CLINICAL STUDY PROTOCOL

AN OPEN-LABEL EXTENSION (OLE) STUDY TO EVALUATE THE EFFICACY AND SAFETY OF NEFECON TREATMENT IN PATIENTS WITH IGA NEPHROPATHY WHO HAVE COMPLETED STUDY NEF-301

Investigational Product: Nefecon™ (budesonide modified-release capsules)
Protocol Number: Nef-301 OLE
EudraCT Number: 2020-003308-14
IND Number: 107950
NCT Number: NCT04541043

Sponsor:
Calliditas Therapeutics AB
Kungsbron 1, C8
111 22 Stockholm
Sweden
Telephone: +46 8 411 3005

Version Number: 1.0
Date: 06 August 2020

SIGNATURE PAGE

STUDY TITLE: An Open-Label Extension (OLE) Study to Evaluate the Efficacy and Safety of Nefecon Treatment in Patients With IgA Nephropathy Who Have Completed Study Nef-301

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

Signature	Date
_____	_____
Chief Medical Officer Calliditas Therapeutics AB	
_____	_____
Clinical Operations Director Calliditas Therapeutics AB	
_____	_____
Vice President, Medical Department Medpace, Inc.	
_____	_____
Vice President, Medical Department Medpace, Inc.	
_____	_____
Senior Medical Director, Medical Department Medpace, Inc.	

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: An Open-Label Extension (OLE) Study to Evaluate the Efficacy and Safety of Nefecon Treatment in Patients With IgA Nephropathy Who Have Completed Study Nef-301

PROTOCOL NUMBER: Nef-301 OLE

EudraCT NUMBER: 2020-003308-14

INVESTIGATIONAL PRODUCT: Nefecon™ (budesonide modified-release capsules; Nefecon™ is a trademark of Calliditas Therapeutics AB [hereinafter Calliditas])

PHASE: 3b

INDICATION: Treatment of primary immunoglobulin A nephropathy (IgAN)

OBJECTIVES:

Primary Objectives:

The primary objectives are the following:

- To assess the effect of 9 months of retreatment with Nefecon on urine protein to creatinine ratio (UPCR) and estimated glomerular filtration rate (eGFR) in patients who completed Study Nef-301 with Nefecon treatment; and
- To assess the effect of 9 months of treatment with Nefecon on UPCR and eGFR in patients who completed Study Nef-301 with placebo treatment.

Secondary Objectives:

The secondary objectives are the following:

- To assess the safety and tolerability of 9 months of retreatment with Nefecon in patients who completed Study Nef-301 with Nefecon treatment;
- To assess the safety and tolerability of 9 months of treatment with Nefecon in patients who completed Study Nef-301 with placebo treatment;
- To assess the effect of 9 months of retreatment with Nefecon on additional aspects of renal function in patients who completed Study Nef-301 with Nefecon treatment; and
- To assess the effect of 9 months of treatment with Nefecon on additional aspects of renal function in patients who completed Study Nef-301 with placebo treatment.

POPULATION:

Patients who have completed Study Nef-301 and meet all eligibility criteria will be able to enter Study Nef-301 OLE and start treatment. Patients must continue to be treated with a stable dose of renin-angiotensin system (RAS) inhibitor therapy (angiotensin-converting enzyme inhibitors [ACEIs] and/or angiotensin II type I receptor blockers [ARBs]). In addition to meeting all other eligibility criteria, patients must have proteinuria based on 2 consecutive measurements separated

by at least 2 weeks and calculated by the central laboratory showing either ≥1 g/day (≥1000 mg/day) or UPCR ≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements. Patients must also have eGFR ≥30 mL/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

STUDY DESIGN AND DURATION:

This is a Phase 3b, multicenter, open-label extension (OLE) study to evaluate the efficacy and safety of Nefecon treatment in patients with IgAN who have completed the Phase 3 Study Nef-301 and continue to be treated with a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs). Patients who previously received Nefecon in Study Nef-301 will receive retreatment, whereas patients who previously received placebo in Study Nef-301 will be treatment naïve to Nefecon. During Study Nef-301 OLE, the patients and Investigators will remain blinded to treatment given in Study Nef-301.

Assuming that 75% of the patients who have completed Study Nef-301 will enter Study Nef-301 OLE, the total number of patients to be included is estimated to be approximately 250 patients, but up to 360 patients may be enrolled.

Preferably, Visit 17a in Study Nef-301 should be combined with Visit 1 in Study Nef-301 OLE, and Visit 17b in Study Nef-301 should be combined with Visit 2 in Study Nef-301 OLE. If the visits are not combined, Visit 3 in Study Nef-301 OLE must occur within 3 months after Visit 17b in Study Nef-301.

Patients who do not meet all of the eligibility requirements may be rescreened in Study Nef-301 OLE within 3 months after Visit 17b in Study Nef-301. Patients who do not meet all of the eligibility requirements within this 3-month period will be screen failures and will not be followed any further.

In addition to meeting all other eligibility criteria, patients must have proteinuria based on 2 consecutive measurements separated by at least 2 weeks and calculated by the central laboratory showing either ≥1 g/day (≥1000 mg/day) or UPCR ≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements. Patients must also have eGFR ≥30 mL/min per 1.73 m^2 using the CKD-EPI formula.

During Study Nef-301 OLE, patients will receive Nefecon 16 mg/day for a 9-month period. The 16 mg/day dose may be reduced to 8 mg/day if clinically relevant adverse events (AEs) develop during the 9-month Treatment Period that the Investigator considers related to the study drug and that mandate dose reduction.

From the first day of dosing, a telephone visit will occur at 1 month, and onsite visits will occur at 3, 6, and 9 months. After completing 9 months of study drug treatment, patients will enter the 2-week Tapering Period with Nefecon 8 mg/day. To perform replicate laboratory sampling, an onsite visit will occur 14 to 35 days after the 9-month visit. An onsite follow-up visit will also occur at 12 months.

Patients will remain on a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) throughout the study. If a patient receives rescue treatment (systemic steroids and/or immunosuppressive treatment), the patient will be withdrawn from Nefecon treatment and continue with study visits for a total of 12 months follow-up after first dose.

Patients who prematurely discontinue Nefecon at 16 mg/day should have the dose reduced to 8 mg/day for 2 weeks, if feasible, to prevent adrenal insufficiency.

Unless a patient withdraws his/her consent to participate in the study, all patients should complete the remaining study visits (especially at 9 and 12 months), regardless of whether they are still receiving study drug.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Nefecon 16 mg (four 4 mg budesonide modified-release capsules once per day [QD]) will be administered orally for 9 months during the Treatment Period.

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 at least 1 hour before breakfast. The capsules must be swallowed whole and may not be chewed or crushed.

The 16 mg/day dose may be reduced to 8 mg/day if clinically relevant AEs develop during the 9-month Treatment Period 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 dose. If a dose reduction is made, then the dose should not be increased back to 4 capsules QD (Nefecon 16 mg).

After completing 9 months of study drug treatment, the daily dose of study drug will be reduced from 4 capsules QD (Nefecon 16 mg) to 2 capsules QD (Nefecon 8 mg) for 2 weeks to prevent adrenal insufficiency (Tapering Period). Patients who have their daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg) due to safety and/or tolerability reasons during the 9-month Treatment Period will remain on this dose during the 2-week Tapering Period. Patients who prematurely discontinue study drug while taking 4 capsules QD (Nefecon 16 mg) should have the daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg) for 2 weeks, if feasible, to prevent adrenal insufficiency.

EFFICACY VARIABLES:

Primary Efficacy Endpoints:

The primary efficacy endpoints will include the following:

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

Secondary Efficacy Endpoints:

The secondary efficacy endpoints will include the following:

- Ratio of urine albumin to creatinine ratio (UACR) at 9 months compared to baseline;
- Short Form 36 quality of life assessment at 12 months compared to baseline;
- Proportion of patients with microhematuria at 9 months compared to baseline;
- Proportion of patients receiving rescue treatment and time to receiving rescue treatment;

- Proportion of patients on dialysis, undergoing kidney transplantation, or with eGFR <15 mL/min per 1.73 m^2; and
- Cortisol suppression at 9 and 12 months, measured as urinary cortisol excretion over 24 hours compared to baseline.

SAFETY VARIABLES:

The safety variables will include the following:

- Treatment-emergent AEs, defined as AEs that occur for the first time after dosing in Study Nef-301 OLE, or exist before dosing in Study Nef-301 OLE but worsen in severity after dosing in Study Nef-301 OLE;
- AEs leading to study drug discontinuation;
- AEs of special interest (AESIs) (severe infections requiring hospitalization, new onset of diabetes, 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:

No formal statistical analyses will be performed. eGFR, UPCR, and UACR are expected to be log-normally distributed; therefore, the ratio of 9 months to baseline for eGFR, UPCR, and UACR will be summarized using geometric mean and its associated 95% confidence interval. If outlying data are present for an endpoint, a supplementary description of the data will be performed using a robust regression approach. Separate summaries will be provided according to whether the patient received Nefecon or placebo in Study Nef-301.

Each efficacy variable will be summarized in 2 different analysis sets, a Completers Analysis Set and a Full Analysis Set. The Completers Analysis Set will include all patients who receive Nefecon for 9 months. The Full Analysis Set will include all patients who receive at least 1 dose of Nefecon, with at least 1 efficacy measurement (UPCR or eGFR) collected after dosing. Any data recorded after rescue treatment will not be included in the analysis for either analysis population.

Baseline eGFR, UPCR, and UACR will be defined as the geometric mean of the 2 consecutive measurements prior to dosing. The 9-month eGFR, UPCR, and UACR values will be defined as the geometric mean of the values recorded at Study Visits 8 and 9.

For UPCR, the primary analysis will calculate the mean of the change from baseline in log(UPCR), with results back-transformed to provide a geometric mean ratio and 95% confidence interval. For eGFR, due to the possible presence of outlying data, the primary analysis will use the same approach but deriving the mean change and its confidence interval using a robust regression model.

If a reasonable proportion of patients do not provide 9-month data, a sensitivity analysis will be performed by fitting a mixed model that incorporates any data recorded at 3, 6, and 12 months with different assumptions made about efficacy after discontinuation of treatment.

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 will be summarized by system organ class. In addition, the time to first occurrence of the most common event will be summarized using cumulative incidence plots. Safety data will be summarized or listed separately for the period between screening and the first dose of study drug. 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.

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

SAMPLE SIZE DETERMINATION:

All patients who have completed Study Nef-301 and meet all eligibility criteria will be able to participate in Study Nef-301 OLE. Assuming that 75% of the patients who have completed Study Nef-301 will enter Study Nef-301 OLE, the total number of patients to be included is estimated to be approximately 250 patients, but up to 360 patients may be enrolled.

In Study Nef-202, a completed, randomized, double-blind study of Nefecon in comparison to placebo, the standard deviation for the change from baseline in log(UPCR) and log(eGFR) was 0.59 and 0.18, respectively. If 125 patients are recruited within each efficacy group (prior Nefecon or prior placebo) and a 25% reduction (ratio of 0.75) in UPCR is observed in this study, the upper 95% confidence limit for the baseline ratio will extend to 0.83. Likewise, if there is no change in eGFR observed in this study (ratio of 1), the lower 95% confidence limit for the baseline ratio will extend to 0.97. Therefore, this study will provide a sufficiently precise estimate of the efficacy of Nefecon according to whether the patient previously received Nefecon or placebo.

SITES:

It is anticipated that there will be approximately 140 sites globally.

TABLE OF CONTENTS

LIST OF TABLES

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
CEC	Central Ethics Committee
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRA	Clinical research associate
CTA	Clinical trial authorization
CYP3A4	Cytochrome P450 3A4
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
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
HRT	Hormone replacement therapy
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
OLE	Open-label extension
OSTA	Osteoporosis Self-Assessment Tool for Asians
QD	Once per day
RAS	Renin-angiotensin system
RSI	Reference Safety Information
SAE	Serious adverse event

Abbreviation	Definition
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 common during the second or third decades of life.[2] IgAN 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 part of the small intestine, could attenuate Gd-IgA1 production and leakage to the systemic circulation, thereby reducing subsequent pathophysiological changes in the kidneys.

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 potent glucocorticoid (GCS) with 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 combines a delayed capsule disintegration with a sustained/prolonged release of the active ingredient in the distal part of the small intestine. By directing release of budesonide to the distal part of the small intestine where the target immune tissues, Peyer's patches, reside in high density, a local pharmacological effect is achieved. Budesonide may suppress local B-cell activation and proliferation in these patches and inhibit subsequent production and leakage of Gd-IgA1 into the systemic circulation. Glomerular mesangial deposition of Gd-IgA1 resulting in nephritis and loss of renal function can thereby be prevented.

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 suggested to be a safe and well-tolerated steroid formulation for adjunctive therapy to ACEI 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 3b, multicenter, open-label extension (OLE) study to evaluate the efficacy and safety of Nefecon treatment in patients with IgAN who have completed the Phase 3 Study Nef-301 and continue to be treated with a stable dose of RAS inhibitor therapy (ACEIs and/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 can, by directing the release of budesonide to the distal part of the small intestine, achieve a local pharmacological effect. 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 ARBs 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 ACEIs and/or ARBs, will be favorable.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives are the following:

- To assess the effect of 9 months of retreatment with Nefecon on urine protein to creatinine ratio (UPCR) and estimated glomerular filtration rate (eGFR) in patients who completed Study Nef-301 with Nefecon treatment; and
- To assess the effect of 9 months of treatment with Nefecon on UPCR and eGFR in patients who completed Study Nef-301 with placebo treatment.

2.2 Secondary Objectives

The secondary objectives are the following:

- To assess the safety and tolerability of 9 months of retreatment with Nefecon in patients who completed Study Nef-301 with Nefecon treatment;
- To assess the safety and tolerability of 9 months of treatment with Nefecon in patients who completed Study Nef-301 with placebo treatment;
- To assess the effect of 9 months of retreatment with Nefecon on additional aspects of renal function in patients who completed Study Nef-301 with Nefecon treatment; and
- To assess the effect of 9 months of treatment with Nefecon on additional aspects of renal function in patients who completed Study Nef-301 with placebo treatment.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 3b, multicenter, OLE study to evaluate the efficacy and safety of Nefecon treatment in patients with IgAN who have completed the Phase 3 Study Nef-301 and continue to be treated with a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs). Patients who previously received Nefecon in Study Nef-301 will receive retreatment, whereas patients who previously received placebo in Study Nef-301 will be treatment naïve to Nefecon. During Study Nef-301 OLE, the patients and Investigators will remain blinded to treatment given in Study Nef-301.

Assuming that 75% of the patients who have completed Study Nef-301 will enter Study Nef-301 OLE, the total number of patients to be included is estimated to be approximately 250 patients, but up to 360 patients may be enrolled.

Preferably, Visit 17a in Study Nef-301 should be combined with Visit 1 in Study Nef-301 OLE, and Visit 17b in Study Nef-301 should be combined with Visit 2 in Study Nef-301 OLE. If the visits are not combined, Visit 3 in Study Nef-301 OLE must occur within 3 months after Visit 17b in Study Nef-301.

Patients who do not meet all of the eligibility requirements may be rescreened in Study Nef-301 OLE within 3 months after Visit 17b in Study Nef-301. Patients who do not meet all of the eligibility requirements within this 3-month period will be screen failures and will not be followed any further.

In addition to meeting all other eligibility criteria, patients must have proteinuria based on 2 consecutive measurements separated by at least 2 weeks and calculated by the central laboratory showing either ≥1 g/day (≥1000 mg/day) or UPCR ≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements. Patients must also have eGFR ≥30 mL/min per 1.73 m^2 using the CKD-EPI formula.

During Study Nef-301 OLE, patients will receive Nefecon 16 mg/day for a 9-month period. The 16 mg/day dose may be reduced to 8 mg/day if clinically relevant adverse events (AEs) develop during the 9-month Treatment Period that the Investigator considers related to the study drug and that mandate dose reduction.

From the first day of dosing, a telephone visit will occur at 1 month, and onsite visits will occur at 3, 6, and 9 months. After completing 9 months of study drug treatment, patients will enter the 2-week Tapering Period with Nefecon 8 mg/day. To perform replicate laboratory sampling, an onsite visit will occur 14 to 35 days after the 9-month visit. An onsite follow-up visit will also occur at 12 months.

Patients will remain on a stable dose of RAS inhibitor therapy (ACEIs and/or ARBs) throughout the study. If a patient receives rescue treatment (systemic steroids and/or immunosuppressive treatment), the patient will be withdrawn from Nefecon treatment and continue with study visits for a total of 12 months follow-up after first dose.

Patients who prematurely discontinue Nefecon at 16 mg/day should have the dose reduced to 8 mg/day for 2 weeks, if feasible, to prevent adrenal insufficiency.

Unless a patient withdraws his/her consent to participate in the study, all patients should complete the remaining study visits (especially at 9 and 12 months), regardless of whether they are still receiving study drug.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

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

1. Completed Study Nef-301, defined as Part A (9-month study drug treatment [Nefecon 16 mg/day or placebo] and 3-month follow-up) and Part B (12-month follow-up);
2. Completed Visit 17b in Study Nef-301 within 3 months before Study Visit 3;
3. 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 KDIGO guidelines[21] (see Appendix C). A stable dose is defined as a dose within 25% of the dose at Visit 17a or 17b in Study Nef-301; and
4. Willing and able to provide written informed consent at screening (at the latest).

In addition, patients must meet all of the following inclusion criteria prior to the start of study drug treatment:

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/day (≥1000 mg/day) in 2 consecutive measurements; or
   - UPCR ≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements; and
6. eGFR ≥30 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. Had a dose reduction to Nefecon 8 mg/day in Study Nef-301;
2. Systemic diseases that may cause mesangial IgA deposition including, but not limited to, Henoch Schönlein purpura, systemic lupus erythematosus, dermatitis herpetiformis, and ankylosing spondylitis;
3. Patients who have undergone a kidney transplant;
4. Patients with presence of other glomerulopathies (e.g., C3 glomerulopathy and/or diabetes nephropathy);
5. Patients with nephrotic syndrome (i.e., proteinuria >3.5 g/day and with serum albumin <3.0 g/dL, with or without edema);
6. Patients with acute, chronic, or latent infectious disease including hepatitis, tuberculosis (TB), human immunodeficiency virus (HIV), and chronic urinary tract infections;
7. Patients with liver cirrhosis, as assessed by the Investigator;

8. 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]);
9. Patients with history of unstable angina, class III or IV congestive heart failure, and/or clinically significant arrhythmia, as judged by the Investigator;
10. 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 1 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);
11. 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;
12. Patients with known osteoporosis in the medium- or high-risk category according to the 2010 American College of Rheumatology recommendations (see Appendix D). 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 D);
13. Patients with known glaucoma, known cataract(s), and/or history of cataract surgery, unless the surgery was performed on both eyes;
14. 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;
15. Patients with hypersensitivity to budesonide or any component of the study drug formulation;
16. Patients with previous severe adverse reactions to steroids, including psychotic symptoms, mood disorders, or suicidal ideation, as assessed by the Investigator;
17. Patients who have received rescue therapy with systemic immunosuppressants, including GCSs, during Study Nef-301;
18. Patients who have been treated with any systemic GCSs within the 3 months before screening;
19. Patients who have been treated with any systemic GCSs within the 12 months before screening 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;
20. Patients taking potent inhibitors of cytochrome P450 3A4 (CYP3A4);
21. Current or prior (within the past 2 years) alcohol or drug abuse;
22. Patients unwilling or unable to meet the requirements of the protocol;
23. Other medical or social reasons for exclusion at the discretion of the Investigator;
24. Life expectancy <5 years;
25. Females who are pregnant, breastfeeding, or unwilling to use highly-effective contraception during 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

26. 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.

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, proteinuria, and creatinine at 9 months. 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 electronic case report form (eCRF).

Unless a patient withdraws his/her consent to participate in the study, all patients should complete the remaining study visits (especially at 9 and 12 months), regardless of whether they are still receiving study drug.

4.3.1 Withdrawal From the Study

Participation of a patient may be permanently discontinued for any of the following reasons:

- The patient requests discontinuation and withdraws consent from the study for any follow-up; or
- The study is terminated by the Sponsor or the regulatory authority.

For patients who are withdrawn from the study, 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 10 procedures (see Section 6.4.1 and Appendix A).

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 at 9 and 12 months) despite discontinuation of study drug.

Patients who prematurely discontinue Nefecon at 16 mg/day should have the dose reduced to 8 mg/day for 2 weeks, if feasible, to prevent adrenal insufficiency (see Section 5.5.3).

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

- Use of rescue treatment (systemic steroids and/or immunosuppressive treatment);
- 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 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.

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 telephone 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 Rescreening Procedures

Patients who do not meet all of the eligibility requirements defined in Sections 4.1 and 4.2 may be rescreened in Study Nef-301 OLE within 3 months after Visit 17b in Study Nef-301. Patients who do not meet all of the eligibility requirements within this 3-month period will be screen failures and will not be followed any further.

If the patient will be rescreened more than once, this must be discussed and agreed upon with the Medical Monitor. All rescreened patients must be reconsented and sign a new Informed Consent Form (ICF) prior to completion of any rescreening study procedures. Rescreened patients will be assigned a new patient number at the time of rescreening 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 rescreened patient's new eCRF casebook will contain a reference to the patient's previous identification number(s).

5 STUDY TREATMENTS

5.1 Treatment Groups

Patients will receive Nefecon 16 mg/day for a 9-month period. The 16 mg/day dose may be reduced to 8 mg/day if clinically relevant AEs develop during the 9-month Treatment Period that the Investigator considers related to the study drug and that mandate dose reduction.

After completing 9 months of study drug treatment, patients will enter the 2-week Tapering Period with Nefecon 8 mg/day to prevent adrenal insufficiency. See Section 5.5.3. Patients will then enter the 3-month Follow-up Period.

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 distal part of the small intestine 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 and Nefecon 8 mg and 16 mg were given daily for 9 months, the Nefecon 16 mg/day dose was selected for Phase 3. Nefecon treatment at doses of up to 16 mg/day 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

This is an open-label study. All patients will receive Nefecon treatment for 9 months.

During Study Nef-301 OLE, the patients and Investigators will remain blinded to treatment given in Study Nef-301.

5.4 Breaking the Blind

Procedures for breaking the blind are not applicable for the current study (Nef-301 OLE).

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, with black printing "CAL10 4MG," 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 with a sugar sphere as the core. The inner coating layer contains the active substance, and the outer coating layer is a prolonged-release polymer coating that controls the rate of release of the active substance once the capsule has dissolved.

Nefecon 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 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

Interactive Response Technology (IRT) will trigger the first shipment of study drug to the site for the patient. The Investigator (or his/her designee) will dispense the study drug to the patient. 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 6 and 7.

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.

5.5.3 Study Drug Administration

Nefecon 16 mg (four 4 mg budesonide modified-release capsules QD) will be administered orally for 9 months during the Treatment Period.

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 at least 1 hour before breakfast. The capsules must be swallowed whole and may not be chewed or crushed.

The 16 mg/day dose may be reduced to 8 mg/day if clinically relevant AEs develop during the 9-month Treatment Period 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 dose. If a dose reduction is made, then the dose should not be increased back to 4 capsules QD (Nefecon 16 mg).

After completing 9 months of study drug treatment, the daily dose of study drug will be reduced from 4 capsules QD (Nefecon 16 mg) to 2 capsules QD (Nefecon 8 mg) for 2 weeks to prevent adrenal insufficiency (Tapering Period). Patients who have their daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg) due to safety and/or tolerability reasons during the 9-month Treatment Period will remain on this dose during the 2-week Tapering Period. Patients who prematurely discontinue study drug while taking 4 capsules QD (Nefecon 16 mg) should have the daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg) for 2 weeks, if feasible, to prevent adrenal insufficiency.

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) are prohibited during the study. Herbs for medicinal use, including Eastern herbs and Eastern traditional medicines, with a known effect on the immune system (e.g., *Tripterygium wilfordii* or ginseng) or with a known effect on proteinuria or creatinine, are not allowed during the study. Patients should be encouraged to not use herbs for medicinal use, including Eastern herbs and Eastern traditional medicines, during the study; however, if used, they should be recorded as concomitant medications. See Appendix E for additional information on immunosuppressive drugs.

Potent inhibitors of CYP3A4 (e.g., ketoconazole) are prohibited during treatment with study drug. See the US Food and Drug Administration website for additional examples.[29] During this time, patients should also be instructed to avoid grapefruit and grapefruit juice.

If a patient receives rescue treatment (systemic steroids and/or immunosuppressive treatment), the patient will be withdrawn from Nefecon treatment and continue with study visits for a total of 12 months follow-up after first dose.

5.6.2 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.

5.6.3 Documentation of Prior and Concomitant Medication Use

Medications taken within 3 months prior to Study Visit 1 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 Eastern herbs and Eastern traditional medicines, should be recorded as concomitant medications.

Patients are required to continue 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 KDIGO guidelines during the study.[21] A stable dose is defined as a dose within 25% of the dose at Visit 17a or 17b in Study Nef-301. Therefore, RAS inhibitor therapies (ACEIs and/or ARBs) must be recorded.

5.6.4 Dietary and Lifestyle Recommendations

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

- 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

The Schedule of Procedures is provided in Table 1 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, the current, approved ICF must be signed and dated by the patient. See Section 11.3 for more information.

6.2 Screening Period (Study Visits 1 to 3)

6.2.1 Study Visit 1

Preferably, Visit 17a in Study Nef-301 should be combined with Visit 1 in Study Nef-301 OLE. If the visits are combined, procedures do not need to be duplicated.

If the visits are not combined, Visit 3 in Study Nef-301 OLE must occur within 3 months after Visit 17b in Study Nef-301.

The following procedures will be performed at Study Visit 1:

- Obtain written informed consent, if not obtained prior to Study Visit 1;
- Update demographic information and medical/surgical history;
- Conduct eligibility assessment based on inclusion and exclusion criteria;
- Conduct laboratory eligibility assessment based on laboratory values from Visit 17a and/or 17b in Study Nef-301;
- 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);
  - Serum pregnancy test (WOCBP 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;
- Complete the Short Form 36 (SF-36) quality of life assessment;

- 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 24-hour urine collection; and
- Assess AEs, including adverse events of special interest (AESIs) and SAEs, and concomitant medications and procedures.

6.2.2 Study Visit 2

Preferably, Visit 17b in Study Nef-301 should be combined with Visit 2 in Study Nef-301 OLE. If the visits are not combined, Study Visit 2 must occur within 2 weeks after Study Visit 1.

The following procedures will be performed at Study Visit 2:

- Obtain the 24-hour urine sample, including cortisol (sample collected by the patient during the 24-hour period prior to the scheduled study visit); and
- Supply the patient with new container(s) for the next 24-hour urine collection.

6.2.3 Study Visit 3 (2 to 4 Weeks After Study Visit 2)

Study Visit 3 must occur 2 to 4 weeks, inclusive, after Study Visit 2 in order to collect the second proteinuria measurement 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 onsite at Study Visit 3:

- Update demographic information and medical/surgical history;
- 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 the 24-hour urine sample, including cortisol (sample collected by the patient during the 24-hour period prior to the scheduled study visit);
- Collect fresh urine sample for the following assessments:
  - Urinalysis; and
  - Pregnancy test via a local urine assessment (WOCBP only);
- Collect blood samples for the following assessments:
  - Hematology (including HbA1c), serum chemistry (including eGFR [CKD-EPI] and fasting blood glucose), and fasting lipid panel; and
- Assess AEs, including AESIs and SAEs, and concomitant medications and procedures.

6.3 Treatment Period (Study Visits 4 to 9 – Study Day 1 to Study Month 9)

After confirming all eligibility criteria (laboratory values from Study Visits 1, 2, 3, etc.) (eGFR values from Study Visits 1 or 3 must be ≥30 mL/min per 1.73 m^2 for the patient to be eligible [see Section 4.1]), IRT 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 6 and 7.

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

6.3.1 Study Visit 4 (Study Day 1)

Study Visit 4 must occur within 4 weeks after Study Visit 3.

The following procedures will be performed at Study Visit 4 (Study Day 1):

- Update demographic information and medical/surgical history;
- 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 fresh urine sample for the pregnancy test via a local urine assessment (WOCBP only);
- Dispense study drug and instruct patient on study drug administration;
- Administer the first dose of study drug;
- Capture the occurrence of dialysis or kidney transplantation;
- Supply the patient with the container(s) for 24-hour urine collection; and
- Assess AEs (occurring after administration of the first dose of study drug), including AESIs and SAEs, and concomitant medications and procedures.

6.3.2 Telephone Study Visit 5 (Study Month 1)

The following procedures will be performed at Study Visit 5 (Study Month 1), which will be conducted with the patient by telephone:

- Capture the occurrence of dialysis or kidney transplantation; and
- Assess AEs, including AESIs and SAEs; concomitant medications and procedures; and treatment compliance.

6.3.3 Study Visits 6 (Study Month 3), 7 (Study Month 6), and 8 (Study Month 9)

The following procedures will be performed onsite at Study Visits 6 (Study Month 3), 7 (Study Month 6) and 8 (Study Month 9):

- Dispense study drug and instruct patient on study drug administration (Study Visits 6 and 7 only);
- Collect study drug from previous visit, assess for treatment compliance, and perform drug accountability;

- 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 the 24-hour urine sample, including cortisol (sample collected by the patient during the 24-hour period prior to the scheduled study visit);
- Supply the patient with new container(s) for the next 24-hour urine collection;
- Collect fresh urine sample for the following assessments:
  - Urinalysis; and
  - Pregnancy test via a local urine assessment (WOCBP only);
- Collect blood samples for the following assessments:
  - Hematology (including HbA1c) and serum chemistry (including eGFR [CKD-EPI]);
- Capture the occurrence of dialysis or kidney transplantation; and
- Assess AEs, including AESIs and SAEs, and concomitant medications and procedures.

After completing 9 months of study drug treatment, patients will enter the 2-week Tapering Period to prevent adrenal insufficiency. During the 2-week Tapering Period, the daily dose of study drug will be reduced from 4 capsules QD (Nefecon 16 mg) to 2 capsules QD (Nefecon 8 mg). Patients who have their daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg) due to safety and/or tolerability reasons during the 9-month Treatment Period will remain on this dose during the 2-week Tapering Period.

6.3.4 Study Visit 9 (14 to 35 Days After Study Visit 8) (For Replicate Laboratory Sampling)

The following procedures will be performed onsite at Study Visit 9 (14 to 35 days after Study Visit 8) (for replicate laboratory sampling):

- Collect blood samples for the following assessments:
  - Hematology (including HbA1c) and serum chemistry (including eGFR [CKD-EPI]);
- Obtain the 24-hour urine sample, including cortisol (sample collected by the patient during the 24-hour period prior to the scheduled study visit);
- Supply the patient with new container(s) for the next 24-hour urine collection; and
- Assess AEs, including AESIs and SAEs, and concomitant medications and procedures.

6.4 Follow-up Period (Study Visit 10 – Study Month 12)

Following completion of the Treatment Period, patients will enter the 3-month Follow-up Period.

6.4.1 Study Visit 10 (Study Month 12)

The following procedures will be performed onsite at Study Visit 10 (Study Month 12) (End of Study Visit):

- Collect study drug from previous visit, assess for treatment compliance, and perform drug accountability;

- Obtain body weight;
- Perform a complete physical examination;
- Obtain the 24-hour urine sample, including cortisol (sample collected by the patient during the 24-hour period prior to the scheduled study visit);
- Collect fresh urine sample for the following assessments:
  - Urinalysis; and
  - Pregnancy test via a local urine assessment (WOCBP only);
- Collect blood samples for the following assessments:
  - Hematology (including HbA1c) and serum chemistry (including eGFR [CKD-EPI]);
- Complete the SF-36 quality of life assessment;
- Capture the occurrence of dialysis or kidney transplantation; and
- Assess AEs, including AESIs and SAEs, and concomitant medications and procedures.

For patients who are withdrawn from the study, 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 10 procedures. See Section 4.3.

7 EFFICACY ASSESSMENTS

7.1 Primary Efficacy Endpoints

The primary efficacy endpoints will include the following:

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

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will include the following:

- Ratio of urine albumin to creatinine ratio (UACR) at 9 months compared to baseline;
- SF-36 quality of life assessment at 12 months compared to baseline;
- Proportion of patients with microhematuria at 9 months compared to baseline;
- Proportion of patients receiving rescue treatment and time to receiving rescue treatment;
- Proportion of patients on dialysis, undergoing kidney transplantation, or with eGFR <15 mL/min per 1.73 m^2; and
- Cortisol suppression at 9 and 12 months, measured as urinary cortisol excretion over 24 hours compared to baseline.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

Ongoing AEs from the patient's involvement in Study Nef-301 will continue to be followed in Study Nef-301 OLE and captured as ongoing AEs. New AEs will be collected from Study Visit 1 through 12 months after the first dose of study drug in Study Nef-301 OLE. New treatment-emergent AEs will be those starting with Study Nef-301 OLE dosing (Study Visit 4).

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.

AEs, including AESIs and SAEs, will be monitored and documented by the Investigator (or his/her designee) from Study Visit 1 until 12 months after the first dose of study drug, inclusive, regardless of whether the patient discontinues the study prematurely. Patients should be instructed to report any AE that they experience to the Investigator (or his/her designee).

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 at Study Visit 1 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 at Study Visit 1 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)?

AESIs may or may not constitute an SAE. However, all types of AESIs must be reported to Medpace Clinical Safety 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 Study Visit 1 until 12 months after the first dose of study drug, inclusive, regardless of whether the patient discontinues the study prematurely.

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 Study Visit 1 until 12 months after the first dose of study drug 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 (telephone

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 in Study Nef-301 OLE, or exist before dosing in Study Nef-301 OLE but worsen in severity after dosing in Study Nef-301 OLE;
- AEs leading to study drug discontinuation;
- AESIs (severe infections requiring hospitalization, new onset of diabetes, 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 Study Visits 1 and 3, 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 Completers Analysis Set will include all patients who receive Nefecon for 9 months.

The Full Analysis Set will include all patients who receive at least 1 dose of Nefecon, with at least 1 efficacy measurement (UPCR or eGFR) collected after dosing.

The Safety Analysis Set will include all patients who have received at least 1 dose of study drug at the time of the analysis.

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

No formal statistical analyses will be performed. eGFR, UPCR, and UACR are expected to be log-normally distributed; therefore, the ratio of 9 months to baseline for eGFR, UPCR, and UACR will be summarized using geometric mean and its associated 95% confidence interval. If outlying data are present for an endpoint, a supplementary description of the data will be performed using a robust regression approach. Separate summaries will be provided according to whether the patient received Nefecon or placebo in Study Nef-301.

Each efficacy variable will be summarized in 2 different analysis sets, the Completers Analysis Set and the Full Analysis Set. Any data recorded after rescue treatment will not be included in the analysis for either analysis population.

Baseline eGFR, UPCR, and UACR will be defined as the geometric mean of the 2 consecutive measurements prior to dosing. The 9-month eGFR, UPCR, and UACR values will be defined as the geometric mean of the values recorded at Study Visits 8 and 9.

For UPCR, the primary analysis will calculate the mean of the change from baseline in log(UPCR), with results back-transformed to provide a geometric mean ratio and 95% confidence interval. For eGFR, due to the possible presence of outlying data, the primary analysis will use the same approach but deriving the mean change and its confidence interval using a robust regression model.

If a reasonable proportion of patients do not provide 9-month data, a sensitivity analysis will be performed by fitting a mixed model that incorporates any data recorded at 3, 6, and 12 months with different assumptions made about efficacy after discontinuation of treatment.

9.2.2 Analysis of Safety

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 will be summarized by system organ class. In addition, the time to first occurrence of the most common event will be summarized using cumulative incidence plots. Safety data will be summarized or listed separately for the period between screening and the first dose of study drug. 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.

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

9.2.3 Sample Size Determination

All patients who have completed Study Nef-301 and meet all eligibility criteria will be able to participate in Study Nef-301 OLE. Assuming that 75% of the patients who have completed Study Nef-301 will enter Study Nef-301 OLE, the total number of patients to be included is estimated to be approximately 250 patients, but up to 360 patients may be enrolled.

In Study Nef-202, a completed, randomized, double-blind study of Nefecon in comparison to placebo, the standard deviation for the change from baseline in log(UPCR) and log(eGFR) was 0.59 and 0.18, respectively. If 125 patients are recruited within each efficacy group (prior Nefecon or prior placebo) and a 25% reduction (ratio of 0.75) in UPCR is observed in this study, the upper 95% confidence limit for the baseline ratio will extend to 0.83. Likewise, if there is no change in eGFR observed in this study (ratio of 1), the lower 95% confidence limit for the baseline ratio will extend to 0.97. Therefore, this study will provide a sufficiently precise estimate of the efficacy of Nefecon according to whether the patient previously received Nefecon or placebo.

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 (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 Institutional Review Board (IRB)/Independent Ethics Committee (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 Informed Consent

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 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.

All rescreened patients must be reconsented and sign a new ICF prior to completion of any rescreening study procedures.

11.4 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.

11.5 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.

11.6 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.

11.7 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.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to Calliditas to permit Calliditas to fulfil 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.

11.9 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.

11.10 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.

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.
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. US Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2. Accessed 10 June 2020.

APPENDIX A: SCHEDULE OF PROCEDURES

Table 1. Schedule of Procedures

Study Period	Screening			Treatment							Follow-Up
Study Visit	(17a) 1	(17b) 2	3[1]	NA	4[2]	5	6	7	8	9	10/EOS[3]
Study Day or Month	See footnote[4]				1d	1m	3m	6m	9m	9m	12m
Visit Window (Days)						±7	±7	±7	±7	14-35 days after Visit 8	±7
Procedure											
Visit conducted by telephone						X					
Informed consent (if not yet obtained)	X										
Update demographics and medical/surgical history	X		X		X						
Eligibility criteria assessment	X		X	X							
Contact IRT to trigger study drug shipment[5]				X							
Concomitant medications and procedures	X[6]		X		X	X	X	X	X	X	X
AE assessment (incl. AESIs, SAEs)	X		X		X	X	X	X	X	X	X
Physical examination	X										X
Vital signs[7]	X		X		X		X	X	X		
Body weight and height[8]	X				X						X
Hematology (incl. HbA1c)[9]	X		X				X	X	X	X	X
Serum chemistry (incl. eGFR [CKD-EPI])[9,10]	X		X				X	X	X	X	X
HIV, TB, HBV, and HCV[11]	X										
Drug and alcohol screen (urine)	X										
Fasting lipid profile			X								
Urinalysis[12]	X		X				X	X	X		X
24-hour urine collection (incl. cortisol)		X	X				X	X	X	X	X
Supply 24-hour urine container(s)	X	X			X		X	X	X	X	
Pregnancy test[13]	X		X		X		X	X	X		X
FSH[14]	X										
Dispense study drug and instruct patient on study drug administration					X		X	X			
Start of study drug[15]					X						

See footnotes at the end of the Schedule of Procedures table

Table 1. Schedule of Procedures (Continued)

Study Period	Screening			Treatment							Follow-Up
Study Visit	(17a) 1	(17b) 2	3[1]	NA	4[2]	5	6	7	8	9	10/EOS[3]
Study Day or Month	See footnote[4]				1d	1m	3m	6m	9m	9m	12m
Visit Window (Days)						±7	±7	±7	±7	14-35 days after Visit 8	±7
Procedure											
Begin 2-week Tapering Period[16]									X		
Collect study drug from previous visit							X	X	X		X
Study drug accountability and compliance assessment[17]						X	X	X	X		X
SF-36 QoL assessment	X										X
Capture dialysis or kidney transplant					X	X	X	X	X		X
Dietary and lifestyle recommendations[18]	X										

Note: Prior to conducting any study-related activities, the current, approved Informed Consent Form must be signed and dated by the patient.

1. Patients will be required to fast for at least 10 hours prior to Study Visit 3.
2. Study Visit 4 must occur within 4 weeks after Study Visit 3.
3. See Section 4.3 for additional details related to withdrawal criteria. For patients who are withdrawn from the study, 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 10 procedures.
4. Preferably, Visit 17a in Study Nef-301 should be combined with Visit 1 in Study Nef-301 OLE. If the visits are combined, procedures do not need to be duplicated. If the visits are not combined, Visit 3 in Study Nef-301 OLE must occur within 3 months after Visit 17b in Study Nef-301. Preferably, Visit 17b in Study Nef-301 should be combined with Visit 2 in Study Nef-301 OLE. If the visits are not combined, Study Visit 2 must occur within 2 weeks after Study Visit 1. Study Visit 3 must occur 2 to 4 weeks, inclusive, after Study Visit 2 in order to collect the second proteinuria measurement to determine eligibility.
5. After confirming all eligibility criteria (laboratory values from Study Visits 1, 2, 3, etc.) (eGFR values from Study Visits 1 or 3 must be ≥30 mL/min per 1.73 m^2 for the patient to be eligible), IRT 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 6 and 7.
6. Medications taken within 3 months prior to Study Visit 1 and concomitant medications and therapies will be recorded in the eCRFs.
7. 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 Study Visits 1 and 3, 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. Height will only be collected at Study Visit 1.
9. See Appendix B for the complete list of analytes.
10. The central laboratory will calculate the eGFR using the CKD-EPI formula.
11. If the patient is rescreened, HBV, HCV, HIV, and TB screenings should not be repeated if done as part of the study within the last 12 months.
12. 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.
13. For women of childbearing potential only. A serum pregnancy test will only be performed at Study Visit 1. A pregnancy test via a local urine assessment will be performed at all other applicable study visits.
14. Postmenopausal women will have a confirmatory FSH test performed at Study Visit 1.
15. 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 at least 1 hour before breakfast.

16. During the 2-week Tapering Period, the daily dose of study drug will be reduced from 4 capsules QD (Nefecon 16 mg) to 2 capsules QD (Nefecon 8 mg). Patients who have their daily dose of study drug reduced to 2 capsules QD (Nefecon 8 mg) due to safety and/or tolerability reasons during the 9-month Treatment Period will remain on this dose during the 2-week Tapering Period.
17. Only treatment compliance will be assessed during study visits conducted by telephone.
18. 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; d = day(s); eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EOS = End of Study; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; incl. = including; IRT = Interactive Response Technology; m = month(s); NA = not applicable; OLE = open-label extension; QD = once per day; QoL = quality of life; SAE = serious adverse event; SF-36 = Short Form 36; TB = tuberculosis.

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 Study 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 ($eGFR = 141 \times \min(SCr/K, 1)^{\alpha} \times \max(SCr/K, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$ 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	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: RENIN-ANGIOTENSIN SYSTEM INHIBITOR AND OTHER ANTIHYPERTENSIVE THERAPY RECOMMENDATIONS ACCORDING TO THE 2012 KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES GUIDELINES

Patients must continue 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.[1] A stable dose is defined as a dose within 25% of the dose at Visit 17a or 17b in Study Nef-301.

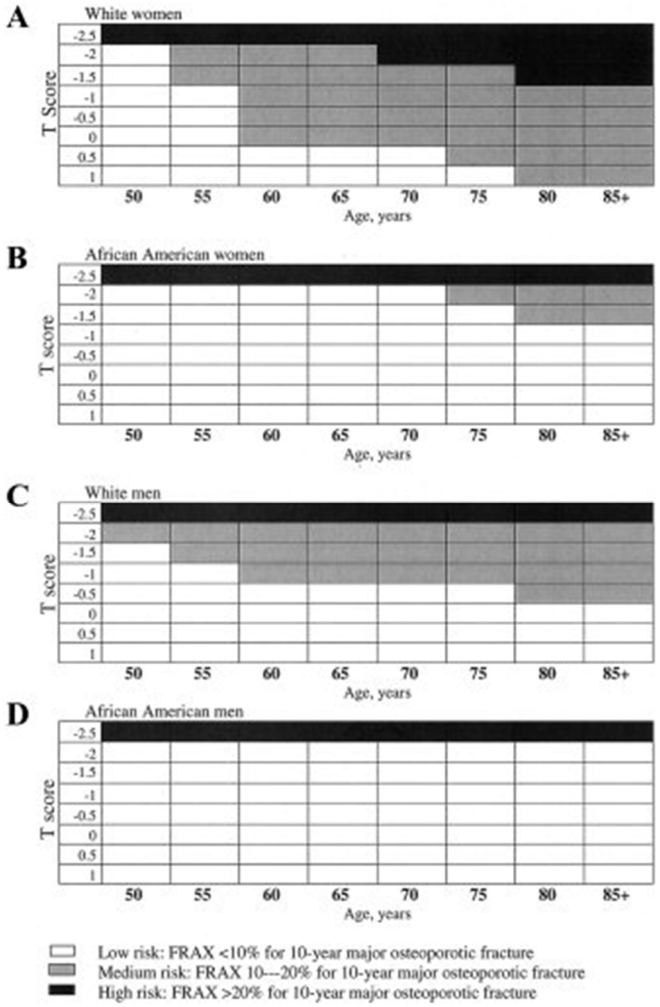
The following are recommendations for optimization and maintenance of RAS/antihypertensive therapy that are in line with the 2012 KDIGO guidelines[1] and should be followed throughout the study:

- 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/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 D: 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 E: IMMUNOSUPPRESSIVE DRUGS OTHER THAN GLUCOCORTICOIDS

Systemic immunosuppressive drugs (including glucocorticoids) are prohibited during the study. Systemic immunosuppressive drugs will include, but will not be limited to the following:

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