patient. The Early Termination Visit will consist of all of the Study Visit 11 procedures (see Section 6.4.4 and Appendix A); however, study drug will only be dispensed at this visit if tapering is applicable, and if so, the daily dose of study drug will be reduced to 2 capsules QD (Nefecon 8 mg or placebo) for 2 weeks to prevent insufficiency of the adrenal glands (see Section 5.5.3). The patient is to continue in the study (unless the patient has withdrawn consent for any follow-up), and eGFR, proteinuria, and creatinine are to be measured at the 9- and 12-month study visits (Study Visits 11 and 13) and the patient is to continue the follow-up in Part B.

6.7.2 End of Study Visit

The study will continue until 25 months after the 360th/last patient is dosed (or, if the 360th/last patient randomized does not receive any study drug, 25 months after the 360th/last patient is randomized).

For patients who are withdrawn from the study after completion of Study Visit 11 but prior to completion of Part B, the End of Study Visit procedures will be completed, if possible, at the time the decision is made to withdraw the patient. The End of Study Visit will consist of all of the Study Visit 17a and 17b procedures (see Sections 6.6.2 and 6.6.3 and Appendix A).

The patient will complete the End of Study Visit (Study Visits 17a and 17b) per protocol and subsequently end participation in the study if any of the following occur after completion of Study Visit 11 but prior to completion of Part B:

- The patient experiences one of the following study endpoints:
  - Initiation of maintenance dialysis for at least 1 month; or
  - Kidney transplantation;
- Termination of the study by Calliditas or the regulatory authority; or
- The patient withdraws consent or requests discontinuation from the study for any reason.

7 EFFICACY ASSESSMENTS

For a detailed description of the statistical methods including the efficacy analyses, see Section 9.2.

7.1 Part A Analysis

The data cut-off for the Part A analysis will occur once the first 201 patients randomized have had the opportunity to complete their 9-month visit. Therefore, it is expected the data cut-off will occur at the latest 9.5 months after the 201st patient randomized is dosed. The details of the Part A analysis are described in Section 9.2.3.

The dataset extracted from the database, and cleaned for analysis, will include all safety data from all patients randomized at the data cut-off date and all efficacy data up to and including the 12-month visit from all patients randomized at the data cut-off date. Therefore, any efficacy data recorded after 12 months will not be extracted from the database.

7.1.1 Part A Analysis Primary Efficacy Endpoint

The primary efficacy endpoint for the Part A analysis is defined as the ratio of UPCR (based on 24-hour urine collections) at 9 months following the first dose of study drug compared to baseline.

7.1.2 Part A Analysis Secondary Efficacy Endpoints

The secondary efficacy endpoints for the Part A analysis are:

- Ratio of eGFR at 9 and 12 months compared to baseline calculated using the CKD-EPI formula, and

  Note: A supportive analysis of 1-year eGFR slope will also be performed.

- Ratio of urine albumin to creatinine ratio (UACR) at 9 months compared to baseline.

Supportive analyses of the above endpoints will also be performed at all time points up to 12 months to describe the time course of effect.

7.2 Part B Analysis

The Part B analysis will be performed when the 360th/last patient randomized has had the opportunity to complete Visit 17b, which can occur up to 35 days after Visit 17a (the 24-month visit).

7.2.1 Part B Analysis Primary Efficacy Endpoint

The primary efficacy endpoint for the Part B analysis is an area under the curve (AUC)-based endpoint of eGFR calculated as a time-weighted average of eGFR recordings observed at each time point over 2 years. The eGFR (CKD-EPI) at 2 years (which must be repeated to provide a second value obtained within 14 to 35 days) will be the geometric mean of the 2 assessments. A supportive analysis of 2-year eGFR slope will also be performed.

7.2.2 Part B Analysis Secondary Efficacy Endpoints

The secondary efficacy endpoints for the Part B analysis are:

- Time to 30% reduction from baseline in eGFR (CKD-EPI) confirmed by a second value, with ≥4 weeks of separation between the 2 sampling time points;
- Time from the first dose of study drug until receiving rescue medication;
- Ratio of UPCR, UACR, and eGFR (CKD-EPI) compared to baseline averaged over time points between 12 and 24 months, inclusive, following the first dose of study drug;
- Proportion of patients without microhematuria in at least 2 of the following time points: 12, 18, and 24 months following the first dose of study drug;
- Proportion of patients receiving rescue treatment; and
- SF-36 quality of life assessment at 9 and 24 months (see Section 7.3).

7.2.3 Part B Analysis Exploratory Efficacy Endpoints

Exploratory analyses may be performed on blood and urine to explore potential changes between the treatment groups that may add to the understanding of the disease mechanism and how the treatment influences these mechanisms (see Section 7.4). In addition, already existing kidney biopsy samples will be collected for exploratory analyses at a central reading unit. Participation and sample shipment for exploratory analyses will be optional.

7.3 Quality of Life Assessment

The SF-36 quality of life assessment will be completed at the time points indicated in Appendix A.

7.4 Exploratory Biomarker Analyses and Genetic Analyses

Where allowed per local regulations and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval and patient consent (and assent, where applicable), optional exploratory blood (48 mL blood sample) and urine (20 mL urine sample) samples will be collected at the time points indicated in Appendix A. An optional exploratory genetic analysis blood (6 mL) sample will be collected at the time points indicated in Appendix A. Where local regulations allow, the samples will be stored at a central facility for up to 10 years and will be analyzed after the study is completed. The samples will be used to identify novel biomarkers predictive of disease progression or a response to Nefecon and to elucidate the biochemical pathways affected by treatment with Nefecon. Exploratory analyses of both blood and urine may include, but will not be limited to, IgA1, IgA2, monomer-polymer ratios, and immune complex levels. Exploratory, limited candidate gene analyses will be performed and may include, but will not be limited to, IgA allotypes, C1GALT1, and TAP1/PSMB genes as polymorphisms that are associated with response or adverse effects. These samples will only be collected and analyzed in countries where this is permitted. Details regarding the collection, processing, storage, and shipping of samples can be found in the laboratory manual. In addition, already existing kidney biopsy samples will be collected for exploratory analyses at a central reading unit. The kidney biopsies will be collected from local hospital pathology units, where allowed and agreed to by the patient, pathology unit, and biobanks, as applicable. All biopsy samples will be returned as required.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. The Investigator will collect AEs with a non-leading question such as "have you experienced any new health problems or worsening of existing conditions" as well as collecting events directly observed or spontaneously volunteered by patients or caregivers. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented by the Investigator (or his/her designee) from administration of the first dose of study drug (Study Visit 4) until 2 years (+14 to 35 days) after the first dose of study drug (Study Visit 17b), inclusive, regardless of whether the patient discontinues the study prematurely. If the patient does not receive study drug at Study Visit 4, AEs should still be monitored and documented from Study Visit 4. Patients should be instructed to report any AE that they experience to the Investigator (or his/her designee).

Serious adverse events will be monitored and reported from signature of informed consent.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure.

Any medical condition already present when the first dose of study drug is administered (Study Visit 4) should not be reported as an AE unless the medical condition or signs or symptoms present at baseline worsens in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g., physical examination) findings that are detected during the study or are present when the first dose of study drug is administered (Study Visit 4) and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Any medical condition or abnormal finding that worsens in severity or seriousness and that fulfils the criteria for an SAE will be reported as such, from signature of informed consent.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable Reference Safety Information (RSI). For Nefecon the RSI is included in the Investigator's Brochure currently in force.[24] The RSI will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of yes or no.

Assessment of Severity:

- Mild – An event that is easily tolerated and generally not interfering with normal daily activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.
- Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality Assessment:

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
    - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drug-
  - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.2 Adverse Events of Special Interest

The following, which are established potentially clinically significant consequences of steroid treatment, will be considered AESIs:

- Severe infection requiring hospitalization,
- New onset of diabetes mellitus,
- Confirmed fracture,
- New osteonecrosis,
- Gastrointestinal bleeding that requires hospitalization,
- Reported occurrence of cataract formation, and
- Reported onset of glaucoma.

If not already determined from the general questions used to capture AE, the patient must be explicitly asked if the following have occurred since the last study visit:

- Have you been hospitalized due to any infection and/or gastrointestinal bleeding?
- Have you had any X-ray confirmed fractures?
- Have you been diagnosed with diabetes mellitus?
- Have you visited an ophthalmologist and been diagnosed with glaucoma or cataract(s)?

Adverse events of special interest may or may not constitute an SAE. However, all types of AESIs must be reported and processed as SAEs, regardless of their formal classification of seriousness, in accordance with the instructions in Section 8.4. The AESIs that do not fall into the category of

SAEs will be recorded from administration of first dose of study drug (Study Visit 4) until 2 years (+14 to 35 days) after the first dose of study drug (Study Visit 17b), inclusive, regardless of whether the patient discontinues the study prematurely. If the patient does not receive study drug at Study Visit 4, AESIs should still be monitored and documented from Study Visit 4.

8.3 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Calliditas, it results in any of the following outcomes:

- Death,
- A life-threatening AE,
    - NOTE: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Calliditas, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations,
    - NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission for more than 24 hours will not be recorded as a SAE under this criterion, nor will elective hospitalization/surgery or hospitalization for treatment of pre-existing (prior to signing of the ICF) conditions that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.4 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs, irrespective of relatedness, occurring from signature of informed consent until 2 years (+14 to 35 days) after the first dose of study drug (Study Visit 17b) must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria).

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an e-mail to Medpace Safety at Medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below). The site should then complete the paper SAE form and send via e-mail or fax to Medpace (e-mail and fax number are listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA/Canada/Australia/Asia Pacific:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

Medpace SAE reporting line – Europe/All other countries:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
e-mail: medpace-safetynotification@medpace.com

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.5 Pregnancy Reporting

If the patient participating in the study becomes pregnant during the study or within 30 days of the last dose of study drug, the Investigator should report the pregnancy to Medpace Clinical Safety via telephone or e-mail within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately discontinue study drug treatment but will not be withdrawn from the study.

The patient should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.6 Expedited Reporting

Calliditas (or their designee) will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening as soon as possible to all regulatory authorities in the concerned countries and Central Ethics Committees (CECs) as applicable in each participating country, and in any case no later than 7 days after knowledge by Calliditas (or their designee) of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to all regulatory authorities in the concerned countries and to the CECs as soon as possible but within a maximum of 15 days of first knowledge by Calliditas.

Calliditas (or their designee) will also inform all Investigators as required.

8.7 Safety Assessments

The safety variables will include the following:

- Treatment-emergent AEs, defined as AEs that occur for the first time after dosing with study drug, or exist before but worsen in severity or relationship to study drug after dosing;
- AESIs (severe infections requiring hospitalization, new onset of diabetes mellitus, confirmed fracture, new osteonecrosis, gastrointestinal bleeding that requires hospitalization, reported occurrence of cataract formation, and reported onset of glaucoma); and
- Vital signs, body weight, clinical laboratory variables, and physical examination findings.

8.8 Clinical Laboratory Evaluations

Clinical safety laboratory assessments will include hematology, serum chemistry, and urinalysis parameters from collection of blood and urine samples as indicated in Appendix A. See Appendix B for a complete list of laboratory analytes.

All laboratory analyses will be performed or managed by a central laboratory. The TB test must be the specific QuantiFERON®-TB Gold test and can be done locally if needed. However, the report must be available to confirm a negative TB result. Details regarding the collection, processing, storage, and shipping of samples can be found in the laboratory manual.

8.9 Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure and heart rate as indicated in Appendix A.

Blood pressure and heart rate will be measured after resting in the supine position for at least 5 minutes. At the applicable study visits in the Screening Period, blood pressure and heart rate will be measured up to 3 times with each measurement separated by 1 minute (the lowest value will be recorded on the eCRF).

8.10 Physical Examinations

A complete physical examination will be performed as indicated in Appendix A and will consist of examination of the head, eyes, ears, nose, throat, lymph nodes, chest, abdomen, and extremities, as well as the respiratory, musculoskeletal, cardiovascular, dermatologic, and nervous systems (including sensory, motor, and deep tendon reflexes).

8.11 Body Weight and Height

Measurement of body weight should be performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty. Height will only be collected at Study Visit 1.

9 STATISTICS

9.1 Analysis Populations

The primary efficacy analyses will be based on the Full Analysis Set (FAS), which will include all randomized patients, regardless of whether the patient received study drug. For Part A, the FAS will include the first 201 patients randomized. The data cut-off for the Part A analysis will occur once the first 201 patients randomized have had the opportunity to complete their 9-month visit. Therefore, it is expected the data cut-off will occur at the latest 9.5 months after the 201st patient randomized is dosed. Two patients are excluded from the Part A FAS due to errors in randomization; this decision was pre-defined in the Statistical Analysis Plan prior to unblinding.

It is a regulatory requirement in China that an appropriate number of patients (approximately 60) are recruited from this region in order to perform a consistency evaluation between China results and global results. If there are less than 60 patients from China when the global target of 360 patients randomized has been reached, recruitment is closed in the global part of the study but continues in China. For Part B, the primary FAS will include all patients randomized at the completion of recruitment to the global part of the study, including any patients already recruited in China, with a data cut-off 25 months after the 360th/last patient is randomized. Any patient recruited in China after recruitment to the global part of the study will not be included in the Part B primary FAS. In addition, the Part A analysis will be repeated using all patients randomized when the Part B analysis is performed.

The Safety Analysis Set will include all patients who receive at least 1 dose of study drug. All patients who have received at least 1 dose of study drug by the time of the data cut-off for Part A will be included in the safety analysis for Part A. Likewise, for Part B, the Safety Analysis Set will include all patients who have received at least 1 dose of study drug by the time recruitment is closed in the global part of the study.

The China Cohort will include all patients randomized from China at any time with the corresponding FAS and Safety Analysis Set defined in the same manner as the global part of the study.

The Per Protocol Set will include all patients in the FAS for whom no major protocol deviations (which may interfere with efficacy evaluation) occurred in Part A and Part B. Full details of inclusions and exclusions from the Per Protocol Set – Part A and Per Protocol Set – Part B will be in the classifications specifications and finalized before unblinding. The Per Protocol Set will be used to assess robustness of the primary analysis results.

9.2 Statistical Methods

Patients will be randomized in a 1:1 ratio to Nefecon 16 mg or placebo. Randomization will be stratified according to baseline proteinuria, eGFR, and geographic region.

A multiplicity strategy will be used to control type I error amongst the primary and key secondary efficacy endpoints across both Part A and Part B. See Section 9.2.1.5 for further details.

Baseline proteinuria, eGFR, UPCR, and UACR will be the geometric mean of the 2 consecutive measurements prior to randomization.

The protocol requires that all randomized patients continue to have assessments performed at each scheduled visit regardless of whether they prematurely discontinue study drug or even if they are

randomized but do not receive any study drug. However, any data recorded after a patient receives rescue medication will be excluded from the primary efficacy analyses in Parts A and B so that the underlying effect of Nefecon can be estimated free from the confounding effects of rescue medication. Rescue is defined as any immunosuppressive medication that would be expected to materially impact efficacy, regardless of whether the medication is used for IgAN. A blinded medical review of concomitant therapy will be performed prior to unblinding to decide and document which patients are to be defined as having rescue and over what time period.

All efficacy assessments, including those from unscheduled visits and regardless of visit label, will be allocated to analysis visits based on Table 1.

Table 1. Time Windows Applied to Efficacy Assessments

Study Period	Scheduled Visit	Time Interval (days after first dose of study drug)
Part A Treatment	Visit 7 (3 months, Day 91)	2 to 137
	Visit 9 (6 months, Day 183)	138 to 228
	Visit 11 (9 months, Day 274)	229 to 319
Part A Follow-up	Visit 13 (12 months, Day 365)	320 to 456
Part B Follow-up	Visit 15 (18 months, Day 548)	457 to 639
	Visit 17 (24 months, Day 730)	640 to 821
If more than one measurement is recorded within a visit window, the geometric mean of all measurements within the window will be used in the analysis.		

9.2.1 Analysis of Efficacy

9.2.1.1 Analysis of Part B primary efficacy endpoint

The primary efficacy endpoint for the Part B analysis is an AUC-based endpoint calculated as a time-weighted average of eGFR (CKD-EPI) measurements recorded over 2 years, where each time point is given a weight in proportion to the time elapsing from the previous recording. Therefore, recordings made at 18 and 24 months receive twice as much weight as those made at 3, 6, 9, and 12 months. The weights will sum to one so that the treatment effect can be interpreted as the average effect of Nefecon over 2 years. Table 2 displays the weight given to each time point.

Table 2. Weight Applied to Each Time Point in the Calculation of the 2-Year eGFR AUC

Time Point	Weight Applied to Each Time Point
3 months	0.125
6 months	0.125
9 months	0.125
12 months	0.125
18 months	0.25
24 months	0.25
AUC = area under the curve; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate (CKD-EPI).	

The eGFR data will be log-transformed prior to analysis. Data included at baseline and 24 months will be the log of the geometric mean of the 2 replicate values recorded at each time point, respectively. Previous eGFR data from Nefecon trials suggest it is possible there will be a small sub-population of patients with extreme outlying data resulting from very rapid progression of disease. Therefore, the primary analysis will be based on a Robust Regression approach.[29] In order to handle missing data, the analysis will be performed over 3 phases: an imputation, analysis, and pooling phase, as described below. Further details are provided in the Statistical Analysis Plan.

Imputation phase

The first step of the imputation phase will create data with a monotone data structure having imputed 20 datasets separately within each treatment arm. For example, in this step, patients with missing data at Month 18 would only have data imputed if they had data recorded at Month 24. The number of burn-in iterations will be set to 200, and observations will be sampled every 100 iterations within the same chain for each imputed dataset. In the second step of the imputation phase, data will be multiply imputed using a regression method sequentially imputing data across successive visits separately by treatment arm from each dataset imputed in the first step.

Analysis phase

In the analysis phase, the AUC will be calculated for each patient within each imputed dataset and analyzed using Robust Regression with independent variables of treatment and log-transformed baseline eGFR. M-estimation will be used with Huber weights and a cut-off value of 2 with the median method used to estimate the scale parameter.

Pooling phase

In the pooling phase, estimated treatment effects and associated standard errors from each imputation will be combined using Rubin's rules to provide an overall treatment effect, associated 95% confidence interval (CI), and 2-sided p-value.

9.2.1.2 Analysis of eGFR slope

A supportive analysis of 2-year eGFR slope will be performed using a random coefficients model.[30] This model is a mixed, repeated measures model which enables the analysis to be performed in a single step, allowing for the eGFR slope to vary between patients. Note, unlike the primary approach, data will not be log-transformed prior to analysis. The actual time measurements taken, in years after randomization, will be included in the model as a continuous variable. Any unscheduled values will be included in the model at the actual time they were recorded.

A sensitivity analysis will be planned in case the normality of the between-patient distribution of slopes is questionable (e.g., if there are outlying data). In this sensitivity analysis, each patient's slope will be estimated from a separate linear regression fitted to each patient, with the resultant slope data compared between arms using Robust Regression.

9.2.1.3 Analysis of time to 30% reduction in eGFR (Part B)

The time to a 30% reduction in eGFR (CKD-EPI) will be measured from the time of the first dose of study drug and will include all data prior to the use of rescue medication even if the clinical event occurs in Part A.

To count as a clinical event and to reduce the presence of false-positive reductions, the 30% reduction should be confirmed at a later time point. When a clinical event is confirmed, the time to the first reduction will be used in the analysis. The first eGFR reduction that is greater than 30% will count as a clinical event in the following situations:

- If a later reduction is observed, but after at most 1 intervening occurrence where the eGFR has not reduced by 30%, and the geometric mean reduction of these 3 values is reduced by greater than 30%;

- The first reduction occurs at 24 months or the visit for the replicate eGFR sample, and there are no later recordings of eGFR; and/or
- The patient receives dialysis, undergoes renal transplantation, or dies after the first reduction, but before a confirmation can be made.

To prevent informative censoring, if a patient dies from a renal-related event, as determined by a blinded medical review, or has dialysis for at least 1 month, kidney transplantation, or kidney failure defined as a sustained eGFR <15 mL/min/1.73 m^2 prior to a 30% reduction, they will be included in the analysis as having had a clinical event occur at that time. Patients will be defined as having a renal-related death if the Investigator provides "Death due to kidney failure" as being the reason for early termination from the study and is confirmed on blinded medical review. Dialysis and kidney transplantation will be identified from the concomitant procedures eCRF. Otherwise, patients will be censored at the time of their last eGFR recording prior to the use of rescue medication.

The time to a 30% reduction in eGFR (CKD-EPI) will be analyzed using an Inverse Probability of Censoring Weights model. This approach estimates the effect of Nefecon in the absence of the use of rescue medication and censors patients who take rescue medication and matches them with those that did not based on their clinical status at the time, such as their change in UPCR or eGFR from baseline and whether they have had an initial 30% reduction from baseline in eGFR, and reweighting based on the outcome of matched patients. Full details are provided in the Statistical Analysis Plan.

9.2.1.4 Analysis of other secondary efficacy endpoints in Part B

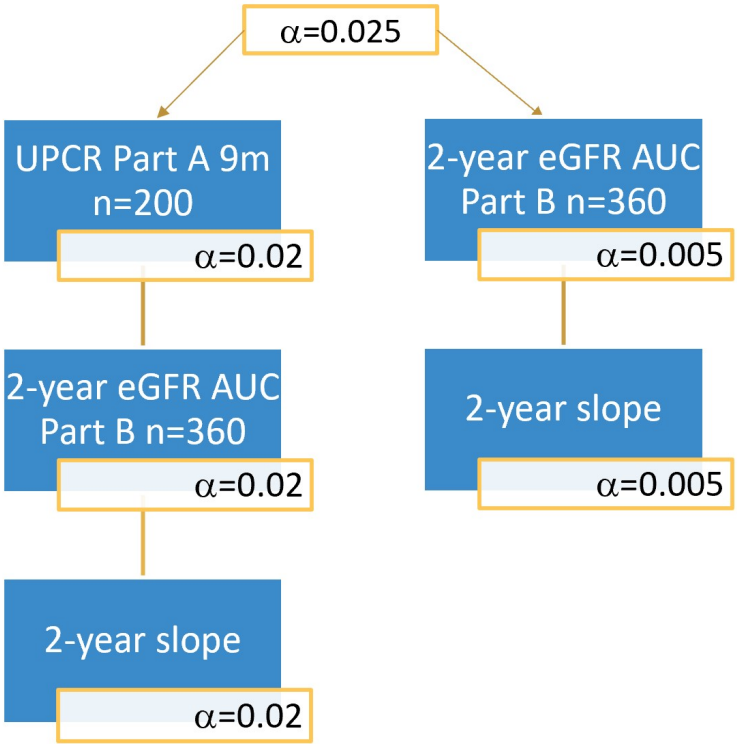
To estimate the average of parameters UPCR and UACR between 12 and 24 months, values will be log-transformed prior to analysis and will be analyzed using a Mixed Model Repeated Measures (MMRM) model with separate visit terms for 3, 6, 9, 12, 18, and 24 months together with terms for treatment-by-visit, baseline, and baseline-by-visit, and back-transformed to estimate the geometric mean of the treatment effects over 12, 18, and 24 months. The corresponding analysis of average eGFR (CKD-EPI) over 12 to 24 months will use the same methodology that is applied to the Part B primary efficacy endpoint, except that the visits at 12, 18, and 24 months will be given equal weight.

Any binary endpoints that compare the proportion of patients with an outcome will be analyzed using a logistic regression model and will include terms for randomized treatment, log-baseline UPCR, log-baseline eGFR, and geographic region. The odds ratio will be estimated together with the associated 95% CI and p-value, with the CI estimated using a profile-likelihood approach and the p-values from a likelihood-ratio test.

9.2.1.5 Hypothesis testing strategy

In order to provide strong control of the type I error rate of 2.5% 1-sided across both Part A and Part B of the study, the endpoints of UPCR at 9 months from Part A and 2-year eGFR AUC from Part B will be tested in an endpoint hierarchy as described in Figure 2. If an endpoint is statistically significant at the specified alpha level, its alpha will be recycled to the next endpoint in the hierarchy.

Figure 2. Summary of the Hypothesis Testing Strategy



Alpha is 1-sided.
2-year slope = 2-year eGFR slope; AUC = area under the curve; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate (CKD-EPI); m = months; UPCR = urine protein to creatinine ratio.

This approach means the primary endpoint in Part A, UPCR at 9 months, will be statistically significant if the 1-sided p-value is ≤0.02, in which case the Part B primary endpoint, 2-year eGFR AUC, will be tested at a 1-sided significance level of 0.025. If the 1-sided p-value for UPCR is >0.02, the Part B primary endpoint will be tested at a 1-sided significance level of 0.005. If the Part B primary endpoint is statistically significant, 2-year eGFR slope will be tested at the same significance level as applied to the Part B primary endpoint.

9.2.1.6 Analysis by subgroup

The primary endpoint will be summarized according to important subgroups. The subgroup analyses performed will include the following:

- Baseline proteinuria,
- Baseline eGFR,
- Dose of RAS inhibitor therapy (ACEIs and/or ARBs) (taking the maximum acceptable dose or MTD versus not taking the maximum acceptable dose or MTD),
- Region,
- Age,
- Gender,

- Ethnicity, and
- Race.

A global interaction test amongst all subgroups will be performed for UPCR at 9 months and 2-year eGFR AUC to assess whether any heterogeneity in the treatment effect between subgroups is consistent with a constant treatment effect across all subgroups. This analysis will be performed by comparing the fit of a model that contains treatment, the main effects for all subgroups, and all treatment-by-subgroup interactions to one without the interaction terms.

9.2.2 Analysis of Safety

For both Part A and Part B, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will include all safety data from patients who have received at least 1 dose of study drug at the time of the analysis. The incidence of treatment-emergent AEs and AESIs, as described in Section 8.2, will be summarized by body system and organ class. In addition, the time to first occurrence of the most common event will be summarized using cumulative incidence plots by each period of the study. Safety data will be summarized or listed separately for the period between screening and the first dose of medication. In addition, the safety data will be summarized for the entire period following the first dose of study drug and separately for periods during and after dosing.

The primary objective of the analyses is to describe the safety and tolerability of Nefecon, for the intended 9-month regimen, while patients are still receiving therapy. The on-treatment period, used to determine whether the patient is still receiving therapy, is defined from the first dose of therapy until 14 days after completion of the Tapering Period. Secondary analyses will be performed to describe the safety recorded during follow-up, after discontinuation of study treatment.

Summary statistics will be presented for changes in vital signs and laboratory tests throughout the study. Physical examinations will be listed.

9.2.3 Part A Analysis

The data cut-off for the Part A analysis will occur once the first 201 patients randomized have had the opportunity to complete their 9-month visit. Therefore, it is expected the data cut-off will occur at the latest 9.5 months after the 201st patient randomized is dosed.

The dataset extracted from the database, and cleaned for analysis, will include all safety data from all patients randomized at the data cut-off date and all efficacy data up to and including the 12-month visit from all patients randomized at the data cut-off date. Therefore, any efficacy data recorded after 12 months will not be extracted from the database.

The primary efficacy endpoint for the Part A analysis, the ratio of UPCR at 9 months to baseline, will be log-transformed prior to analysis, as will data from the other time points used in the analysis model. The treatment effect will be expressed as a percent reduction in UPCR for Nefecon compared to placebo and will be derived from the geometric least squares mean ratios estimated at 9 months for each treatment arm. The primary analysis of the log-transformed baseline ratios in UPCR will be analyzed using an MMRM analysis based on the FAS and incorporating UPCR data from baseline, 3 months, 6 months, 9 months, and 12 months. Baseline UPCR will be included as a covariate and will be calculated as the geometric mean of the 2 pre-randomization UPCR measurements. The model will also include terms for treatment group, visit, baseline by visit, and

visit by treatment group interaction. Patient will be included as a random effect. An unstructured covariance matrix will be used to model the within-patient correlation of data. The Kenward-Roger's degrees-of-freedom adjustment will be used. Restricted maximum likelihood will be used to obtain parameter estimates. The least-squares means will be estimated by visit along with the associated 95% CI and p-values with the primary analysis taken from the estimate at 9 months. Model assumptions of the MMRM will be assessed using residual plots (such as q-q plots, histograms, box plots, and scatter plots).

The following sensitivity analyses will be performed on the primary efficacy endpoint for Part A:

1. Sensitivity to missing data at 9 months: While it is intended that complete data will be recorded at 9 months, if there is a reasonable amount of missing data, the robustness of the primary analysis will be assessed. The objective of the primary analysis is to estimate the net effect of Nefecon despite any early patient withdrawal. If missing data are observed following discontinuation, the MMRM will estimate what would have happened had patients not discontinued and the treatment effect may be biased. To assess the robustness, a multiple imputation approach will be performed where the relationship between 9-month data and discontinuation will be modelled separately within each treatment group, and using that relationship, data missing post-discontinuation will be multiply imputed based on data observed post-discontinuation in other patients. The exact specification of the model used will be defined in the Statistical Analysis Plan. In the unlikely event a patient dies before 9 months, they will have the worst observed outcome across treatment arms imputed;
2. Sensitivity to assumption of normality: If examination of residual plots indicates clear non-normality, then UPCR data at 9 months will additionally be analyzed using a Robust Regression approach after first multiply imputing any missing data in the same manner as described for the analysis of 2-year eGFR AUC (Section 9.2.1.1);
3. Sensitivity to handling of rescue medication: In this analysis, the primary analysis will be repeated, except any data observed after rescue treatment will be included;
4. Tipping point analysis: A 2-dimensional tipping point analysis will be performed, whose purpose is to assess how much worse the outcomes on Nefecon patients, and how much better the outcomes on placebo patients, with missing data would need to be before the statistical significance of the primary endpoint is lost. Further details are provided in the Statistical Analysis Plan; and
5. Supplementary analysis including all patients randomized: When the primary efficacy analysis is performed, there will be additional patients who have been randomized but have yet to be followed for 9 months. A supplementary analysis will be performed where the MMRM is repeated but includes all patients randomized and hence will increase the amount of data included at 3 and 6 months. This analysis would be expected to produce a very similar treatment effect and CI at 9 months, unless the treatment effect at 3 and 6 months amongst patients recruited after the 201st patient is different than those included in the primary analysis.

9.2.4 Data and Safety Monitoring Board

A DSMB will be established to review and discuss the available study data as patients are randomized and followed throughout the study. The DSMB may also act as an expert, independent advisory to study conduct. The DSMB will meet periodically throughout the course of the study to review unblinded safety data. Details of the composition, roles, and responsibilities of the DSMB will be documented in the DSMB Charter.

9.2.5 Sample Size Determination

9.2.5.1 Part A analysis

The Nefecon Phase 2b study (Nef-202) gave an estimated standard deviation of 0.59 for the change in the log of UPCR from baseline after 9 months of treatment. Based on this assumption, 200 patients in Part A will provide >90% power to demonstrate statistical significance at a 1-sided alpha level of 0.025 given a true 25% relative reduction in UPCR with Nefecon treatment compared to placebo.

9.2.5.2 Part B analysis

A 28% reduction in UPCR, relative to placebo, was observed with the 16 mg dose of Nefecon in the Phase 2b study. Based on an analysis of the relationship between treatment effects on proteinuria at 1 year and the 2-year eGFR slope[31] using aggregate data for trials in IgAN presented at the March 2018 NKF/FDA/EMA workshop Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of Chronic Kidney Disease, a 28% reduction in UPCR is predicted to translate into a treatment effect of 1.12 mL/min/1.73 m^2/year on 2-year eGFR slope, and hence, a 2.24 mL/min/1.73 m^2 treatment effect for the difference in mean eGFR at 2 years. If 360 patients are recruited and followed for 2 years, and replicate values of eGFR are recorded both at baseline and at 2 years, Part B will have 90% power to detect a statistically significant difference in eGFR at 2 years, using a 2-sided alpha of 5%, if the true effect of Nefecon is 2.24 mL/min/1.73 m^2. This calculation is based on the following set of assumptions:

- The mean eGFR at 2 years in the placebo group is 60 mL/min/1.73 m^2 so that the treatment effect corresponds to a difference of 0.03665 on the log-scale;
- The between-patient standard deviation of eGFR at baseline and 2 years is 0.32 and 0.35, respectively, on the log-scale as observed at baseline and 1 year in the Phase 2b study;
- The correlation between repeat log-transformed values at baseline and 2 years is 0.946 and 0.939, respectively, and the correlation between baseline and 2-year eGFR values is 0.935. These values were based on data observed in the Phase 2b study;
- Combining the between-patient variability and correlation coefficients leads to an expected standard deviation for a log-transformed analysis of covariance of the mean of replicate eGFR values of 0.093;
- A 1-sided significance level of 2.5%; and
- A worst-case assumption for dropout rate by 2 years of 25%.

The power for the primary efficacy endpoint for Part B, 2-year eGFR AUC, is >90% for the expected mean eGFR profiles for Nefecon and placebo over 2 years. A worst-case analysis of eGFR data from Nef-202 demonstrated a 3.7 mL/min/1.73 m^2 improvement in eGFR at 12 months.

In this case, the power for 2-year eGFR AUC is >99%, assuming efficacy reduces linearly after 12 months to a mean difference of 2.24 mL/min/1.73 m^2 at 2 years. Supportive simulations demonstrated that Part B remains fully powered for 2-year eGFR AUC, using the primary analysis method of Robust Regression with imputation, even if the rate of outlying data more than doubles compared to Nef-202.

A total of 360 randomized patients are planned to be evaluable for the final primary efficacy analysis for the study.

It is estimated that approximately 900 patients will be screened.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Patient numbers will be assigned in IRT at Study Visit 1 and will be automatically downloaded into the EDC system. Data will be recorded at the site in the eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system against source documents. All corrections or changes made to any study data will be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using ClinTrak EDC, which is a validated computer system that conforms to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. Site personnel are expected to enter data into EDC within 5 business days of each study visit, as well as respond to data queries in EDC and enter/update any applicable data within 5 business days of the queries being issued in EDC. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the current and updated versions of the following thesauri will be used:

- The MedDRA for medical history and AEs, and
- The World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The data on the eCRFs must be reviewed and the eCRFs must be electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Calliditas correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a

clinical study necessary for the evaluation and reconstruction of the clinical study. Additionally, the definition of source data will be specified in the Site Source Documentation Process Form. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, Calliditas must be notified in writing and be given the opportunity to further store such records.

11 SPONSOR/INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible. The study will be conducted in compliance with the protocol, regulatory requirements, International Council for Harmonisation (ICH) for GCP and the ethical principles of the latest version of the Declaration of Helsinki as adopted by the World Medical Association.

11.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, ICFs, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and ICH Guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by Calliditas or their designee (i.e., Medpace).

It is the responsibility of Calliditas or their designee (i.e., Medpace) to obtain the approval of the responsible IRB/IEC according to the national regulations.

11.3 Delegation of Investigator Duties

The Investigator should ensure that all persons assisting with this study are adequately qualified and informed about their study-related duties and functions, including the study treatment.

The International Coordinating Investigator selected by Calliditas will be a representative of all Investigators for this study. The International Coordinating Investigator will be the signatory on the clinical study report. Each Investigator will maintain a list of Sub-Investigators and other appropriately qualified persons to whom they delegate significant study-related duties.

Should the Investigator delegate the supervision of the administration of study treatment, the designee should have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

11.4 Informed Consent

The ICF will include Part A and Part B of the study. The ICF and any changes to the ICF made during the course of the study must be agreed to by Calliditas or their designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and

legal requirements. The Covid-19 pandemic-related ICF addendum will be implemented at the time of IRB submission of the current protocol amendment (Version 5.0).

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed ICF must be maintained by the Investigator and is subject to inspection by a representative of Calliditas, their representatives, auditors, the IRB/IEC and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

Patients will also be given the option to participate in the exploratory kidney biopsy and biomarker analyses and to provide a genetic sample for exploratory, limited candidate gene analyses; participation will require completion of a separate ICF and separate consents each for the biomarker analyses, kidney biopsy analyses, and genetic analyses.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC (EU sites only), applicable regulatory requirements, and the Declaration of Helsinki and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, Calliditas in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, Calliditas or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit Calliditas or their designee to monitor the study, which will require direct access to source data, as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

All relevant patient source data and eCRF data must be available for inspection by regulatory health authorities, Calliditas or their designee, and the IRB/IEC as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient source data is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or Calliditas, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from Calliditas before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, Calliditas should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Calliditas.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with Calliditas before any study data are submitted for publication. Calliditas reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to Calliditas to permit Calliditas to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, Calliditas has taken out patient liability insurance for all patients who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (i.e., initiation of study centers) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or Calliditas. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

12.2 Address List

12.2.1 Sponsor

Calliditas Therapeutics AB
Kungsbron 1
SE-111 22 Stockholm, Sweden
Telephone: +46 8 411 3005

12.2.2 Contract Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-513-579-9911
Fax: +1-513-579-0444

12.2.3 Serious Adverse Event Reporting

Medpace SAE reporting line – USA/Canada/Australia/Asia Pacific:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

Medpace SAE reporting line – Europe/All other countries:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
e-mail: medpace-safetynotification@medpace.com

12.2.4 Biological Specimens

Medpace Reference Laboratories (US, Belgium and/or Singapore locations)*
Corporate address:
5365 Medpace Way
Cincinnati, OH 45227
United States
Telephone: +1-513-366-3270
Fax: +1-513-366-3273
**For specific shipping information refer to the laboratory manual*.

13 REFERENCES

1. Schena FP and Pesce F. Epidemiology and ancestral difference. In: Kar Neng Lai editor(s). Recent advances in IgA nephropathy. Singapore: World Scientific, 2009:9-19.
2. Donadio JV, Bergstralh EJ, Grande JP, Rademcher DM. Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. Nephrol Dial Transplant. 2002;17(7):1197-1203.
3. Moriyama T, Tanaka K, Iwasaki C, et al. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. PLoS One. 2014;9(3):e91756.
4. Vecchio M, Bonerba B, Palmer SC, et al. Immunosuppressive agents for treating IgA nephropathy. Cochrane Database Syst Rev. 2015;(8):CD003965.
5. Lai KN, Leung JC, Tang SC. Recent advances in the understanding and management of IgA nephropathy. F1000Res. 2016;5:161.
6. Donadio JV, Grande JP. IgA nephropathy. N Engl J Med. 2002;347(10):738-748.
7. Alamartine E, Sabatier JC, Guerin C, Berliet JM, Berthoux F. Prognostic factors in mesangial IgA glomerulonephritis: an extensive study with univariate and multivariate analyses. Am J Kidney Dis. 1991;18(1):12-19.
8. Gallo GR, Katafuchi R, Neelakantappa K, Baldwin DS. Prognostic pathologic markers in IgA nephropathy. Am J Kidney Dis. 1988;12(5):362-365.
9. Manno C, Strippoli GF, D'Altri C, Torres D, Rossini M, Schena FP. A novel simpler histological classification for renal survival in IgA nephropathy: a retrospective study. Am J Kidney Dis. 2007;49(6):763-775.
10. Neelakantappa K, Gallo GR, Baldwin DS. Proteinuria in IgA nephropathy. Kidney Int. 1988;33(3):716-721.
11. Galla JH. IgA nephropathy. Kidney Int. 1995;47(2):377-387.
12. Aucella F, Netti GS, Piemontese M, Cincione IR, Infante B, Gesualdo L. Proteinuria in the prognosis of IgA nephropathy. Minerva Urol Nefrol. 2009;61(3):235-248.
13. Floege J and Eitner F. Current therapy for IgA nephropathy. J Am Soc Nephrol. 2011;22(10):1785-1794.
14. Wyatt RJ and Julian BA. IgA nephropathy. N Engl J Med. 2013;368(25):2402-2414.
15. Kiryluk K, Li Y, Scolari F, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet 2014;46(11):1187-1196.
16. McCarthy DD, Kujawa J, Wilson C, et al. Mice overexpressing BAFF develop a commensal flora-dependent, IgA-associated nephropathy. J Clin Invest. 2011;121(10):3991-4002.
17. Lai KN. Pathogenesis of IgA nephropathy. Nat Rev Nephrol. 2012;8(5):275-283.
18. Suzuki H, Kiryluk K, Novak J, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011;22(10):1795-1803.
19. Tomana M, Novak J, Julian BA, Matousovic K, Konecny K, Mestecky J. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. J Clin Invest. 1999;104 (1):73-81.
20. Smith AC, Molyneux K, Feehally J, Barratt J. O-glycosylation of serum IgA1 antibodies against mucosal and systemic antigens in IgA nephropathy. J Am Soc Nephrol. 2006;17(12):3520-3528.

21. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl. 2012;2:139-274.
22 . UCERIS® (budesonide) [package insert]. Bridgewater, NJ. Salix Pharmaceuticals. November 2016.
23. ENTOCORT® EC (budesonide) [package insert]. Wilmington, DE. AstraZeneca Pharmaceuticals LP. December 2011.
24. Nefecon® budesonide modified-release capsules Investigator's Brochure Version 8, dated 28 February 2019.
25. PULMICORT RESPULES® (budesonide) [package insert]. Wilmington, DE. AstraZeneca Pharmaceuticals LP. October 2016.
26. PULMICORT FLEXHALER® (budesonide) [package insert]. Wilmington, DE. AstraZeneca Pharmaceuticals LP. October 2016.
27. Locatelli F, Pozzi C, Andrulli S. IgA nephritis: ACE inhibitors, steroids, both or neither? Nephrol Dial Transplant. 2006;21(12):3357-3361.
28. Lv J, Zhang H, Wong MG, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING randomized clinical trial. JAMA. 2017;318(5):432-442.
29. Maronna RA, Martin RD, Yohai VJ, et al. Robust statistics: theory and methods. 2nd ed. West Sussex, UK: John Wiley & Sons Ltd; 2019.
30. Brown H, Prescott R. Applied mixed models in medicine. 3rd ed. John Wiley & Sons, Ltd; 2015.
31. Stone AM, Cattran DC, Floege J, et al. Relationship between treatment effects for proteinuria and eGFR slope over 2 years in patients with IgA nephropathy. Abstract TH-OR108. American Society of Nephrology. 07 November 2019.

APPENDIX A: SCHEDULE OF PROCEDURES

Table 3. Schedule of Procedures – Part A

Study Period	Screening			Treatment									Follow-Up[1]	
Study Visit	**1**	**2**	**3[2]**	**NA**	**4[3]**	**5**	**6**	**7**	**8**	**9**	**10**	**11/ET[4]**	**12**	**13**
Study Day, Week, or Month	**See footnote[5]**				**1d**	**3w**	**6w**	**3m**	**4.5m**	**6m**	**7.5m**	**9m[6]**	**10.5m**	**12m**
Visit Window (Days)						**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-7 to +28**	**±7**	**±7**
Procedure														
Visit conducted by telephone						X	X		X		X		X	
Informed consent[7]	X													
Demographics and medical/surgical history	X													
Update medical/surgical history			X		X									
Eligibility criteria assessment	X		X	X										
Contact IRT to trigger study drug shipment and randomization[8]				X[9]										
Concomitant medications and procedures[10]	X[11]		X		X	X	X	X	X	X	X	X	X	X
AE assessment[12,13]	X[13]		X[13]		X[12]	X	X	X	X	X	X	X	X	X
Physical examination	X											X		X
Vital signs[14]	X		X		X			X		X		X		X
Body weight and height[15]	X				X			X		X		X		X
Confirm biopsy slide and report availability[16]	X													
Hematology[17]	X		X					X		X		X		X
Serum chemistry[18]	X		X					X		X		X		X
HIV, tuberculosis, HBV, and HCV[19]	X													
Drug and alcohol screen (urine)	X													
Fasting lipid profile			X											
eGFR (CKD-EPI)[20]	X		X					X		X		X		X
Urinalysis[21]	X		X					X		X		X		X
24-hour urine collection[10]		X	X					X		X		X		X
Supply 24-hour urine container	X	X			X			X		X		X		X
Exploratory sampling (optional)[7,22]			X					X		X		X		X

See footnotes at the end of the Schedule of Procedures – Part A table

Table 3. Schedule of Procedures – Part A (Continued)

Study Period	Screening				Treatment								Follow-Up[1]	
Study Visit	**1**	**2**	**3[2]**	**NA**	**4[3]**	**5**	**6**	**7**	**8**	**9**	**10**	**11/ET[4]**	**12**	**13**
Study Day, Week, or Month	**See footnote[5]**				**1d**	**3w**	**6w**	**3m**	**4.5m**	**6m**	**7.5m**	**9m[6]**	**10.5m**	**12m**
Visit Window (Days)						**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-7 to +28**	**±7**	**±7**
Procedure														
Genetic sample (optional)[7,23]								X						
Pregnancy test[24]			X		X			X		X		X		X
FSH[25]	X													
Dispensing of study drug[8]					X			X		X		X[26]		
Start of study drug[9]					X									
Begin 2-week Tapering Period												X		
Return of unused study drug								X		X		X		X[26]
Study drug accountability and compliance assessment[27]						X	X	X	X	X	X	X	X	X
SF-36 QoL assessment			X									X		
Capture dialysis, transplant, or death[28]					X	X	X	X	X	X	X	X	X	X
Dietary and lifestyle recommendations[29]	X													

Note: Prior to conducting any study-related activities, written informed consent must be signed and dated by the patient.

1. Following completion of the Treatment Period, patients will enter the 3-month Part A Follow-up Period. The first 2 weeks of this Follow-up Period will consist of a 2-week Tapering Period to reduce the risk of insufficiency of the adrenal glands. During the 2-week Tapering Period, the study drug dose will be reduced from 4 capsules QD (Nefecon 16 mg or placebo) to 2 capsules QD (Nefecon 8 mg or placebo). For patients who are withdrawn from the study after completion of Study Visit 11 but prior to completion of Part B, the End of Study Visit procedures (see Table 4) will be completed, if possible, at the time the decision is made to withdraw the patient.
2. Patients will be required to fast for at least 10 hours prior to Study Visit 3.
3. Study Visit 4 should occur within 10 days after randomization.
4. See Section 4.3 for additional details related to withdrawal criteria. For patients who are withdrawn from the study prior to completion of Study Visit 11, the ET Visit procedures will be completed, if possible, at the time the decision is made to withdraw the patient. The ET Visit will consist of all of the Study Visit 11 procedures; however, study drug will only be dispensed at this visit if tapering is applicable, and if so, the daily dose of study drug will be reduced to 2 capsules QD (Nefecon 8 mg or placebo) for 2 weeks to prevent insufficiency of the adrenal glands.
5. Patients will have a Screening Period lasting up to 35 days (prior to randomization). If informed consent has been obtained, SAEs have been assessed, and the patient has been supplied with container(s) for the next 24-hour urine collection, the remaining Study Visit 1 procedures may, at the discretion of the Investigator, be performed at Study Visit 2. Study Visit 3 must occur at least 2 weeks after Study Visit 2 in order to collect 2 proteinuria measurements separated by at least 2 weeks to determine eligibility.
6. Study Visit 11 may occur at 10 months, when applicable, due to the Covid-19 pandemic.
7. The ICF will include Part A and Part B of the study. The estimated duration of individual patient participation in Part A will be approximately 1 year and the estimated median duration of individual patient participation in Part B will be approximately 1 year (maximum of 26.5 months of individual patient participation in the study). As part of the informed consent process, only patients who fully understand and agree to full participation and follow-up should be consented to participate. At Study Visit 1 (screening), patients will be given the option to participate in the exploratory kidney biopsy and biomarker analyses and to provide a genetic sample for exploratory, limited candidate gene analyses; participation will require signing of separate ICFs, one for the biomarker analyses, one for the kidney biopsy analyses, and one for the genetic analyses. If a re-screened patient agrees to participate in the exploratory kidney biopsy and/or biomarker analyses and signed the specific ICF for the previous screening, then

this patient must be re-consented and the biomarker samples must be repeated (except for the already existing kidney biopsy samples). A separate Covid-19 pandemic-related ICF addendum will be signed by patients to be treated for up to 10 months.

8. After confirming all eligibility criteria (laboratory values from Study Visits 1, 2, 3, etc.) (eGFR values from Study Visits 1 or 3 must be within the limits defined by the inclusion criteria for the patient to be eligible), randomization will be performed through IRT which will trigger the first shipment of study drug to the site for the patient. Following initial shipment, there will be an automatic resupply of study drug to the site for dispensing to the patient at Study Visits 7, 9, and 11 (for the Tapering Period). When study drug is dispensed, the patient will also be instructed on study drug administration.
9. Patients must take the first dose of study drug in the presence of site staff during Study Visit 4. As a result, the first dose of study drug may be administered at any time of day and without regard to the timing of meals. Patients may self-dose for all other doses of study drug and should take study drug in the morning approximately 1 hour before breakfast.
10. Systemic immunosuppressive drugs (including GCSs), except when used as rescue medications, are prohibited during the study. However, over the entirety of the study (Parts A and B), patients will be allowed up to 3 courses of treatment with GCSs in any 2-year period for non-IgAN indications, provided no treatment course is greater than 2 weeks and the GCS dose does not exceed the equivalent of 0.5 mg/kg/day prednisolone. Such short-term treatment will not require change or stop of study drug treatment in Part A. For both Part A and Part B, study visits that include collection of 24-hour urine samples for efficacy assessments must not be performed within 4 weeks of such short-term GCS treatment. A 24-hour urine collection can be repeated if the Investigator suspects that the sampling is insufficient. Study visits are to be postponed as needed.
11. Medications taken within 3 months prior to Study Visit 1 (screening) and concomitant medications and therapies will be recorded in the eCRFs.
12. Beginning at Study Visit 4, AEs and AESIs will be assessed after administration of the first dose of study drug until 2 years (+14 to 35 days) after the first dose of study drug (Study Visit 17b), inclusive, regardless of whether the patient discontinues the study prematurely. If the patient does not receive study drug at Study Visit 4, AEs should still be monitored and documented from Study Visit 4.
13. Serious adverse events will be monitored and reported from signature of informed consent.
14. Vital sign measurements will include systolic and diastolic blood pressure and heart rate. Blood pressure and heart rate will be measured after resting in the supine position for at least 5 minutes. At the applicable study visits in the Screening Period, blood pressure and heart rate will be measured up to 3 times with each measurement separated by 1 minute (the lowest value will be recorded on the eCRF).
15. Height will only be collected at Study Visit 1.
16. Confirm that the kidney biopsy report(s) verifies IgAN diagnosis and that the kidney biopsy slide(s), or equivalent, can be obtained for central reading.
17. Hematology, including HbA1c. See Appendix B for the complete list of analytes.
18. Serum chemistry. See Appendix B for the complete list of analytes.
19. If the patient is re-screened, HBV, HCV, HIV, and tuberculosis screenings should not be repeated if done as part of the study within the last 12 months.
20. The central laboratory will calculate the eGFR using the CKD-EPI formula. The eGFR values from Study Visits 1 or 3 must be within the limits defined by the inclusion criteria for the patient to be eligible.
21. A fresh urine sample will be collected for the urinalysis, and in addition urine will be assessed by dipstick. See Appendix B for the complete list of analytes.
22. Blood (48 mL) and urine (20 mL) samples will be collected for exploratory biomarker analyses (optional).
23. A blood (6 mL) sample will be collected for exploratory genetic analysis (optional).
24. For women of childbearing potential only. A serum pregnancy test will only be performed at Study Visit 3. A pregnancy test via a local urine assessment will be performed at all other applicable study visits.
25. Postmenopausal women will have a confirmatory FSH test performed at Study Visit 1.
26. Study drug will be dispensed for the Tapering Period at Study Visit 11 and patients will return unused study drug at the next onsite study visit (Study Visit 13).
27. Only treatment compliance will be assessed during study visits conducted by telephone.
28. Assess the occurrence of one of the following study endpoints: initiation of maintenance dialysis for at least 1 month, kidney transplantation, or any death.
29. The following lifestyle choices should be recommended to the patient: weight normalization, smoking cessation, physical activity, and diet (low salt and low protein). Patients should be encouraged to maintain stable lifestyle choices while participating in the study.

AE = adverse event; AESI = adverse event of special interest; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; Covid-19 = Coronavirus Disease 2019; d = day(s); eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; ET = Early Termination; FSH = follicle-stimulating hormone; GCS = glucocorticoid; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = Informed Consent Form; IgAN = immunoglobulin A nephropathy; IRT = Interactive Response Technology; m = month(s); NA = not applicable; QD = once per day; QoL = quality of life; SF-36 = Short Form 36; w = week(s).

Table 4. Schedule of Procedures – Part B

Study Period	Part B Follow-Up[1]				
Study Visit	**14**	**15**	**16**	**17a/EOS[2]**	**17b/EOS[2]**
Study Year/Month	**1y 3m**	**1y 6m**	**1y 9m**	**2 years**	**2 years**
Visit Window (Days)	**±7**	**±30**	**±7**	**±30**	**14 to 35 days after Visit 17a**
Procedures					
Visit conducted by telephone	X		X		
Concomitant medications and procedures[3]	X	X	X	X	X
AE assessment (including AESIs and SAEs)	X	X	X	X	X
Physical examination				X	
Vital signs[4]		X		X	
Body weight		X		X	
Hematology[5]		X		X	
Serum chemistry[6]		X		X	X
eGFR (CKD-EPI)[7]		X		X	X
Urinalysis[8]		X		X	
24-hour urine collection[3]		X		X	
Supply 24-hour urine container		X			
Exploratory sampling (optional)[9]		X			
SF-36 QoL assessment				X	
Capture dialysis, transplant, or death[10]	X	X	X	X	

1. Part B will continue until 25 months after the 360th/last patient is dosed (or, if the 360th/last patient randomized does not receive any study drug, 25 months after the 360th/last patient is randomized).
2. See Section 4.3 for additional details related to withdrawal criteria. For patients who are withdrawn from the study after completion of Study Visit 11 but prior to completion of Part B, the EOS Visit procedures will be completed, if possible, at the time the decision is made to withdraw the patient. The EOS Visit will consist of all of the Study Visit 17a and 17b procedures. The patient will complete the EOS Visit (Study Visits 17a and 17b) per protocol and subsequently end participation in the study if any of the following occur: the patient experiences initiation of maintenance dialysis for at least 1 month or kidney transplantation; the 360th/last patient randomized has been followed for 25 months; termination of the study by Calliditas Therapeutics AB or the regulatory authority; or the patient withdraws consent or requests discontinuation from the study for any reason.
3. Systemic immunosuppressive drugs (including GCSs), except when used as rescue medications, are prohibited during the study. However, over the entirety of the study (Parts A and B), patients will be allowed up to 3 courses of treatment with GCSs in any 2-year period for non-IgAN indications, provided no treatment course is greater than 2 weeks and the GCS dose does not exceed the equivalent of 0.5 mg/kg/day prednisolone. Such short-term treatment will not require change or stop of study drug treatment in Part A. For both Part A and Part B, study visits that include collection of 24-hour urine samples for efficacy assessments must not be performed within 4 weeks of such short-term GCS treatment. A 24-hour urine collection can be repeated if the Investigator suspects that the sampling is insufficient. Study visits are to be postponed as needed.
4. Vital sign measurements will include systolic and diastolic blood pressure and heart rate. Blood pressure and heart rate will be measured after resting in the supine position for at least 5 minutes.
5. Hematology, including HbA1c. See Appendix B for the complete list of analytes.
6. Serum chemistry. See Appendix B for the complete list of analytes. At Study Visit 17b, only serum creatinine will be assessed.
7. The central laboratory will calculate the eGFR using the CKD-EPI formula.
8. A fresh urine sample will be collected for the urinalysis, and in addition urine will be assessed by dipstick. See Appendix B for the complete list of analytes.

9. Blood (48 mL) and urine (20 mL) samples will be collected for exploratory biomarker analyses (optional).
10. Assess the occurrence of one of the following study endpoints: initiation of maintenance dialysis for at least 1 month, kidney transplantation, or any death.

AE = adverse event; AESI = adverse event of special interest; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; EOS = End of Study; GCS = glucocorticoid; HbA1c = hemoglobin A1c; IgAN = immunoglobulin A nephropathy; m = month(s); QoL = quality of life; SAE = serious adverse event; SF-36 = Short Form 36; y = year(s).

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel [1]

Alanine aminotransferase (ALT)	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase (AST)	Blood urea nitrogen (BUN)
Calcium	Creatine kinase
Creatinine	Estimated glomerular filtration rate (eGFR) [2]
Gamma-glutamyl transferase (GGT)	Glucose (fasting), only at visit 3
Inorganic phosphorus	Lactate dehydrogenase
Potassium	Sodium
Total bilirubin	Total protein
Uric acid	

1. The chemistry panel will be assessed under fasting conditions at Study Visit 3 and non-fasting conditions for all other applicable study visits.
2. Calculated by the central laboratory using the following:
    a. Chronic Kidney Disease Epidemiology Collaboration formula ($eGFR = 141 \times \min(SCr/K, 1)^{\alpha} \times \max(SCr/K, 1)^{-1.209} \times 0.993^{Age} \times 1.018$[if female] $\times 1.159$[if black] where SCr is standardized serum creatinine in mg/dL, K is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/K or 1, and max indicates the maximum of SCr/K or 1).[1]

Fasting Lipid Panel

High-density lipoprotein (HDL) cholesterol	Low-density lipoprotein (LDL) cholesterol [1]
Total cholesterol	Total triglyceride

1. Assessed as follows by the Friedewald calculation:
    a. Conventional units (mg/dL) LDL cholesterol = Total cholesterol – HDL cholesterol - triglycerides/5, or
    b. International System of Units (mmol/L) LDL cholesterol = Total cholesterol – HDL cholesterol – triglycerides/2.2.[2]

Endocrinology

Follicle-stimulating hormone (FSH) [1]

1. Postmenopausal is defined as amenorrhoeic for at least 1 year AND, if aged under 60 years have a serum follicle-stimulating hormone level of at least 30 IU/L.

Additional Serology

Tuberculosis (TB)	Human immunodeficiency virus (HIV)
Hepatitis B virus (HBV)	Hepatitis C virus (HCV)

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Additional Hematology

Glycosylated hemoglobin (HbA1c)

Urinalysis (Freshly Voided Urine)

Assessed by Dipstick

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Nitrite
pH	Protein
Specific gravity	Urobilinogen

Assessed by Chemical Assay

Albumin	Cortisol
Creatinine	Protein
Sodium	

Urine Screen (Freshly Voided Urine)

Alcohol	Amphetamines
Cannabinoids	Cocaine
Ecstasy	Methamphetamine
Opiates	Oxycodone

24-Hour Urine Analysis

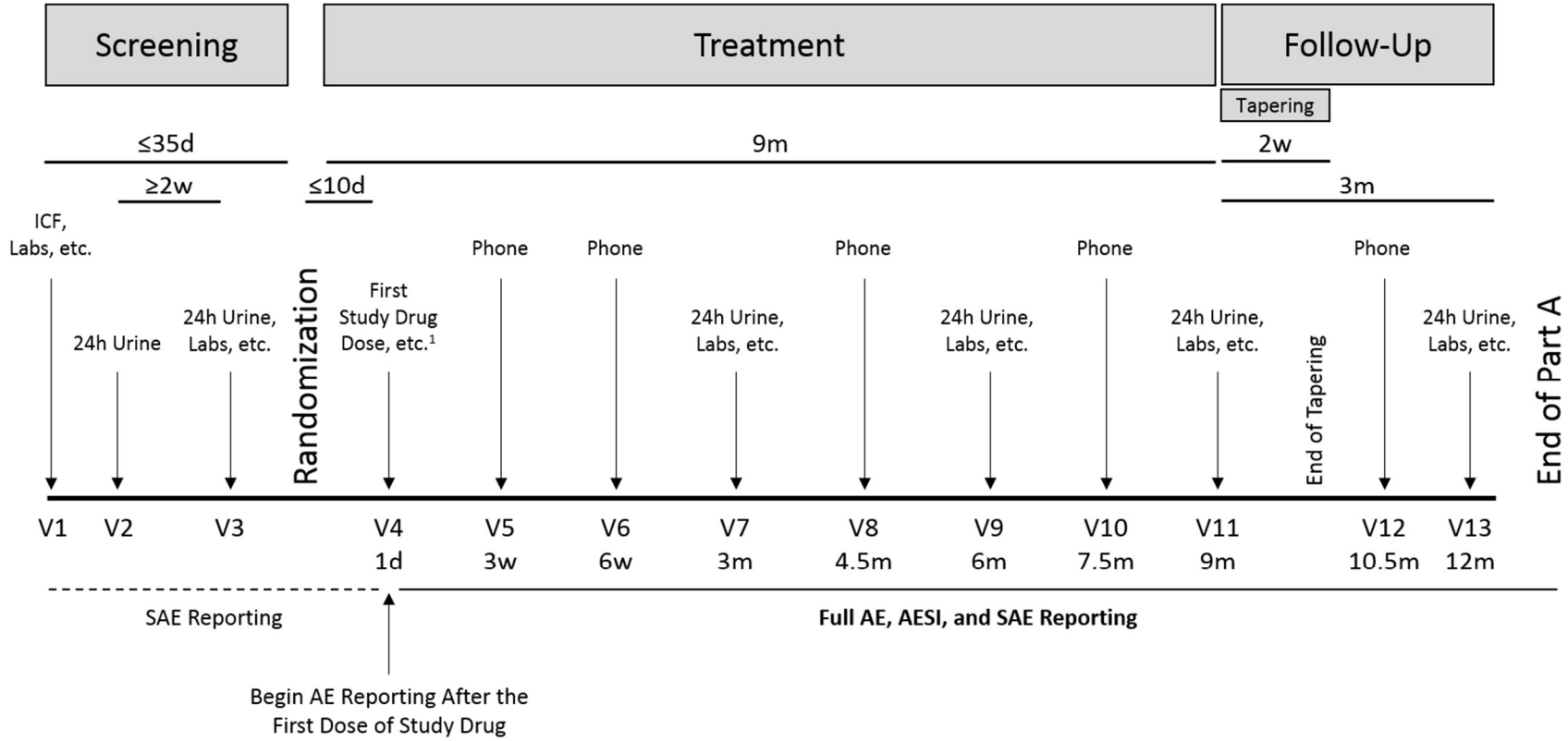
Creatinine clearance	Total albumin
Total cortisol	Total creatinine
Total protein	Urine albumin to creatinine ratio (UACR)
Urine protein to creatinine ratio (UPCR)	

Sources:

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.
2. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative centrifuge. Clin Chem. 1972;18(6): 499-502.

APPENDIX C: SUMMARY OF PART A AND PART B

Figure 3. Summary of Part A*

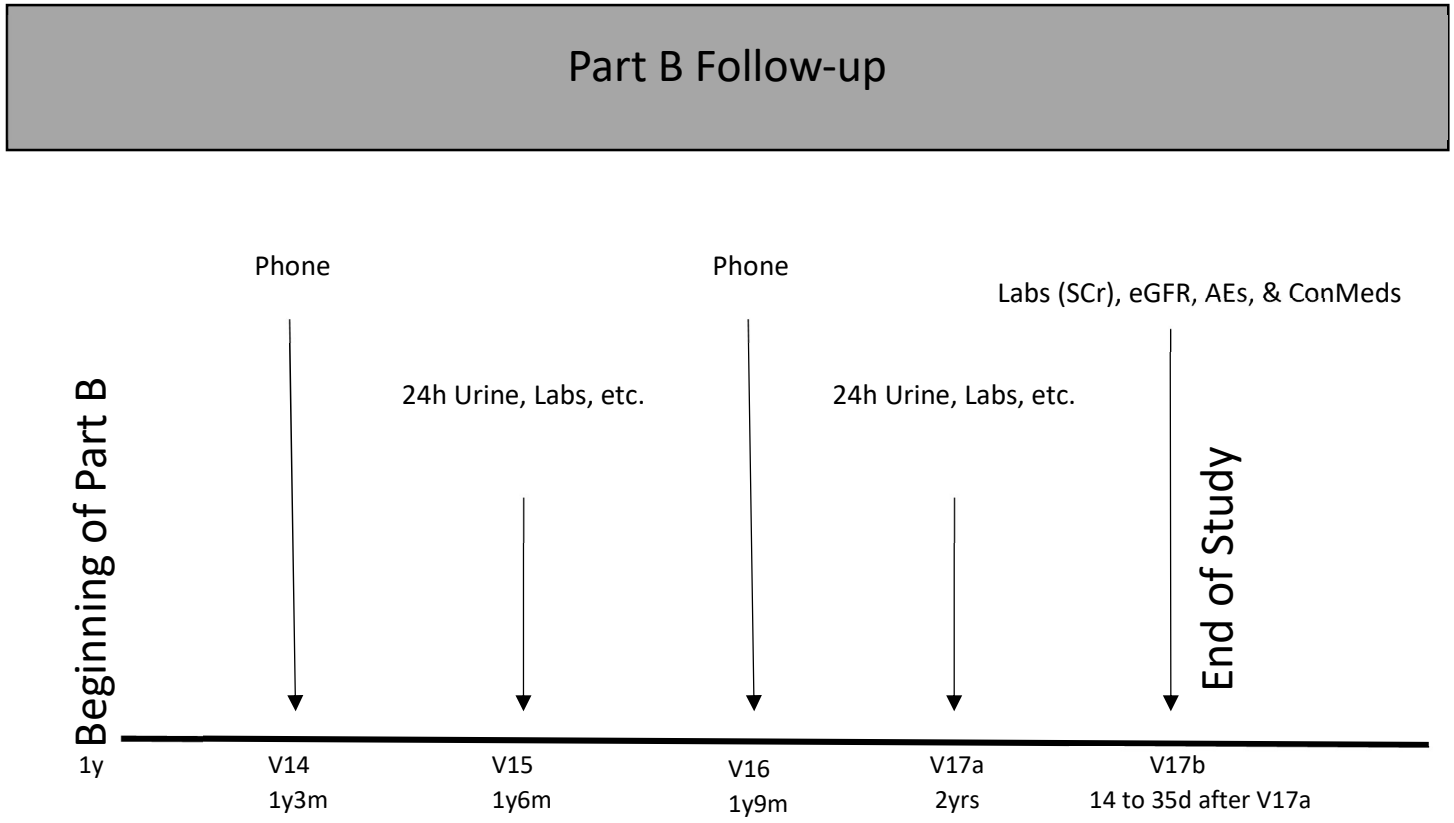


1. Assessments for AEs, including AESIs, and the occurrence of one of the study endpoints (initiation of maintenance dialysis for at least 1 month, kidney transplantation, or any death) will begin at Study Visit 4.

*Patients may be treated for up to 10 months, when applicable, due to the Covid-19 pandemic.

AE = adverse event; AESI = adverse event of special interest; Covid-19 = Coronavirus Disease 2019; d = day(s); h = hour; ICF = Informed Consent Form; m = months; labs = laboratory assessments; SAE = serious adverse event; V = Study visit; w = weeks.

Figure 4. Summary of Part B



Note: Assessments for the occurrence of one of the study endpoints (initiation of maintenance dialysis for at least 1 month, kidney transplantation, or any death) will continue until the end of the study.
AE = adverse event; conmeds = concomitant medications; d = days; eGFR = estimated glomerular filtration rate; h = hour; labs = laboratory assessments; m = months; SCr = serum creatinine; V = Study visit; y = year.

APPENDIX D: RENIN-ANGIOTENSIN SYSTEM INHIBITOR AND OTHER ANTIHYPERTENSIVE THERAPY RECOMMENDATIONS ACCORDING TO THE 2012 KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES GUIDELINES

Patients must be on a stable dose of renin-angiotensin system (RAS) inhibitor therapy (angiotensin-converting enzyme inhibitors [ACEIs] and/or angiotensin II type I receptor blockers [ARBs]) at the maximum allowed dose or maximum tolerated dose according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the 3 months prior to randomization. In this instance, a stable dose is defined as doses within 25% of the dose at randomization.[1] For all patients, two 24-hour urine samplings separated by at least 2 weeks must be performed prior to randomization for measurement of proteinuria.

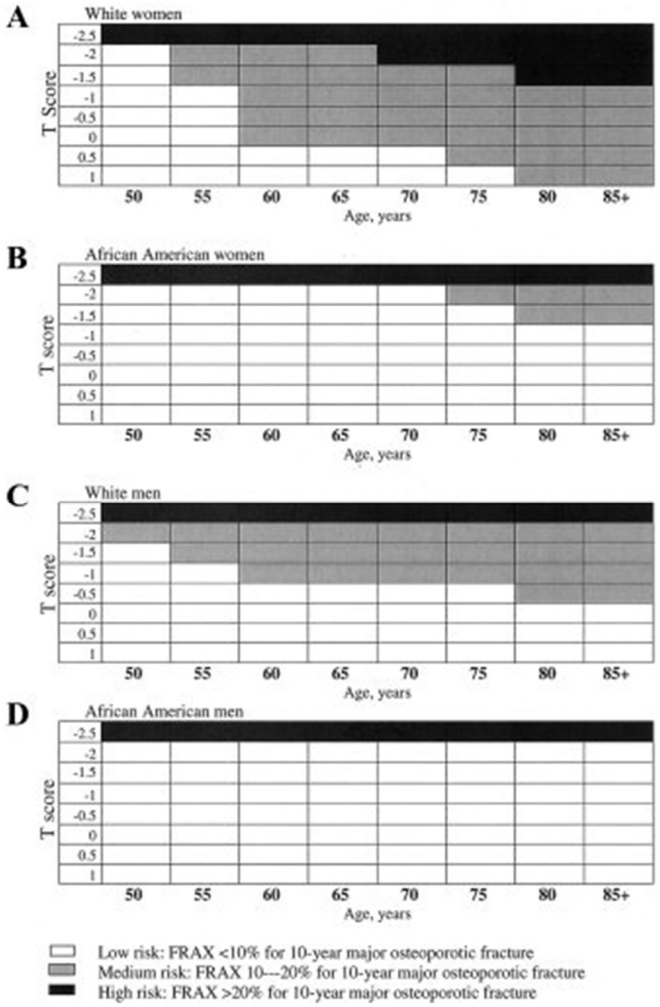
The following are recommendations for optimization and maintenance of RAS/antihypertensive therapy that are in line with the 2012 KDIGO guidelines and should be in place for at least 3 months prior to randomization.[1] These recommendations are also to be followed after randomization:

- Antihypertensive therapy is recommended to achieve a target systolic blood pressure <125 mmHg and target diastolic blood pressure <75 mmHg. Antiproteinuric therapy should be used to try to achieve a target proteinuria level <1 g per day. Antihypertensive therapy in these patients will follow current clinical guidelines;
- ACEIs are recommended as a first-line therapy and increased to the maximum tolerated daily dose (not to exceed the maximum recommended daily dose) depending on the degree of arterial hypertension and proteinuria. Patients can be converted to an ARB when ACEIs are not tolerated. Combination ACEI and ARB therapy is discouraged, but may be used at the discretion of the Investigator. If combination therapy is used, the stable dose should be based on the maximum tolerated dose rather than the maximum allowed dose;
- In patients who do not tolerate ACEIs or ARBs, other antihypertensive treatments may be used according to local treatment guidelines to achieve the target blood pressure. Study centers are not limited to the use of specific compounds;
- Antihypertensive therapy with other agents including diuretics, aldosterone agonists, calcium channel blockers, and β-blockers may be maintained or added according to the 2012 KDIGO guidelines and the clinical guideline of the individual study center in order to achieve the target blood pressure;[1]
- In the case of hypotension, withdrawal of other antihypertensive (non-ACEI/non-ARB) medications should be considered as the first alternative; and
- In the case of hypertension, addition or dose increase of other antihypertensive (non-ACEI/non-ARB) medications, as recommended by the 2012 KDIGO guidelines, should be considered.[1]

Source:

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl. 2012;2:139-274.

APPENDIX E: RECOMMENDATIONS FOR DEFINING MEDIUM- OR HIGH-RISK OSTEOPOROSIS



Source: Grossman JM, Gordon R., Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Car Res (Hoboken). 2010;62(11):1515-1526.

For patients in China, the medium- or high-risk category is defined according to the Osteoporosis Self-Assessment Tool for Asians (OSTA) index:

- OSTA index = (Weight [kg] – Age [year]) × 0.2
- High-risk subgroup = index < -4
- Intermediate-risk subgroup = index -1 to -4
- Low-risk subgroup = index > -1

Source: Koh LK, Sedrine WB, Torralba TP, et al. A simple tool to identify asian women at increased risk of osteoporosis. Osteoporos Int. 2001;12(8):699-705.

APPENDIX F: IMMUNOSUPPRESSIVE DRUGS OTHER THAN GLUCOCORTICOIDS

Systemic immunosuppressive drugs, except when used as rescue medications, are prohibited during the study. Systemic immunosuppressive drugs will include, but will not be limited to the following:

Azathioprine	Calcineurin inhibitors (e.g., cyclosporin, tacrolimus)
Cyclophosphamide	Mycophenolate mofetil
Rituximab	Herbs for medicinal use, including Chinese herbs and Chinese traditional medicines, with a known effect on the immune system (e.g., *Tripterygium wilfordii*)
	Hydroxychloroquine

Note: Topical or inhalation products containing immunosuppressants are allowed.