OMEROS CORPORATION

CLINICAL PROTOCOL

PROTOCOL NO. OMS721-IGA-001
Amendment 07

EUDRACT: 2018-000075-33

Investigational New Drug
NARSOPLIMAB [redacted]

PHASE 3

A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of the Safety and Efficacy of OMS721 in Patients with Immunoglobulin A (IgA) Nephropathy (ARTEMIS – IGAN)

19 June 2023

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Date

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Date

1.1. Investigator Agreement

I have read Omeros Protocol No. OMS721-IGA-001 Amendment 07 and agree to conduct the study as described in this protocol and to provide the necessary assurances that this study will be conducted according to the stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

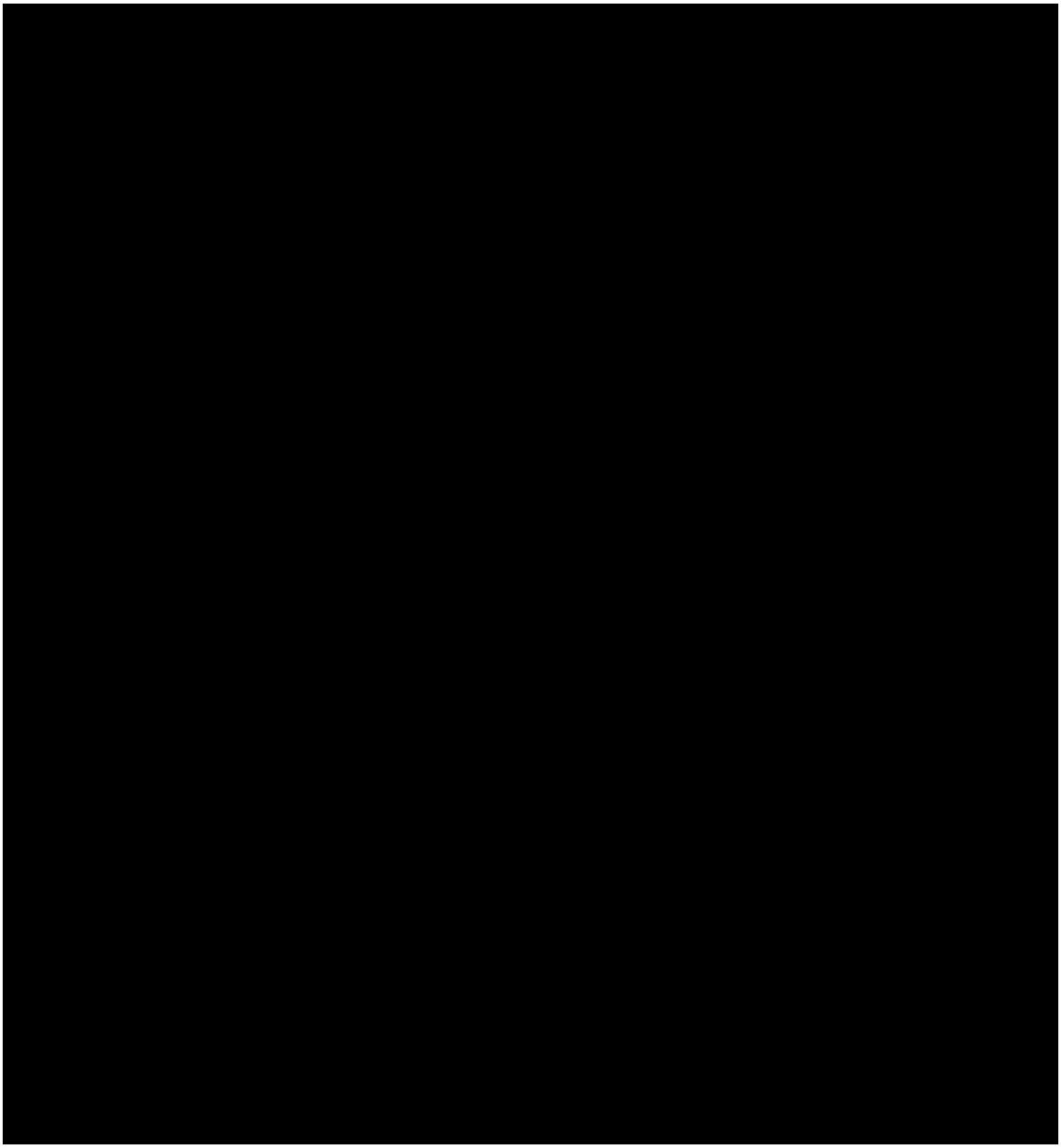
_____

Principal Investigator Name

_____ _____

Principal Investigator Signature Date

1.2. Contact Information



1.3. Revision History

Original Protocol Dated	11 January 2018
Amendment 01 Dated	19 February 2019
Amendment 02 Dated	11 May 2020 (never released)
Amendment 03 Dated	01 June 2020
Amendment 03 Addendum Dated	12 September 2022
Amendment 04 Dated	04 November 2022 (only released where required)
Amendment 05 Dated	07 April 2023 (never released)
Amendment 06 Dated	09 May 2023 (never released)
Amendment 07 Dated	19 June 2023

2. SYNOPSIS

Name of Sponsor/Company: Omeros Corporation	
Name of Investigational Product: Narsoplimab [redacted]	
Name of Active Ingredient(s): Narsoplimab (MASP-2 monoclonal antibody)	
Title of Study: A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of the Safety and Efficacy of OMS721 in Patients with Immunoglobulin A (IgA) Nephropathy **(ARTEMIS – IGAN)**	
Planned Number of Clinical Study Center(s): Approximately 200 study sites in North America, South America, Europe, Australia, and Asia	
Expected Duration of Study: The entire duration of study for each patient is expected to be approximately 112 weeks, comprising a 2-year study including follow up	**Phase of Development:** Phase 3

Key Objectives:

Primary Objective:

- To evaluate the effect of narsoplimab on 24-hour UPE in IgA nephropathy (IgAN) patients with high baseline proteinuria (high-risk proteinuria group; 24-hour urine protein excretion (UPE) ≥ 2 g/day) assessed at 36 weeks from baseline

Secondary Objectives:

To evaluate the effect of narsoplimab in patients with IgAN on:

- Renal function as determined by the rate of change in estimated glomerular filtration rate (eGFR) up to 96 weeks from baseline in patients with high baseline proteinuria (the high-risk proteinuria group; 24-hour UPE ≥ 2 g/day)
- Proteinuria assessed by 24-hour UPE at 36 weeks from baseline in the all-patients population
- Renal function as determined by the rate of change in eGFR at up to 96 weeks from baseline in the all-patients population
- Durability of proteinuria response from 36 weeks in patients with high baseline proteinuria (the high-risk proteinuria group; 24-hour UPE ≥ 2 g/day) and in the all-patients population
- Change from baseline in log-transformed 24-hour UPE at Week 36 in the all-patients population (24-hour UPE > 1 g/day)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 48 weeks in patients with ≥ 2 g/day UPE at baseline (high-risk proteinuria group)

- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 72 weeks in patients with ≥ 2 g/day UPE at baseline (high-risk proteinuria group)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 48 weeks in the all-patients population
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 72 weeks in the all-patients population
- Safety and tolerability in patients with high baseline proteinuria (the high-risk proteinuria group; 24-hour UPE ≥ 2 g/day) and in the all-patients population
- Pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of narsoplimab

Methodology:

This is a Phase 3, double-blind, randomized, placebo-controlled study in patients aged 18 years and above with a biopsy-confirmed diagnosis of IgAN and with 24-hour UPE that is > 1 g at baseline. Primary efficacy analysis will include the subset of patients with 24-hour UPE ≥ 2 g at baseline (the high-risk proteinuria group). During the study, all patients will continue optimized renin-angiotensin system (RAS) blockade. The study consists of five periods: Screening, Run-In, Initial Treatment (Weeks 1-12), Response Evaluation (Weeks 13-36), and Follow-Up (Weeks 37 to Week 96/end-of-study [EOS]). The study duration for each patient is expected to last approximately 112 weeks.

A pre-planned blinded sample size re-estimation (SSRE) for UPE in the all-patients population was performed when 60% (168) of the planned number of patients (280) completed the Week 36 visit. The independent data monitoring committee (IDMC) statistician re-calculated the sample size using this adjusted variance and the same method as specified in Section 1.3.3 of the SAP. The log scale SD was estimated to be lower than anticipated and, hence, no change to sample size was made.

In addition, a conditional power-based SSRE for the key secondary endpoint of eGFR is planned in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day; N = at least 180) at the time of the primary endpoint analysis.

Special considerations have been added to protect patient safety during the COVID-19 pandemic:

When considering how to handle ongoing participation of patients in this clinical trial during the COVID-19 pandemic, patient safety is the highest priority. Study visit activities should be conducted in an environment that protects the patient from potential COVID-19 exposure. All study activities must be conducted in compliance with the advice and restrictions established by each institution, the IRB/IEC, and the respective local authorities. Restrictions imposed during this time may result in study visits and study treatment being unavoidably canceled, skipped, or delayed. Some study visits may be conducted remotely at the patient's home (if service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service) or virtually via telephone or video conference. Each

patient currently in study treatment should be evaluated for risk vs. benefit of continuing treatment within the framework of institutional guidelines and local regulations. If permitted by local authorities, the IRB/IEC, and the site/institution, and if the patient agrees, a patient in study treatment may complete the full treatment course. Patients who miss 2 or fewer study treatment visits due to COVID-19 restrictions may continue their treatment period after the site/institution allows study visits to re-commence. Patients who miss more than 2 consecutive study treatment visits due to COVID-19 restrictions will be contacted by the site via telephone to check for adverse events and changes in medications and to confirm patient safety. These telephone calls will occur every 4 weeks (+/- 7 days) or more frequently if needed.

After the site/institution allows study visits to re-commence, these patients may reinitiate study treatment. Prior to reinitiating treatment, patients will collect a 24-hour urine specimen. The 24-hour UPE results will be used to determine the next steps for the patient, as per the instructions below:

- If the 24-hour UPE result is > 1 g/day, the patient will be given the option to reinitiate treatment in the same treatment arm to which they were originally assigned. Before treatment is repeated, blood and urine will be collected for safety testing
- If the 24-hour UPE result is ≤ 1 g/day, the patient will not reinitiate treatment, but will continue in the protocol defined timepoints for further treatment assessments

Patients who test positive for COVID-19 must immediately discontinue infusions of study treatment. Re-initiation of study treatment will be considered on a case-by-case basis by the sponsor. No patients will be allowed to resume study treatment or attend any in-person study visits until at least 1 week after all COVID-19-related symptoms have resolved and the patient is allowed by applicable health authorities and the site/institution to attend in-person study visits.

Specific guidance for handling visits is provided in the full protocol.

Screening Period (Up to 28 days)

The Screening Period will last up to 28 days, during which patients will be evaluated for possible inclusion into the study. Patients who do not meet the screening criteria may be rescreened a minimum of 30 days after Screen Failure. Patients may be rescreened once, with additional rescreening allowed based on Medical Monitor approval.

Run-In Period (4 weeks to 12 weeks)

The aim of the 4-week to 12-week Run-In Period is to continue to evaluate patient eligibility for the trial, optimize compliance, and optimize background therapies, in particular to optimize blood pressure (BP) control and RAS blockade. Patients will not receive study treatment during the Run-In Period. All patients must be on maximum labeled or tolerated RAS blockade prior to randomization. The length of time patients will spend in the Run-In Period will be contingent on duration of their RAS blockade treatment and response, as noted below:

- Patients who have received treatment with angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) at maximum or near-maximum labeled or tolerated dose for 8 weeks or more prior to Screening and have stable BP control (i.e., have an unchanged dose regimen of BP medications for at least 4 weeks prior to Screening) will have a Run-In Period of 4 weeks, consisting of two study visits. Patients receiving Sparsentan for a minimum of 12 weeks prior to screening will continue on this drug in place of ACEi/ARB and spend 4 weeks in the Run-In Period.
- All other patients will have a Run-In Period of 12 weeks, consisting of four study visits.

During the entire study period, including the Run-In Period, patients will receive standard background therapy for IgAN, including RAS blockade to control BP according to current guidelines. All patients will receive ACE inhibitors and/or ARBs (if intolerant to ACE inhibitors) titrated to the maximum labeled or tolerated dose (whichever is reached first) according to local or national guidelines and/or the discretion of the Investigator. At every study visit, patients will be asked to confirm consistent use of RAS blockade medication and whether there have been any dosage changes since the last study visit.

During the Run-In Period, patients will have appropriate lifestyle changes initiated and medications optimized to attain/maintain a BP target of less than 125/75 mm Hg. Considering that some patients may not tolerate this target, there will be deference to the clinical judgment of the managing physician/Investigator regarding patients who have attained a stable maximum tolerable-dose regimen.

Clinical and laboratory evaluations conducted at the end of the Run-In Period will provide the baseline measurements for the study. Baseline proteinuria will be the mean of two 24-hour UPE measurements performed at the end of the Run-In Period, and the mean value should be > 1 g/day for the patient to be randomized. If a patient does not meet the criteria to enter the Initial Treatment Period, the patient may be rescreened after a minimum of 30 days have passed. During the Run-In Period and throughout the entire study, patients will be advised to avoid nonsteroidal anti-inflammatory drugs and any other nephrotoxic medicines.

Initial Treatment Period (Weeks 1-12)

Patients who are eligible to enter the Initial Treatment Period will be randomized in a double-blind manner equally into one of two groups: the placebo or active (narsoplimab) treatment group. Randomization will be stratified by the baseline eGFR level (≥ 30 to ≤ 45 mL/min/1.73 m^2 and > 45 mL/min/1.73 m^2) and by baseline UPE (> 1 to < 2 g/day and ≥ 2 g/day). During the Initial Treatment Period, starting at Treatment Visit 1 (T1, Week 1) patients will receive either narsoplimab (370 mg) or placebo administered intravenously (IV) once weekly for 12 weeks.

Response Evaluation Period (Weeks 13-36)

Following the 12-week Initial Treatment Period, patients will receive extended treatment with study drug if they meet the criteria detailed below.

Extended Treatment Criteria Post Week 12:

Patients who have a 24-hour UPE > 1 g at Treatment Visit 12 (T12, Week 12) will receive 6 additional weeks of treatment (extended treatment) according to their originally assigned treatment group in a blinded fashion. Please see Section 10.2.4, Extended Treatment Following Week 12, for guidance on handling Extended Treatment interruptions due to COVID-19 restrictions.

The Response Evaluation Period will consist of one study visit at Week 36, where 24-hour UPE and other laboratory measurements will be taken, and patients will be assessed for response.

Phone calls will occur at Weeks 16, 20, 24, 30, and 34. At the Week 24 and Week 30 timepoints, 24-hour UPEs will be collected to assess for response.

Patients who relapse at Week 24, Week 30, or Week 36 will require additional office visits to receive 6 weeks of relapse retreatment as detailed below.

Please see Section 10.2.7.1, Six-Week Relapse Retreatment (Response Evaluation Period), for guidance on handling 6-Week Relapse Retreatment interruptions due to COVID-19 restrictions.

Retreatment Criteria Post Weeks 24, 30, or 36

Relapsers: Relapsers are patients who show a response to treatment of at least 30% reduction from baseline proteinuria at any post-treatment assessment timepoint but subsequently demonstrate an increase in 24-hour UPE by ≥ 30% from the value of their lowest measured post-treatment UPE and have a 24-hour UPE > 1 g. Those who relapse at Week 24, Week 30, or Week 36 will require additional office visits to receive 6 weeks of relapse retreatment. Once a patient receives retreatment for relapse at Week 24, Week 30, or Week 36, the patient will not be given additional retreatment for relapse in the Response Evaluation Period. Please see Section 10.2.7.1, Six-Week Relapse Retreatment (Response Evaluation Period), for guidance on handling 6-Week Relapse Retreatment interruptions due to COVID-19 restrictions.

At Week 36, the clinical and laboratory evaluations conducted represent the primary efficacy measures.

Follow-Up Period (Weeks 37-96)

Following the Response Evaluation Period, all patients will enter the Follow-Up Period from Week 37 through Week 96. Visits will occur at Weeks 48, 72, and 96/EOS. Patients will be assessed for response and offered retreatment if they relapse after Week 48. Patients who relapse will be given weekly IV treatment for an additional 12 weeks according to the patient's randomized treatment assignment. Once a patient receives retreatment for relapse in the Follow-Up period, the patient will not be given additional retreatment for relapse. As Week 96 is the end-of-study visit, no relapse retreatment will be offered at that time.

Between visits, interim telephone contacts with patients will occur at Weeks 40, 44, 60, and 84 to monitor patient safety. Telephone contacts may be skipped if they overlap with a relapse retreatment visit.

All patients will continue optimized antihypertensive medication treatment and attempt to maintain optimized blood pressure throughout the study.

Rescue Therapy: A patient may be considered for rescue therapy (which may include corticosteroids or immunosuppressants) by the Investigator according to local practice if all the following conditions are met:

- It is recommended that the patient be in the study for over one year. However, rescue therapy may be administered if the patient has been in the study for less than one year, if clinically warranted
- Patient meets study eligibility criteria (other than eGFR ≥ 30), including 24-hour UPE > 1 g or 24-hour uPCR > 0.75, twice over an 8-week period
- Patient has 100% increase in 24-hour UPE from baseline and patient has a 30% decrease in eGFR from baseline, as measured twice over an 8-week period

The Investigator is strongly encouraged to contact the Medical Monitor to discuss the use of rescue therapy.

Rescue therapy for study patients is not encouraged given that there is very limited or no specific medication or treatment regimen approved for IgAN. However, if the Investigator feels that rescue therapy is required after discussing the case with the Medical Monitor, and the patient meets the above criteria, the patient may be managed per local practice at the Investigator's discretion. Patients requiring rescue therapy will be discontinued from study treatment and will continue to be followed in the study.

Open-Label Option for a Sub-Group of the High-Risk Proteinuria Group

Patients with 24-hour UPE > 2 g/day at baseline will be allowed to receive 12-weeks of open-label active drug (narsoplimab) on Week 72 (18 months post randomization) per protocol, provided they meet the conditions stipulated below:

- Patient has less than 30% reduction in UPE at the OL assessment visit when compared to baseline UPE, and
- Proteinuria is ≥ 3.0 g/day at 72 weeks from randomization, as confirmed by two measurements at least 2 weeks apart, but completed within 3 weeks, and
- Patient has worsening renal function, defined as a decline in eGFR of > 5 mL/min/m^2 from baseline

The Investigator is encouraged to contact the Omeros Medical Monitor to discuss the use of open-label treatment. Open-label treatment with narsoplimab will be administered IV once weekly for 12 weeks. Patients who receive treatment with open-label narsoplimab should continue to attend all study visits and complete all required study procedures. Neither the Investigator nor the patient who receives open-label treatment will be unblinded to the patient's original treatment assignment. Following the 12 weeks of open-label treatment, patients with 24-hour UPE > 1 g can receive 6 additional weeks of open-label treatment with narsoplimab (open-label extended treatment).

Number of Patients (Planned): Approximately 450 patients are to be enrolled in two groups of approximately 225 patients per arm.

Diagnosis and Main Criteria for Inclusion:

Key inclusion criteria include:

- Age 18 years or older at the onset of Screening
- Biopsy confirmed diagnosis of IgAN within 8 years prior to Screening or Run-In Visit 1
- Documented history of proteinuria of > 1 g/day within 6 months prior to Screening, or uPCR > 0.75 by spot urine, at Screening
- Mean of two proteinuria measurements > 1 g/day at baseline
- Estimated glomerular filtration rate of ≥ 30 mL/min/1.73 m^2 at Screening and baseline

Key exclusion criteria include:

- Treatment with immunosuppressants (e.g., azathioprine or cyclophosphamide), Chinese Traditional Medicine with immunosuppressive function, cytotoxic drugs, or eculizumab within 8 weeks prior to Screening, unless such treatment is given for indications other than IgAN
- Treatment with systemic corticosteroids within 8 weeks prior to Screening
- Uncontrolled BP, a systolic BP of > 150 mmHg and a diastolic BP of > 100 mmHg at rest despite the combination of two or more anti-hypertensives including ACE inhibiters, ARBs, or direct renin inhibitors
- Female patients who are pregnant, breast feeding, or planning to become pregnant up through 12 weeks after the last dose of study drug, including possible retreatments. Males who are planning to father children up through 12 weeks after the last dose of study drug, including possible retreatments
- Clinical or biological evidence of Type 1 diabetes mellitus (DM) or poorly controlled DM with hemoglobin A1c > 7.5, or with evidence of diabetic nephropathy on biopsy, systemic lupus erythematosus, IgA vasculitis (Henoch-Schonlein purpura), secondary IgAN, or other renal disease, during Screening or Run-In
- Presence of significant morbidity or other major illness or disease that may confound the interpretation of the clinical trial results or may result in death within 2 years of Screening
- History of renal transplantation
- Have a known hypersensitivity to any constituent of the investigational product
- Rapidly progressive glomerulonephritis, defined as a fall in eGFR of > 30 mL/min/1.73 m^2 within 24 weeks or > 15 mL/min/1.73 m^2 within 12 weeks prior to Screening
- Significant abnormalities in clinical laboratory values

- History of human immunodeficiency virus (HIV), evidence of immune suppression, active hepatitis C virus (HCV) infection (patients with positive anti-HCV antibody but a non-detected HCV RNA PCR can enroll), and/or hepatitis B virus (HBV) infection (patients with positive HBsAg are excluded; for patients with isolated positive anti-HBc antibody, HBV DNA test by PCR must be non-detectable to enroll)
- Diagnosis of a malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated *in situ* disease, or other cancer from which the patient has been disease-free for ≥ 5 years
- Have received any other investigational drug or device or experimental procedures within 30 days of the Screening Visit (SV) or within 5 times the plasma half-life of the administered experimental drug, whichever is longer
- Initiation or change in dosing of sodium glucose co-transporter 2 inhibitors (SGLT2i) during Screening and Run-In Periods. However, a stable dose regimen established at least 8 weeks prior to screening is acceptable
- Treatment with Tarpeyo™ (budesonide) or other approved treatments for IgAN within 6 months prior to screening. Treatment with Tarpeyo is not allowed during Screening and Run-In Periods
- Treatment with Kerendia® (finerenone) within 6 months prior to screening. Treatment with Kerendia is not allowed during Screening and Run-In Periods
- Initiation of treatment with Filspari™ (sparsentan), a dual Endothelin Angiotensin Receptor Antagonist (dEARA) or similar medication within three months prior to screening. A stable dose initiated at minimum 3 months before screening is acceptable and will take the place of ACEi/ARB as background therapy

Investigational Product, Dosage, and Mode of Administration:

[redacted]Narsoplimab [redacted]

[redacted] narsoplimab in 50 mL of D5W or normal saline solution infused IV over approximately 30 minutes

Duration of Treatment:

Weekly treatment for 12 weeks, with either narsoplimab or placebo, with possibility of extended treatment for 6 weeks and/or retreatment in the Response Evaluation and Follow-Up Periods

Reference Therapy, Dosage, and Mode of Administration:

- Placebo (vehicle control): 5% dextrose (D5W) or normal saline solution
- 50 mL of D5W or normal saline solution, infused IV over approximately 30 minutes

Study Endpoints:

Primary Endpoint:

- The primary endpoint of this study is the change from baseline in log-transformed 24-hour UPE in g/day at 36 weeks in patients with high baseline proteinuria (high-risk proteinuria group; 24-hour UPE ≥ 2 g/day)

Key Secondary Endpoints

- The rate of change in eGFR up to 96 weeks from baseline in patients with high baseline proteinuria (high-risk proteinuria group; 24-hour UPE ≥ 2 g/day)
- The rate of change in eGFR up to 96 weeks from baseline in the all-patients population (24-hour UPE > 1 g/day)

Other Secondary Endpoints

- Change from baseline in log-transformed 24-hour UPE at Week 36 in the all-patients population. (24-hour UPE > 1 g/day)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 48 weeks in patients with ≥ 2 g/day UPE at baseline (high-risk proteinuria group)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 72 weeks in patients with ≥ 2 g/day UPE at baseline (high-risk proteinuria group)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 48 weeks in the all-patients population
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 72 weeks in the all-patients population

Safety and Other Endpoints

- Safety and tolerability of narsoplimab for the treatment of IgAN as assessed by AEs, vital signs, clinical laboratory tests, and ECGs
- Change from baseline in log-transformed 24-hour uPCR over time in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Achievement of ≥ 50% reduction from baseline in 24-hour UPE at 36 weeks in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Achievement of ≥ 30% reduction from baseline in 24-hour UPE at 36 weeks in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Change from baseline in log-transformed 24-hour uPCR over time in the all-patients population
- Achievement of ≥ 50% reduction from baseline in 24-hour UPE at 36 weeks in the all-patients population
- Achievement of ≥ 30% reduction from baseline in 24-hour UPE at 36 weeks in the all-patients population
- Time averaged change from baseline in the log-transformed 24-hour uPCR through 36 weeks in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Achievement of partial proteinuria remission defined as 24-hour UPE < 0.6 g at any time post baseline in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)

- Achievement of complete proteinuria remission defined as 24-hour UPE < 0.3 g at any time post baseline in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Time averaged change from baseline in the log-transformed 24-hour uPCR through 36 weeks in the all-patients population
- Achievement of partial proteinuria remission defined as 24-hour UPE < 0.6 g at any time post baseline in the all-patients population
- Achievement of complete proteinuria remission defined as 24-hour UPE < 0.3 g at any time post baseline in the all-patients population
- Use of rescue therapy for IgAN at any time post baseline in the all-patients population and in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Change from baseline in eGFR at 36 weeks in the all-patients population and in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Pharmacokinetics and pharmacodynamics of narsoplimab
- Occurrence of anti drug antibodies (ADA) and, if present, neutralizing antibodies (NAb)

Statistical Methods:

Sample Size Determination

The planned sample size is determined using the primary endpoint (change in log-transformed 24-hour UPE from baseline to 36 weeks) in the high-risk proteinuria group and the two key secondary endpoints: the rate of change in eGFR for the high-risk proteinuria group and the rate of change in eGFR for the all-patients population. The planned sample size for the primary endpoint (change in log-transformed 24-hour UPE from baseline to 36 weeks) is 180 patients for the high-risk proteinuria group, 280 patients for the eGFR rate of change endpoint in the high-risk proteinuria group, and 450 patients for the eGFR rate of change in the all-patients population.

Analysis Populations

The primary efficacy analysis population will be the Full Analysis Set (FAS) population, defined as all randomized patients in the high-risk proteinuria group. Patients will be grouped by their assigned treatment. When considering the all-patients population (baseline 24-hour UPE > 1 g/day), the same principal applies, i.e. the FAS for this population is defined as all randomized patients.

The supporting efficacy analysis population will be the Per-Protocol Analysis Set (PAS) population, which includes all randomized high UPE ≥ 2 g/day patients who receive at least 10 doses of study drug in the Initial Treatment Period and have non-missing primary endpoint data (24-hour UPE at baseline and Week 36). Patients will be grouped by their assigned treatment.

Safety analyses will be based on the Safety Analysis Set, which includes all patients who receive any positive amount of study drug. Patients will be grouped by their actual treatment received. Supportive safety summaries will also be made in the population of all patients who receive any positive amount of study drug.

Multiple Comparisons and Multiplicity

The primary efficacy endpoint (change in log-transformed 24-hour UPE from baseline to 36 weeks) in the high-risk proteinuria group and, if positive, the two key secondary endpoints will be tested sequentially to preserve the overall type I error rate of 5%.

Key Secondary Efficacy Endpoints:

i. the rate of change in eGFR over 2 years in the high-risk proteinuria group

ii. the rate of change in eGFR over 2 years in the all-patients population

If the primary efficacy endpoint is statistically significant at 5% level in a 2-sided test, then key secondary endpoint (i), the rate of change in eGFR over 2 years in the high-risk proteinuria group, will be tested in a two-sided test at 5% level of significance. If the key secondary eGFR endpoint for the high-risk proteinuria group is statistically significant in a two-sided test at 5% level, then the key secondary eGFR endpoint (ii), the rate of change in eGFR over 2 years in the all-patients population, will be tested in a two-sided test at 5% level.

Testing of other efficacy endpoints will not be subject to type-1 error control and, therefore, will be viewed as supportive.

In the blinded sample size re-estimation (SSRE) for the key secondary UPE endpoint (primary endpoint in the original protocol), no alpha level penalty was applied.

A conditional power-based SSRE for the key secondary endpoint of eGFR is planned in the high-risk proteinuria group (at least N = 180) at the time of the primary endpoint analysis. At this SSRE, no formal statistical testing will be performed on eGFR data.

Efficacy Analyses

The primary UPE efficacy endpoint will be based on the natural logarithm transformed 24-hour UPE. This analysis will be performed after the interim database snapshot for the FAS population. The interim dataset will include at least 180 patients in the high-risk proteinuria group through 36 weeks in the FAS population.

The analysis of secondary UPE endpoint, change from baseline in log-transformed 24-hour UPE in g/day at Week 36 in all patients (24-hour UPE > 1 g/day) will also be analyzed following the same methods listed above for the primary UPE endpoint, change from baseline in log-transformed 24-hour UPE in g/day at Week 36 in the all-patients group.

The analysis of the key secondary efficacy eGFR endpoints (i) the rate of change in eGFR over 2 years in the high-risk proteinuria group and (ii) the rate of change in eGFR over 2 years in all patients will be performed only if the primary UPE efficacy endpoint in the ≥ 2 g/day population is significant at 5% level of significance in a 2-sided test. If the

primary endpoint is met, then key secondary endpoints (i) and (ii) will be sequentially tested at 5% level of significance in a 2-sided test respectively.

The key secondary rate of change in eGFR over 2 years in the high-risk proteinuria group and the all-patients population will be analyzed by a random coefficients model for the FAS population. This analysis will be performed after the final database lock.

Safety Analyses

The safety endpoints will be summarized descriptively by treatment group. Patient incidence of treatment-emergent adverse events (TEAEs), treatment-related AEs, treatment-emergent serious AEs, TEAEs leading to study treatment discontinuation and TEAEs leading to death, as well as maximum severity of TEAEs will be summarized by Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term.

Laboratory tests, including ECG and vital signs, will be descriptively summarized by treatment group and visit.

Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

By sparse sampling, blood will be collected from patients at intervals to enable population pharmacokinetic (PK) analyses. Biomarker, ADA, NAb, and pharmacodynamic (PD) data will be summarized. An exploratory evaluation of other relevant biomarkers may be conducted.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
ACEI	angiotensin converting enzyme inhibitor
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
ALT	alanine aminotransferase
ANOVA	analysis of variance
AP	alternative pathway
APC	allophycocyanin
ARB	angiotensin receptor blocker
AUC	area-under-the-curve
AST	aspartate aminotransferase
BIW	twice weekly
BP	blood pressure
C1q	complement component 1q
C3	complement component 3
C4	complement component 4
C4a	complement component 4a
C4d	complement component 4d
C5b-C9	terminal complement complex
C4d-APC	antibody against C4d conjugated to allophycocyanin
CBC+diff	complete blood count with differential
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran–Mantel–Haenszel
CMP	comprehensive metabolic panel
CP	classical pathway
CRF	case report form
D5W	5% dextrose in water
DM	diabetes mellitus
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate

Abbreviation or Specialist Term	Explanation
EDC	electronic data capture
EMA	European Medicines Agency
EOS	end of study
EOT	end of initial treatment
ESRD	end-stage renal disease
FAS	Full Analysis Set
FCS	fully conditional specification
FDA	US Food and Drug Administration
FU	Follow-Up Visit
GCP	Good Clinical Practice
gCMH	generalized Cochran–Mantel–Haenszel
GMR	geometric mean ratio
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPF	high-powered field
IB	Investigator's Brochure
IC_{50}	concentration leading to 50% inhibition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDI	intended dose intensity
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IgA	immunoglobulin A
IgA1	immunoglobulin A1
IgAN	immunoglobulin A nephropathy
IgG4	human immunoglobulin G4
IRB	institutional review board
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
KIM-1	kidney injury molecule 1
KM	Kaplan–Meier
LP	lectin pathway
LS	least squares
mAb	monoclonal antibody

Abbreviation or Specialist Term	Explanation
MASP	mannan-binding lectin-associated serine protease
MBL	mannan-binding lectin
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMF	mycophenolate mofetil
MPV	mean platelet volume
NAb	neutralizing antibody
NGAL	neutrophil gelatinase-associated lipocalin
OL	Open Label
PD	pharmacodynamic
PK	pharmacokinetic
PI	Principal Investigator
PVG	Pharmacovigilance
QTcF	QTc interval calculated by Fridericia's formula
RAS	renin-angiotensin system
RBC	red blood cell
RE	response evaluation
RI	Run-In Visit
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCr	serum creatinine
SOC	System Organ Class
SV	Screening Visit
T	Treatment Visit
TEAE	treatment-emergent adverse events
TMA	thrombotic microangiopathy
UA	urinalysis
ULN	upper limit of normal
uACR	urine albumin/creatinine ratio
uPCR	urine protein/creatinine ratio
UPE	urine protein excretion
WBC	white blood cells

5. INTRODUCTION

5.1. Background

5.1.1. Description of Narsoplimab

Omeros Corporation (Omeros, Sponsor) is developing narsoplimab (OMS721), a human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds to and inhibits mannan-binding lectin-associated serine protease (MASP)-2, for the treatment of lectin complement pathway-mediated diseases.

The primary function of the complement system is to protect the host against infectious agents [Ricklin 2010]. This complex system targets immune and inflammatory responses to surfaces that display molecular patterns not usually present on healthy host cells. Activation of the complement system initiates a series of proteolytic steps that culminate in the formation of a membrane attack complex, which disrupts the membranes of targeted cells, causing lysis and cell death. In addition, complement activation triggers opsonization and the recruitment of phagocytic cells to further engage the infectious agents.

Three pathways activate complement in response to distinct initiating events: the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP). The CP is triggered by immune complexes and mediates important immune effector functions. The LP can be activated by specific types of cell-surface carbohydrate patterns that are usually found on microbes but not on healthy host cell surfaces. These carbohydrate patterns are also found on injured host tissue. Members of the MASP enzyme family initiate LP activation. These proteases are synthesized as proenzymes that form a complex in blood with lectins, such as the mannan-binding lectin (MBL), ficolins, and collectins. These lectins bind to carbohydrate patterns on foreign or injured host cell surfaces, targeting MASPs to their site(s) of action and leading to activation of MASPs. There are three known MASPs: MASP-1, MASP-2, and MASP-3 [Yongqing 2012]. MASP-2 is thought to be the key enzyme responsible for activation of the LP; upon activation, it cleaves its substrates, complement component 2 (C2) and complement component 4 (C4), both of which contribute to the formation of the complement component 3 (C3) convertase, a central component of complement activation. Narsoplimab blocks the action of MASP-2, thereby inhibiting LP activation.

The AP, by contrast, is continuously activated at a low level and is kept in check by a series of regulatory proteins. The AP also acts as an amplification loop, increasing the host immune response following activation of the CP and/or the LP. While the complement system supports innate host defense against pathogens, mutations in the genome or tissue damage can cause inappropriate activation and lead to serious disease, e.g., thrombotic microangiopathies (TMA)s in which endothelial damage as well as fibrin and platelet-rich thrombi in the microvasculature lead to end-organ damage.

Narsoplimab avidly binds to recombinant MASP-2 (apparent equilibrium dissociation constant of approximately 100 pM) and exhibits greater than 5,000-fold selectivity over the homologous proteins complement components 1s and 1r (C1s, C1r), and MASP-1. In functional assays reported to date, narsoplimab inhibits the human LP with nanomolar potency (concentration leading to 50% inhibition [IC_{50}] of approximately 3 nM) but has no significant effect on the CP

or AP. Narsoplimab administered either by intravenous (IV) or subcutaneous (SC) injection to mice, non-human primates, and humans resulted in high narsoplimab serum concentrations that were associated with suppression of LP activation in *ex vivo* assays. Narsoplimab treatment reduced terminal complement complex (C5b-C9) deposition and thrombus formation in *in vitro* and *in vivo* animal models of TMA, as well as in *ex vivo* human models using serum from TMA patients both in the acute and remission phases of disease, thus demonstrating that narsoplimab is a candidate for the treatment of diseases that result from inappropriate LP activation.

Based on the mechanism of action and results of nonclinical studies, narsoplimab is in development for the treatment of diseases thought to be mediated by the LP of complement, including immunoglobulin A nephropathy (IgAN).

5.1.2. Immunoglobulin A Nephropathy

Immunoglobulin A nephropathy is an immune-mediated kidney disease resulting in intrarenal inflammation and kidney injury. IgAN is the most common type of glomerulonephritis in the world [D'Amico 1987, Levy 1988] and causes end-stage renal disease (ESRD) in a significant percentage of patients [D'Amico 2000, Donadio 2002]. About 10% of all dialysis patients globally have IgAN [Pettersson 1997]. A systemic review of biopsy-based studies spanning multiple countries suggests an overall population incidence of at least 2.5 per 100,000 [McGrogan 2011]. The prevalence of IgAN is higher in Asia, Europe, and Australia [D'Amico 2000]. It is less common in populations of African descent.

Patients typically present with microscopic hematuria with mild to moderate proteinuria and variable levels of renal insufficiency [Wyatt 2013]. Clinical markers such as impaired kidney function, sustained hypertension, and heavy proteinuria (> 1 g per day) are associated with poor prognosis [Berthoux 2011, Goto 2009]. Proteinuria is the strongest prognostic factor independent of other risk factors in multiple large observational studies and prospective trials [Coppo 2005, Reich 2007]. It is estimated that up to 40% of patients reach ESRD within 20 years of diagnosis [Schena 1990, Xie 2012].

The histopathology of IgAN is characterized by immunoglobulin A (IgA) deposits in the glomerular mesangium. Complement components C3, C4 or complement component 4d (C4d), MBL, and C5b-C9 are frequently detected, whereas the absence of complement component 1q (C1q) suggests that the CP is not activated [Wyatt 2013]. At the molecular level, IgAN is linked to immunoglobulin A1 (IgA1) subclass antibodies with reduced terminal galactose residues on N-linked and O-glycans of IgA1. Abnormally-glycosylated IgA form immune complexes with anti-glycan antibodies that deposit in the mesangium [Maillard 2015]. IgA1 lacking terminal galactose have exposed oligomannose moieties [Oortwijn 2006], a known ligand for MBL binding, and activate the LP of complement [Maillard 2015, Ohsawa 2012, Oortwijn 2006, Roos 2001].

Scientific and clinical evidence suggest a role for the LP in glomerular complement activation. Glomerular MBL deposition, usually co-localized with IgA and other hallmarks of complement activation, is associated with an unfavorable prognosis; patients with glomerular MBL deposition have more severe proteinuria, decreased renal function, lower levels of serum albumin, and more severe histological changes and mesangial proliferation than patients without MBL deposition [Liu 2013, Matsuda 1998, Roos 2006]. Follow-up data demonstrate a lower renal remission rate

for patients with MBL deposition [Liu 2013]. Further evidence of LP involvement in IgAN is the direct association between high levels of urinary MBL and an unfavorable prognosis in IgAN [Liu 2012].

The current treatment strategies including blood pressure (BP) control with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) lead to a reduction of proteinuria. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines [KDIGO Glomerular Diseases Work Group 2021] suggest that corticosteroids should be considered, only after a thorough risk assessment, to patients with proteinuria of ≥ 1 g/day following 3 to 6 months of optimized supportive care and acknowledge that many patients may chose not to have systemic corticosteroids on the basis of treatment emergent toxicity. The usual treatment duration is 6 months. Other strategies to control intra-renal inflammation have been evaluated but are not recommended to be used in IgAN and these include the administration of fish oil, cyclophosphamide, azathioprine, and mycophenolate mofetil (MMF), except in the setting of rapidly progressive IgAN. Since the 2021 KDIGO guidelines were published two new therapies have been approved by the regulators: Tarpeyo™ (FDA, MHRA, EMA) and sparsentan (FDA). These drugs have been approved for IgAN patients with >1.5g/g proteinuria despite optimized supportive care. These drugs have not thus far been included the KDIGO guidelines but this is likely to change in 2023 when the IgAN guidelines will be updated.

5.2. Previous Experience

5.2.1. Nonclinical Experience

[redacted]

5.2.2. Clinical Experience

Narsoplimab has been administered by IV infusion and SC injection to normal healthy volunteers in a Phase 1, single-ascending-dose study (OMS721-NHV-001). The study enrolled 41 male patients to seven dose cohorts at doses up to 2 mg/kg, administered both SC and IV. Narsoplimab treatment by either IV or SC routes of administration was well tolerated. There were no clinically significant abnormalities on vital signs, clinical laboratory tests, or electrocardiogram (ECG) monitoring.

Study OMS721-NHV-002 was a Phase 1 randomized, double-blind, placebo-controlled study evaluating IV and SC multiple-dose administration, higher doses, and a new formulation of narsoplimab in healthy volunteers. The IV dose cohorts received 2 mg/kg and 4 mg/kg once weekly for 6 weeks using the [redacted] mg/mL formulation. The SC-dose cohorts received 2.0 mg/kg, 4.0 mg/kg, 6.0 mg/kg, and 8.0 mg/kg using the original [redacted] mg/mL formulation and 370 mg and 740 mg using the newer [redacted] mg/mL formulation, all once weekly for 6 weeks. Cohorts receiving 50 mg and 150 mg SC once daily for 3 weeks using the [redacted] mg/mL formulation were also included. This study completed enrollment of a total of 90 subjects. Narsoplimab treatment with both formulations ([redacted] mg/mL and [redacted] mg/mL), and by either IV or SC route of administration was well tolerated.

Study OMS721-TMA-001 was a Phase 2 study for the treatment of TMA (NCT02222545), and was the pivotal study to support a biologics license application (BLA) for narsoplimab for the treatment of hematopoietic stem cell transplant-associated (HSCT) TMA, which is pending with FDA's Division of Nonmalignant Hematology. Narsoplimab was well tolerated at doses up to 4 mg/kg IV BIW for more than 52 weeks in patients with TMA. Improvements in laboratory

measures of TMA activity in patients with atypical hemolytic uremic syndrome (aHUS) were observed. Response rate for patients with HSCT-TMA was 17/28 or 61% [Khaled 2022].

Study OMS721-GNP-001 (NCT02682407) was a Phase 2 study for the treatment of patients with IgAN, lupus nephritis, membranous nephropathy, or C3 glomerulopathy [Lafayette 2020]. Four Cohorts have been enrolled. Cohort 1 included patients with steroid dependent disease. Cohort 2 included IgAN patients who were not receiving corticosteroids, and patients received either 4 mg/kg narsoplimab or vehicle once weekly, IV, for 12 weeks. Cohort 3 includes IgAN patients that are not on steroids and patients in the study receive either 370 mg narsoplimab or vehicle once weekly, IV, for 12 weeks. Regardless of treatment assignment, patients in Cohort 3 were eligible for additional open-label narsoplimab treatment if they failed to achieve a 24-hour urine protein < 50% of baseline or their 24-hour urine protein was > 1000 mg/24 hours after 12 weeks of dosing (plus a 6-week follow-up period). Cohort 4 enrolled Asian patients with IgA nephropathy who were not receiving corticosteroids. Patients in Cohort 4 received a single dose of narsoplimab 370 mg IV followed 2 weeks later by daily subcutaneous (SC) injections of narsoplimab 150 mg for 12 weeks. Cohort 4 enrolled 2 patients with IgA nephropathy at the time of study completion. This study was stopped due to slow enrollment.

The administration of narsoplimab IV once weekly to patients with glomerulonephropathies was generally well tolerated with commonly expected adverse events (e.g., rash) that resolved. Improvements in proteinuria were observed in patients across those glomerulonephropathies (i.e., IgA nephropathy, MN, and LN). Stabilization of eGFR was observed in patients with advanced IgA nephropathy.

Study OMS721-HUS-002 (NCT03205995) is an ongoing Phase 3 uncontrolled, open-label study for aHUS. At the time of this protocol amendment, six patients have been treated in the study.

5.3. Potential Risk and Benefits

5.3.1. Known and Potential Risks

5.3.1.1. Human MASP-2 Deficiency

MASP-2 deficiency has been reported to occur in humans and the clinical phenotype of MASP-2 deficiency may be relevant to risk assessment of MASP-2 inhibition with narsoplimab. The literature contains conflicting reports as to whether patients with MASP-2 deficiency are at risk for adverse effects.

Two case reports described individuals with MASP-2 deficiency due to a homozygous mutation (D120G) with clinical associations with autoimmunity or recurrent bacterial infections; one patient was healthy until 13 years of age and the other patient had cystic fibrosis [Olesen 2006, Stengaard-Pedersen 2003]. A genetic screen of 335 Polish children with recurrent respiratory tract infections identified one child with MASP-2 deficiency [Cedzynski 2004]. In contrast, in a genetic screen of 868 healthy Spaniards, two homozygous D120G individuals were identified; both patients were healthy without clinical evidence of recurrent infections or autoimmune disorders and both had normal levels of circulating complement [Garcia-Laorden 2006].

The gene frequency of the D120G mutation is 2% to 4% in European populations, which would predict that approximately 1 in 625 to 2000 individuals in this population would be homozygotes

with MASP-2 deficiency [Garcia-Laorden 2006, Thiel 2007]. Polymorphisms in the MASP-2 gene, as well as the plasma concentration of MASP-2, are influenced by race. For example, the D120G mutation is the most common one in Caucasians, but it is not found in Chinese or Africans [Thiel 2007]. Moreover, the circulating levels of MASP-2 were lowest in Africans (median 196 ng/mL), followed by Chinese (262 ng/mL), and Amerindian (290 ng/mL), and highest in Caucasian Danes (416 ng/mL) [Thiel 2007]. The initial studies were in Danes and a plasma concentration below 100 ng/mL was suggested as indicating MASP-2 deficiency since only individuals homozygous for the D120G mutation had this level. Subsequent studies in broader populations showed that this cutoff was inappropriate as 5% of Chinese and 19% of Africans tested had values below 100 ng/mL.

Several studies have examined the relationship between MASP-2 concentration and susceptibility to infections. In a Swiss study of 94 pediatric cancer patients, MASP-2 deficiency defined as serum levels below 200 ng/mL was identified in nine children [Schlapbach 2007]. Patients with low MASP-2 levels had significantly more episodes of febrile neutropenia with no identified microbial etiology and had longer duration of IV antibacterial therapy than those with normal MASP-2 levels. In a Polish study of 1788 neonates, cord blood serum MASP-2 concentration correlated with gestational age and birth weight and was significantly lower in premature babies and other pre-term babies compared with term babies [St Swierzko 2009]. Neonates with low MASP-2 concentrations did not have a higher incidence of perinatal infections when compared with those with normal MASP-2. Indeed, there was a trend towards higher MASP-2 concentrations among babies with infections. A study in Spain evaluated the frequency of the D120G mutation in 868 healthy patients as well as in 967 adult patients with community-acquired pneumonia, in 43 children with recurrent respiratory infections, and in 130 patients with systemic lupus erythematosus and found that the allelic frequency of the D120G mutation was similar in each of these clinical groups [Garcia-Laorden 2006]. These investigators conducted a follow-up study in which they evaluated the significance of MASP-2 deficiency in the susceptibility and outcome of community-acquired pneumonia in adults and found similar MASP-2 alleles and genotypes among patients and control patients, leading to the conclusion that MASP-2 deficiency was not associated with an increased risk of community-acquired pneumonias [Garcia-Laorden 2008].

In summary, the literature does not provide a clear indication as to the risk for increased susceptibility to infections in individuals with MASP-2 deficiency. The researchers in Denmark who were the first to describe MASP-2 deficiency and have done the most work in this area stated in one article [Thiel 2007] that “One must thus conclude that (MASP-2) deficiency in itself does not result in disease, rather, it is a modifier, which may penetrate when also other elements are compromised.”

5.3.1.2. Animal Models of Infection

The role of MASP-2 in bacterial infection has been evaluated in animal models and the results vary depending on the model, ranging from disease worsening to no effect to protection. In a murine model of pneumococcal infection, inhibition of MASP-2 with a MASP-2 mAb prior to nasal inoculation of *Streptococcus pneumoniae* resulted in increased severity of disease compared to isotype control mAb [Ali 2012]. In this model, antibiotic treatment was effective in MASP-2 mAb-treated animals, resulting in a similar outcome to that in untreated controls. In

contrast, in a murine model of pneumococcal meningitis, MASP-2-deficient mice had a better outcome compared to wild-type littermates [Kasanmoentalib 2017]. In a murine model of *Pseudomonas aeruginosa* infection, MASP-2-deficient mice had no significant survival disadvantage compared to wild-type littermates [Kenawy 2012]. In a murine model of meningococcal infection, treatment with a MASP-2 mAb prior to bacterial challenge resulted in increased survival compared to treatment with isotype control mAb, demonstrating a protective effect [Omeros data on file].

5.3.1.3. Pregnancy

The effect of narsoplimab on human embryos has not been characterized.

Embryo-fetal development studies conducted in mice and rabbits demonstrated reduced fetal body weights, but no malformations, when narsoplimab was administered during the period of organogenesis. In addition, a slight increase in abnormal sperm was observed in male mice administered narsoplimab in a fertility study, although this finding had no impact on mating or fertility indices and was considered non-adverse.

Therefore, patients who are pregnant or breastfeeding should not receive narsoplimab. Males should either a) not be of reproductive potential or b) irrespective of sexual activity, must agree to use a medically reliable form of contraception throughout the study.

5.3.2. Potential Benefits

Reductions in proteinuria have been observed in patients with IgAN who were treated with narsoplimab.

5.3.3. Risk – Benefit Summary

Overall, narsoplimab has been well tolerated. As narsoplimab is a therapeutic protein, possible risks that are not related to its target include infusion reactions, injection-site reactions, and allergic reactions. Self-limited injection-site reactions have been observed in healthy volunteers following SC administration. Nonclinical studies did not show any unexpected effects in this regard and clinical studies to date have not shown any of these reactions.

The evidence supports a low risk of increased susceptibility to infection with inhibition of MASP-2. Moreover, patients with active human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infections will be excluded from this study and enrolled patients will be closely monitored for infections and empiric antimicrobial therapy will be administered if they develop symptoms or signs of infection.

Based on the mechanism of action, narsoplimab may provide benefit to patients with IgAN. Treatment options for this disease are limited. There are very limited specific treatments approved by the U.S. Food and Drug Administration (FDA). Also, many current therapies of this disease, such as systemic corticosteroids and immunosuppressants, have undesirable side effects. Therefore, this study has an acceptable risk-benefit balance.

6. STUDY PURPOSE AND OBJECTIVES

6.1. Primary Objective(s)

The primary objective of this study is to evaluate the effect of narsoplimab on 24-hour UPE in IgAN patients with high baseline proteinuria (high-risk proteinuria group; 24-hour UPE ≥ 2 g/day) assessed at 36 weeks from baseline.

6.2. Secondary Objective(s)

The secondary objectives of this study are to evaluate the effect of narsoplimab in IgAN patients on:

- Renal function as determined by the rate of change in eGFR up to 96 weeks from baseline in patients with high baseline proteinuria (high-risk proteinuria group; 24-hour UPE ≥ 2 g/day)
- Proteinuria assessed by 24-hour UPE at 36 weeks from baseline in the all-patients population
- Renal function as determined by the rate of change in eGFR up to 96 weeks from baseline in the all-patients population
- Durability of proteinuria response from 36 weeks in patients with high baseline proteinuria (the high-risk proteinuria group; 24-hour UPE ≥ 2 g/day) and in the all-patients population
- Change from baseline in log-transformed 24-hour UPE at Week 36 in the all-patients population (24-hour UPE > 1 g/day)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 48 weeks in patients with ≥ 2 g/day UPE at baseline (high-risk proteinuria group)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 72 weeks in patients with ≥ 2 g/day UPE at baseline (high-risk proteinuria group)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 48 weeks in the all-patients population
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 72 weeks in the all-patients population
- Safety and tolerability in patients with high baseline proteinuria (the high-risk proteinuria group; 24-hour UPE ≥ 2 g/day) and in the all-patients population
- Pharmacokinetics, pharmacodynamics, and immunogenicity of narsoplimab

7. STUDY DESIGN AND PROCEDURES

7.1. Summary of Study Design

This is a Phase 3, double-blind, randomized, placebo-controlled study in patients aged 18 years and above with a biopsy-confirmed diagnosis of IgAN and with 24-hour UPE > 1 g at baseline. Primary efficacy analysis will include the subset of patients with 24-hour UPE ≥ 2 g at baseline (the high-risk proteinuria group). The study will be conducted at approximately 200 study sites in North America, South America, Europe, Australia, and Asia.

Approximately 450 patients are to be enrolled in two groups of 225 patients per arm.

During the study, all patients will continue optimized renin-angiotensin system (RAS) blockade. The study consists of five periods: Screening, Run-In, Initial Treatment (Weeks 1-12), Response Evaluation (Weeks 13-36), and Follow-Up (Weeks 37 to Week 96/end-of-study). The duration of study for each patient is expected to be approximately 112 weeks, comprising a 2-year study including follow-up.

All patients will receive 12 weeks of initial study drug treatment. Following treatment completion, the proteinuria response will be evaluated at several timepoints and additional study drug treatment will be given to patients as follows:

Six weeks of extended treatment will be given after Week 12 to:

- Patients who have a 24-hour UPE > 1 g at Treatment Visit 12 (T12/Week 12). These patients will receive 6 additional weeks of treatment (extended treatment) according to their originally assigned treatment group in a blinded fashion.

Six weeks of relapse retreatment will be given after Week 24, Week 30, or Week 36 to:

- Patients who initially show a response to treatment of at least 30% from baseline proteinuria at any assessment timepoint but subsequently relapse (defined as an increase in 24-hour UPE by ≥ 30% from the value of their lowest measured post-treatment UPE and 24-hour UPE > 1 g).

Patients who relapse during the Response Evaluation period will only be retreated once; at Week 24, Week 30, or Week 36.

Twelve weeks of relapse retreatment will be given after Week 48 or Week 72 to:

- Patients who initially show a response to treatment of at least 30% from baseline proteinuria at any assessment timepoint but subsequently relapse (defined as an increase in 24-hour UPE by ≥ 30% from the value of their lowest measured post-treatment UPE and 24-hour UPE > 1 g).

Patients who relapse on or after Week 48 will only be retreated once.

Rescue therapy will be available for eligible patients per local practice at the Investigator's discretion.

Open-label treatment will be available for eligible patients at 72 weeks (18 months) post randomization (see Section 10.2.8 for more detail).

As an optional procedure, blocks of the original renal biopsy specimen, where available, may be stained for MBL and, potentially, other biomarkers of lectin pathway activity. Findings from this investigation will address the following issues and, potentially, others:

- Determine the proportion of patients in this study with MBL deposition
- Clarify whether MBL deposition is associated with disease severity and progression in IgAN
- Determine whether MBL deposition impacts response to narsoplimab

Randomization will be stratified by the baseline eGFR level (≥ 30 to ≤ 45 mL/min/1.73 m^2 and > 45 mL/min/1.73 m^2) and by baseline UPE (> 1 to < 2 g/day and ≥ 2 g/day).

All study visits will include assessment of adverse events (AEs), concomitant medications, and vital signs. Safety laboratory measures and ECGs will be evaluated at scheduled timepoints throughout the study. Efficacy measures of proteinuria will be evaluated at pre-specified assessment timepoints. The study periods and assessment timepoints are described below and in more detail in Section 10.2. A schematic representation of the study design is provided in Figure 1 and Table 1. A detailed Schedule of Events is provided in Section 20.2.

Screening Period*:* The Screening Period will be used to determine whether patients meet all inclusion criteria and do not meet any exclusion criteria for the study. The Screening Period will be a maximum of 28 days. Patients who do not meet the study entrance criteria may be rescreened a minimum of 30 days after Screen Failure. Patients may be rescreened once, with additional rescreening allowed based on Medical Monitor approval.

Run-In Period*:* The aim of the 4-week to 12-week Run-In Period is to continue to evaluate patient eligibility for the trial, optimize compliance, and optimize background therapies, in particular to optimize BP control and RAS blockade. Patients will not receive study treatment during the Run-In Period. All patients must be on maximum labeled or tolerated RAS blockade prior to randomization. The length of time patients will spend in the Run-In Period will be contingent on duration of their RAS blockade treatment and response, as noted below:

- Patients who have received treatment with ACE inhibitors and/or ARBs at maximum or near-maximum labeled or tolerated dose for 8 weeks or more prior to Screening and have stable BP control (i.e., have an unchanged dose regimen of BP medications for at least 4 weeks prior to Screening), will have a Run-In Period of 4 weeks, consisting of two study visits. Patients receiving Sparsentan for a minimum of 12 weeks prior to screening will continue on this drug in place of ACEi/ARB and spend 4 weeks in the Run-In Period.
- All other patients will have a Run-In Period of 12 weeks, consisting of four study visits.

During the entire study period including the Run-In Period, participants will receive standard background therapy for IgAN, including RAS blockade to control BP according to current guidelines. All patients will receive ACE inhibitors and/or ARBs (if intolerant to ACE inhibitors) titrated to the maximum labeled or tolerated dose (whichever is reached first) according to local or national guidelines and/or the discretion of the Investigator. At every study visit, patients will

be asked to confirm consistent use of RAS blockade medication and whether there have been any dosage changes since the last study visit.

During the Run-In Period, patients will have appropriate lifestyle changes initiated and medications optimized to attain/maintain a BP target of less than 125/75 mm Hg. Considering that some patients may not tolerate this target, there will be deference to the clinical judgment of the managing physician/Investigator regarding patients who have attained a stable maximum tolerable-dose regimen.

Clinical and laboratory evaluations conducted at the end of the Run-In Period will provide the baseline measurements for the study. Baseline proteinuria will be the mean of two 24-hour UPE measurements performed at the end of the Run-In Period, and the mean value should be > 1 g/day for the patient to be randomized. If a patient does not meet the criteria to enter the Initial Treatment Period, the patient may be rescreened after a minimum of 30 days. During the Run-In Period and throughout the entire study, patients will be advised to avoid nonsteroidal anti-inflammatory drugs and any other nephrotoxic medicines.

Initial Treatment Period (Weeks 1-12)*:* Patients who are eligible to enter the Initial Treatment Period will be randomized in a double-blind manner 1:1 to receive narsoplimab or placebo. Randomization will be stratified by the baseline eGFR level (≥ 30 to ≤ 45 mL/min/1.73 m^2 and > 45 mL/min/1.73 m^2) and by baseline UPE (> 1 to < 2 g/day and ≥ 2 g/day). During the Initial Treatment Period, starting at Treatment Visit 1 (T1, Week 1) patients will receive 12 once-weekly IV doses of assigned study drug. Measures of proteinuria will be taken near the end of the Initial Treatment Period (Treatment Visit 12 [T12]/Week 12). During this period, laboratory measures will be taken at Treatment Visit 1 (T1/Week 1), Treatment Visit 2 (T2/Week 2), Treatment Visit 4 (T4/Week 4), Treatment Visit 8 (T8/Week 8), Treatment Visit 10 (T10/Week 10) and Treatment Visit 12 (T12/Week 12).

Response Evaluation Period (Weeks 13-36)*:* Following the 12-week Initial Treatment Period, patients will receive extended treatment with study drug if they meet the criteria detailed below:

Extended Treatment Criteria Post Week 12:

- Patients who have a 24-hour UPE > 1 g at Treatment Visit 12 (T12, Week 12) will receive 6 additional weeks of treatment (extended treatment) according to their originally assigned treatment group in a blinded fashion.

The Response Evaluation Period will consist of one study visit at Week 36, where 24-hour UPE and other laboratory measurements will be taken, per the Schedule of Events (Section 20.2) and patients will be assessed for response.

Phone calls will occur at Weeks 16, 20, 24, 30, and 34. At the Week 24 and Week 30 timepoints, 24-hour UPEs will be collected in order to assess for response, per the Schedule of Events (Section 20.2).

Patients who relapse at Week 24, Week 30, or Week 36 will receive 6 weeks of relapse retreatment as detailed below.

- **Relapsers**: Relapsers are patients who show a response to treatment of at least 30% reduction from baseline proteinuria at any post-treatment assessment timepoint but subsequently demonstrate an increase in 24-hour UPE by ≥ 30% from the value of

their lowest measured post-treatment UPE and have a 24-hour UPE > 1 g. Those who relapse at Week 24, Week 30, or Week 36 will require additional office visits to receive 6 weeks of relapse retreatment. Once a patient receives retreatment for relapse, the patient will not be given additional retreatment in the Response Evaluation Period.

At Week 36, the clinical and laboratory evaluations conducted represent the primary efficacy measures.

Follow-Up Period (Weeks 37-96): Following the Response Evaluation Period, all patients will enter the Follow-Up Period from Week 37 through Week 96. Visits will occur at Weeks 48, 72, and 96/EOS. Patients will be assessed for response and offered retreatment if they relapse on or after Week 48. Patients who relapse will be given weekly IV treatment for an additional 12 weeks according to the patients' randomized treatment assignment. Once a patient receives retreatment for relapse during the Follow-Up Period, the patient will not be given additional retreatment for relapse. As Week 96 is the end-of-study visit, no relapse retreatment will be offered at that time.

Between visits, interim telephone contacts with patients will occur per the Schedule of Events at Weeks 40, 44, 60, and 84 to monitor patient safety (Section 20.2). Telephone contacts may be skipped if they overlap with a relapse retreatment visit.

All patients will continue optimized RAS blockade and attempt to maintain optimized blood pressure throughout the study.

A quick reference guide and treatment algorithm guiding retreatment based on patient status and study timepoint is provided as an appendix to the study protocol (Section 20.3).

See Section 20.4 for special considerations to protect patient safety during the COVID-19 pandemic.

Specific guidance for handling visits during each study period is provided in Section 10.

Figure 1: Schematic of Study Flow

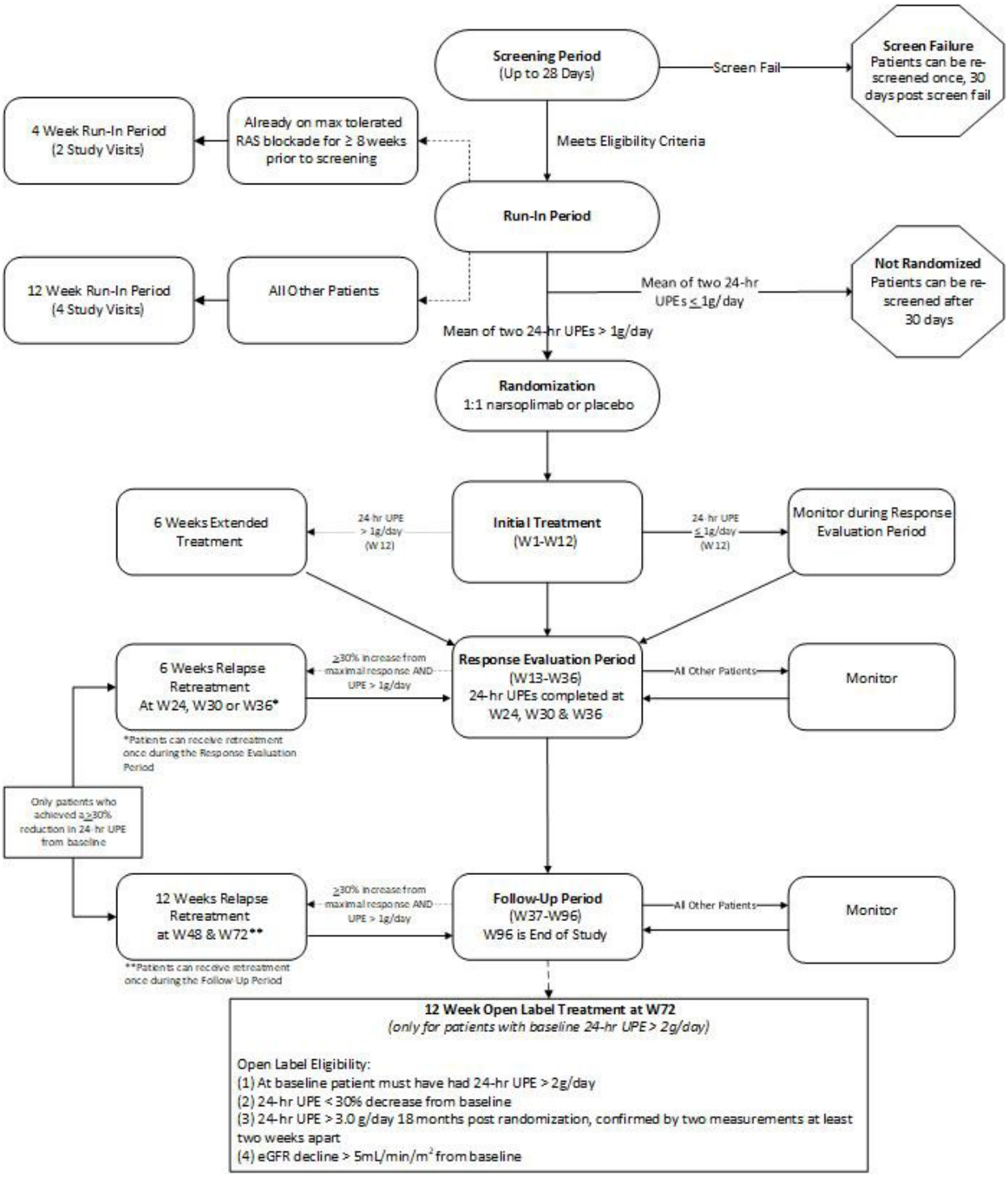


Table 1: Study Design for Additional Treatment Decisions

Assessment Timepoint	Criteria	Treatment
Week 12	24-hour UPE > 1g	6-Week Extended Treatment in a blinded fashion
Week 24, 30, or 36	Relapser	6-Week Relapse Retreatment in a blinded fashion
Week 48 or 72	Relapser	12-Week Relapse Retreatment in a blinded fashion
Week 72	Patients with 24-hour UPE > 2 g at baseline who: • Have less than 30% reduction in UPE at the OL assessment visit when compared to baseline UPE, and • Proteinuria is ≥ 3.0 g/day at 72 weeks from randomization, as confirmed by two measurements at least 2 weeks apart, and • Patient has worsening renal function, defined as a decline in eGFR of > 5 mL/min/m^2 from baseline	12-Week Open-Label Treatment Note: Patients who are eligible for and receive 12-Week Open-Label Treatment may be eligible for an additional 6 weeks of Open-Label Extended Treatment if their 24-hour UPE at OLT12 is > 1 g
Week 96/EOS	Final response assessment	No study treatment required

Relapsers are patients who show a response to treatment of at least 30% reduction from baseline proteinuria at any post-treatment assessment timepoint but subsequently demonstrate an increase in 24-hour UPE by ≥ 30% from the value of their lowest measured post-treatment UPE and have a 24-hour UPE > 1 g. Retreatment for relapse can occur once during the Response Evaluation Period (either Week 24, Week 30, or Week 36) and once during the Follow-Up Period (at either Week 48 or 72).

Study Rationale and General Considerations

The study is designed to evaluate whether narsoplimab reduces proteinuria in patients with IgAN. There is evidence of LP activation and glomerular inflammation in IgAN, and persistent renal inflammation is associated with progressive deterioration in renal function. Consequently, IgAN patients are often treated with chronic corticosteroids and immunosuppressants, drugs that result in increased morbidity and serious adverse events (SAEs). This study will evaluate the potential effect of narsoplimab on reducing proteinuria in IgAN patients, which could be associated with improved clinical outcomes.

Because continued suppression of urinary protein has been observed in IgAN patients treated with narsoplimab, patients will undergo extended follow-up to determine the duration of the urine protein suppression. Patients will receive additional study drug treatment if their urinary protein levels increase after achieving a therapeutic response. Chronic animal toxicology has been completed and supports indefinite dosing. Follow-up through 2 years from the beginning of treatment with visits occurring approximately every 3 to 6 months will allow for the assessment

of duration of therapeutic response with minimal burden to patients. The 1-year follow-up will provide an opportunity to:

- Evaluate the time course of intervention on proteinuria reduction
- Determine the number of patients who relapse following initial response
- Identify non-responders
- Understand the response to retreatment of those who relapse
- Evaluate the impact of narsoplimab on renal function

The relationship between treatment effects on annualized 2-year eGFR rate of decline and treatment effects on mean change in proteinuria at 9 months shows a clear and strong association in a trial-level meta regression analysis with slope = -6.69 mL/min (95% CI: -12.03 to -3.04 mL/min), intercept = -0.8 mL/min (95% CI: -2.88, 0.68 mL/min) and R^2 = 0.99 (95% CI: 0.58 to 1.00). These data indicate that treatment effects on proteinuria at 9 months can reliably predict treatment effects on annualized 2-year eGFR rate of decline [Inker 2021, Inker 2016]. For a treatment effect on proteinuria of 50%, being in line with that hypothesized for narsoplimab at 9 months, the predicted treatment effect on annualized 2-year eGFR rate of decline is 4.0 mL/min (95% CI: 2.4 to 5.5 mL/min); 95% PI (1.7 to 6.7 mL/min). Because of these considerations, analyses of eGFR changes will be conducted over a 2-year period.

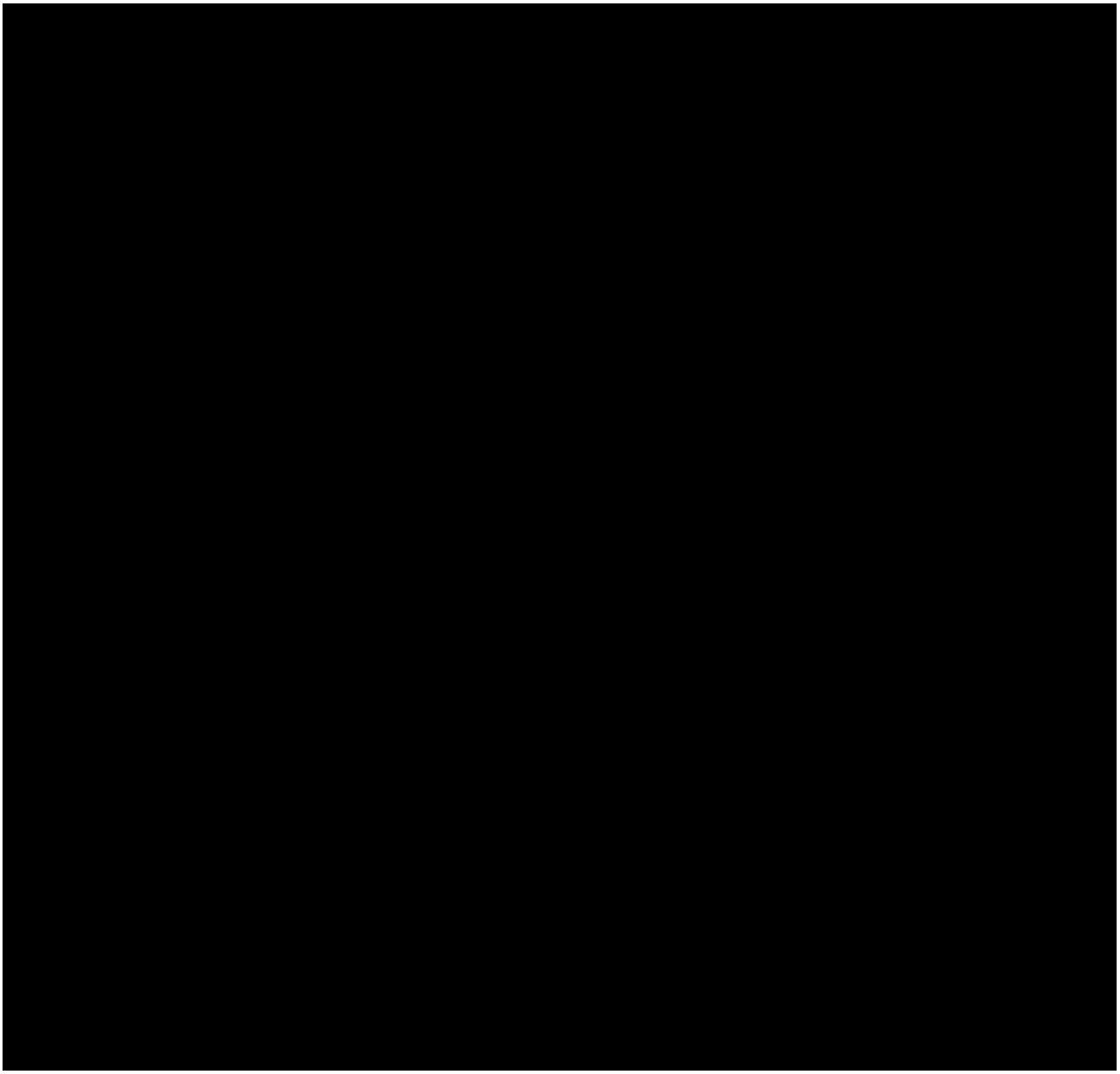
The Run-In Period is planned to last either 4 weeks or 12 weeks. Several studies have demonstrated the effectiveness of RAS blockade in reducing proteinuria in IgAN patients [Lv 2008, Praga 2003], and this therapy is a current standard of care for these patients. The KDIGO guidelines recommend RAS blockade for IgAN patients with persistent proteinuria of > 1 g/day and that the doses should be up-titrated as far as can be tolerated to achieve proteinuria of < 1 g/day [KDIGO Work Group 2012]. The Run-In Period will allow any proteinuria improvement due to RAS blockade to occur prior to study drug treatment and avoid potential confounding of the data interpretation.

For the treatment of patients with persistent proteinuria of > 1 g/day and GFR > 50 mL/min/1.73m^2 despite 6 months of optimized RAS blockade, KDIGO guidelines recommend 6 months of treatment with high-dose corticosteroids. However, use of high-dose corticosteroids results in development of AEs and increased morbidity that significantly impair the health of patients [Cai 2017, Lv 2017, Waljee 2017]. Also, a recent study reported that immunosuppression, including the use of corticosteroids, did not improve renal function [Rauen 2015]. Considering this, patients taking systemic corticosteroids will be excluded from participation in this trial.

The Oxford Classification of IgAN was recently updated with inclusion of crescent formation in the mesangial and endocapillary proliferation (hypercellularity), glomerulosclerosis and tubular atrophy, and interstitial fibrosis scoring system [Trimarchi 2017]. Patients with the presence of crescents in > 25% of the glomeruli on renal biopsy have an increased risk of poorer outcome, even if treated with immunosuppressive medication [Haas 2016]. In this study, it is expected that our inclusion criterion of eGFR of 30 mL/min/1.73 m^2 or greater will also reduce the likelihood of recruiting patients with significant glomerulosclerosis or crescents > 25%. Scientific and clinical evidence suggest that there is a role for the LP of complement in glomerular complement

activation [Endo 1998]. In the study reported by Endo et al., MBL was deposited in 11 of 45 kidneys of IgAN patients. However, MBL was only positive in 1 of 34 of other glomerular nephritis patients [Endo 1998]. In another study, MBL was deposited in the kidneys of 15 of 60 IgAN patients and was associated with increased severity and disease progression [Roos 2006]. In a more recent study of 131 IgAN patients who were followed for 39.8 months, MBL was deposited in 45 patients (34.35%) and was associated with poorer prognosis and lower remission rates [Liu 2013]. In this study, MBL will be evaluated from urine and serum samples, and as an optional procedure, a block section of the original renal biopsy specimen used to confirm IgAN, if available, will be stained for MBL.

An exploratory evaluation of other relevant biomarkers may also be conducted.



7.2. Study Endpoints

7.2.1. Primary Endpoint

The primary endpoint of this study is the change from baseline in log-transformed 24-hour UPE in g/day at 36 weeks in patients with high baseline proteinuria (high-risk proteinuria group; 24-hour UPE ≥ 2 g/day).

7.2.2. Key Secondary Endpoints

The key secondary endpoints of this study are:

- The rate of change in eGFR up to 96 weeks from baseline in patients with high baseline proteinuria (high-risk proteinuria group; 24-hour UPE ≥ 2 g/day)
- The rate of change in eGFR up to 96 weeks from baseline in the all-patients population (24-hour UPE > 1 g/day)

7.2.3. Other Secondary Endpoints

- Change from baseline in log-transformed 24-hour UPE at Week 36 in the all-patients population. (24-hour UPE > 1 g/day)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 48 weeks in patients with ≥ 2 g/day UPE at baseline (high-risk proteinuria group)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 72 weeks in patients with ≥ 2 g/day UPE at baseline (high-risk proteinuria group)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 48 weeks in the all-patients population
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 72 weeks in the all-patients population

7.2.4. Safety and Other Endpoints

- Safety and tolerability of narsoplimab for the treatment of IgAN as assessed by AEs, vital signs, clinical laboratory tests, and ECGs
- Change from baseline in log-transformed 24-hour uPCR over time in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Achievement of a ≥ 50% reduction from baseline in 24-hour UPE at 36 weeks in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Achievement of ≥ 30% reduction from baseline in 24-hour UPE at 36 weeks in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Change from baseline in log-transformed 24-hour uPCR over time in the all-patients population
- Achievement of ≥ 50% reduction from baseline in 24-hour UPE at 36 weeks in the all-patients population
- Achievement of ≥ 30% reduction from baseline in 24-hour UPE at 36 weeks in the all-patients population
- Time-averaged change from baseline in the log-transformed 24-hour urine protein/creatinine ratio (uPCR) through 36 weeks in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group).
- Achievement of partial proteinuria remission defined as 24-hour UPE < 0.6 g at any time post baseline in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Achievement of complete proteinuria remission defined as 24-hour UPE < 0.3 g at any time post baseline in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)

- Time averaged change from baseline in the log-transformed 24-hour uPCR through 36 weeks in the all-patients population
- Achievement of partial proteinuria remission defined as 24-hour UPE < 0.6 g at any time post baseline in the all-patients population
- Achievement of complete proteinuria remission defined as 24-hour UPE < 0.3 g at any time post baseline in the all-patients population
- Use of rescue therapy for IgAN at any time post baseline in the all-patients population and in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Change from baseline in eGFR at 36 weeks in the all-patients population and in patients with baseline 24-hour UPE ≥ 2 g (high-risk proteinuria group)
- Pharmacokinetics and pharmacodynamics of narsoplimab
- Occurrence of ADA and, if present, neutralizing antibody (NAb)

7.2.5. Exploratory Endpoints

The exploratory endpoints of this study are:

- Change from baseline in eGFR over time
- Change from baseline in 24-hour UPE over time
- Change from baseline in 24-hour uPCR over time
- Change from baseline in uACR (from spot urine) over time
- Change from baseline in 24-hour uACR over time
- Achievement of ≥ 50% reduction from baseline in 24-hour UPE at any time post baseline
- Achievement of ≥ 30% reduction from baseline in 24-hour UPE at any time post baseline
- Duration of treatment response defined as the number of weeks between the first timepoint at which the patient achieves a ≥ 30% reduction from baseline in 24-hour UPE and the first timepoint at which the patient relapses (a relapse is defined as an increase in 24-hour UPE by ≥ 30% from the value of the lowest measured post-treatment UPE in a patient whose 24-hour UPE is > 1 g)
- Achievement of 24-hour UPE of < 0.3 g at 36 weeks (complete proteinuria remission)
- Duration of complete proteinuria remission defined as the number of consecutive weeks with UPE < 0.3 g/day from the first timepoint at which UPE < 0.3 g/day to the first timepoint at which UPE ≥ 0.3 g/day
- Duration of partial proteinuria remission defined as the number of consecutive weeks with UPE < 0.6 g/day from the first timepoint at which UPE < 0.6 g/day to the first timepoint at which UPE ≥ 0.6 g/day

- 24-hour UPE following narsoplimab retreatment in patients who relapse after treatment
- Change from baseline in the number of red blood cells per high-powered field (RBC/HPF) over time from baseline

8. SELECTION AND WITHDRAWAL OF PATIENTS

The inclusion and exclusion criteria will be assessed during the Screening and Run-In periods, and only those patients who continue to meet all the inclusion criteria and who do not meet any of the exclusion criteria will be eligible to continue into the Initial Treatment period.

8.1. Patient Inclusion Criteria

Patients may be included in the study only if they meet all the following criteria during the Screening Period and Run-In Period:

1. Age 18 years or older at the onset of Screening
2. Understand and voluntarily sign an informed consent form in accordance with regulations and governing institutional review board (IRB) or independent ethics committee (IEC) requirements prior to any procedures or evaluations performed specifically for the sole purpose of the study
3. Biopsy-confirmed diagnosis of IgAN within 8 years prior to Screening or Run-In Visit 1
4. Documented history of proteinuria > 1 g/day within 6 months prior to Screening, or uPCR > 0.75 by spot urine, at Screening
5. Mean of two proteinuria measurements > 1 g/day at baseline

6. Estimated glomerular filtration rate of ≥ 30 mL/min/1.73 m^2 calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [Levey 2009] at Screening and baseline
7. Females should either a) not be of childbearing potential (i.e., surgically sterilized or postmenopausal for > 1 year), b) have a negative pregnancy test at Screening and baseline and, irrespective of sexual activity, must agree to use two medically reliable forms of contraception from study entry, throughout the study, and for at least 12 week after the last dose of study drug, including possible retreatments, or c) have a medically sterilized male partner. Acceptable methods of contraception include a reliable intrauterine device, hormonal contraception, a barrier method, or complete abstinence (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).
8. Males should either a) not be of reproductive potential or b) irrespective of sexual activity, must agree to use a medically reliable form of contraception from study entry, throughout the study, and for at least 12 weeks after the last dose of study drug, including possible retreatments. Acceptable methods of birth control include spermicide in combination with a barrier method, complete abstinence (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception), or patient's female partner is willing to use medically acceptable methods of birth control (i.e., intrauterine device, hormonal contraception, or a barrier method).
9. Male patients must be willing to avoid fathering children for at least 12 weeks following the last dose of study medication

8.2. Patient Exclusion Criteria

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

1. Treatment with immunosuppressants (e.g., azathioprine or cyclophosphamide), or Chinese Traditional Medicine with immunosuppressive function, cytotoxic drugs, for IgAN within 8 weeks prior to Screening. Treatment with immunosuppressants, Chinese Traditional Medicine with immunosuppressive function, or cytotoxic drugs for IgAN is not allowed during the Run-In Period. Treatment with immunosuppressants are allowed if such treatment is for indications other than IgAN.
2. Treatment with eculizumab within 8 weeks prior to Screening. Treatment with eculizumab is not allowed during the Run-In Period.
3. Treatment with systemic corticosteroids within 8 weeks prior to Screening. Treatment with systemic corticosteroids is not allowed during the Run-In Period.
4. Uncontrolled BP, a systolic BP of > 150 mmHg and a diastolic BP of > 100 mmHg at rest despite the combination of two or more anti-hypertensives including ACEIs, ARBs, or direct renin inhibitors at Screening and baseline
5. Female patients who are pregnant, breast feeding, or planning to become pregnant until 12 weeks after the last dose of study drug, including possible retreatments. Males who are

planning to father children up through 12 weeks after the last dose of study drug, including possible retreatments.

6. Clinical or biological evidence of Type 1 diabetes mellitus (DM) or poorly controlled DM with hemoglobin A1c > 7.5 or with evidence of diabetic nephropathy on biopsy, systemic lupus erythematosus, IgA vasculitis (Henoch-Schonlein purpura), secondary IgAN, or other renal disease during Screening and Run-In
7. Presence of significant morbidity or other major illness or disease that may confound the interpretation of the clinical trial results or may result in death within 2 years of Screening
8. History of renal transplantation
9. Have a known hypersensitivity to any constituent of the investigational product
10. Rapidly progressive glomerulonephritis, defined as a fall in eGFR of > 30 mL/min/1.73 m^2 within 24 weeks or > 15 mL/min/1.73 m^2 within 12 weeks of Screening. During the Run-In period a patient will be excluded if they experience a decrease in eGFR of > 15 mL/min/1.73 m^2 from their best eGFR from the beginning of Screening.
11. Significant abnormalities in clinical laboratory values including any of the following at the time of evaluation during Screening and Run-In:
    - hemoglobin < 9.0 g/dL
    - platelet count < 100,000 cells/mm^3
    - absolute neutrophil count < 500 cells/mm^3
    - alanine transaminase or aspartate transaminase (AST) > 3.0 × the upper limit of normal (ULN)
    - serum bilirubin > 2 × ULN
12. History of HIV, evidence of immune suppression, active HCV infection (patients with positive anti-HCV antibody but a non-detected HCV RNA PCR can enroll), and/or HBV infection (patients with positive HBsAg are excluded; for patients with isolated positive anti-HBc antibody, HBV DNA test by PCR must be non-detectable to enroll).
13. Diagnosis of a malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated *in situ* disease, or other cancer from which the patient has been disease-free for ≥ 5 years
14. Have received any other investigational drug or device or experimental procedures within 30 days of the Screening Visit or within 5 times the plasma half-life of the administered experimental drug, whichever is longer
15. Previously received narsoplimab[1]

[1] Patients currently participating in OMS721-IGA-001 whose study treatment was interrupted due to the COVID-19 pandemic may resume or reinitiate study treatment once it is allowed by their institution. See Section 10.2, Study Schedule, for specific guidance on resumption of study treatment.

16. Is an employee of Omeros, the investigative site (whereas site is meant as the clinic, department, or Clinical Research Unit in which the Investigator works or conducts the trial), a study staff member, or their immediate family member
17. Presence of any condition that the Investigator believes would put the patient at risk from participation
18. Any patient who, in the opinion of the Investigator, is likely to be noncompliant or who is not suitable for the study
19. Presence of active infection occurring within 7 days of Screening or at the time of Screening
20. Treatment with or change in dosing of sodium glucose co-transporter 2 inhibitors (SGLT2i) during Screening and Run-In Periods. However, a stable dose regimen established at least 8 weeks prior to screening is acceptable.
21. Treatment with Tarpeyo™ (budesonide) or other approved treatments for IgAN within 6 months prior to screening. Treatment with Tarpeyo™ is not allowed during Screening and Run-In Periods or any time throughout the study.
22. Treatment with Kerendia® (finerenone) within 6 months prior to screening. Treatment with Kerendia® is not allowed during Screening and Run-In Periods.
23. Initiation of treatment with Filspari™ (sparsentan), a dual Endothelin Angiotensin Receptor Antagonist (dEARA) or similar medication within three months prior to screening. A stable dose initiated at minimum 3 months before screening is acceptable and will take the place of ACEi/ARB as background therapy.

8.3. Patient Withdrawal Criteria

Patients may voluntarily withdraw from receipt of study drug or from the study at any time for any reason without prejudice to further treatment.

8.3.1. Early Discontinuation of Study Drug

A patient must permanently discontinue study drug under any of the following circumstances:

- The patient becomes pregnant. Study drug must be discontinued immediately, and the pregnancy reported to the Sponsor.
- The patient wishes to discontinue study drug treatment for any reason.
- The patient experiences a medical emergency that necessitates discontinuing study drug treatment.
- The Investigator, Sponsor, or patient's primary care provider decides to discontinue treatment for medical reasons other than nonresponse to study treatment, or due to the patient's significant noncompliance with the protocol.

The reason for termination of study drug before study completion must be recorded in the patient's case report form (CRF). The patient should complete all scheduled study visits provided

written consent to do so has not been withdrawn. Patients who discontinue study drug prematurely will not be replaced.

8.3.2. Patient Withdrawal from the Study

A patient must be withdrawn from the study and discontinue study drug under the following circumstances:

- The patient wishes to withdraw consent to participate in the study.
- The Investigator or patient's primary care provider decides that the patient should be withdrawn from the study.
- The Sponsor decides that the patient should be withdrawn, or the Sponsor discontinues the study for any reason.
- Patient begins prohibited medications that necessitate withdrawal from study.

Prior to patient withdrawal from the study, the Investigator is strongly encouraged to contact the Medical Monitor to discuss withdrawal.

The reason for withdrawal must be recorded in the patient's source documents and CRF. The patient should complete the evaluations scheduled for the Week 96/End-of-Study (EOS) visit, provided written consent to do so has not been withdrawn. Patients who withdraw from the study will not be replaced.

8.3.3. Notification of Withdrawal

When a study participant is withdrawn from the study, voluntarily or involuntarily, the Investigator or designee will notify the Sponsor and the IRB/IEC as required and provide the reasons for patient withdrawal.

9. STUDY DRUG

Further information on the study drug, including storage and handling requirements, is provided in the Investigator's Brochure (IB).

9.1. Narsoplimab

Narsoplimab is manufactured under current Good Manufacturing Practices (cGMP) for investigational use. Narsoplimab is a human IgG4 mAb directed against MASP-2.

[redacted]

Narsoplimab will be further diluted for IV administration in accordance with the preparation instructions described in Section 9.4.

9.1.1. Packaging and Labeling

Narsoplimab is packaged in 2-mL clear-glass vials containing 2 mL of narsoplimab. Each vial will come packaged in a single carton.

The vials and single outer cartons will be labeled in accordance with applicable regulations, including at a minimum the following information:

- Name of the drug product (narsoplimab [redacted]
- Product identification number
- Regulatory cautionary statement regarding investigational or clinical trial use

9.2. Vehicle Control to Match Narsoplimab

Vehicle control, 50 mL solution, for patients randomized to the control arm, will be commercially packaged 5% dextrose in water (D5W) or normal saline solution.

9.2.1. Packaging and Labeling

Commercial packaging of polyvinyl chloride or polyolefin (including polypropylene, a common polyolefin) infusion bags containing a minimum of 50 mL of D5W or normal saline solution should remain intact. For infusion bags with volume over 50 mL, refer to Section 9.4 for guidance regarding disposition of additional volume.

9.3. Blinding

Patients will be randomized in a 1:1 fashion to receive either narsoplimab or placebo. Randomization will be stratified by the baseline eGFR level (≥ 30 to ≤ 45 mL/min/1.73 m^2 and > 45 mL/min/1.73 m^2) and by baseline UPE (> 1 to < 2 g/day and ≥ 2 g/day).

Treatment assignment will be blinded to all trial personnel and to Omeros and its representatives, with the following exceptions:

- Drug Safety personnel – to meet safety reporting requirements, select serious adverse events and suspected unexpected serious adverse event reactions must be unblinded to submit for expedited reporting. Aggregate safety reports may also require an 'unblinded' report for regulatory submission.
- Investigative site pharmacist or designee who is responsible for maintaining the blind at the site and who will receive investigational product, request additional investigational product, prepare, and label the infusion. To maintain the blind, this unblinded pharmacist will also be responsible for receiving open-label narsoplimab, requesting additional narsoplimab, as well as preparing and labeling the narsoplimab for infusion.
- An independent site monitor (Clinical Research Associate) who will only monitor study drug accountability
- Omeros Chemistry, Manufacturing, and Controls representative who will manage drug supply

- Omeros Clinical Data Manager or designee overseeing the implementation of the randomization module
- Designated Omeros Clinical Trial Manager and CRO Lead Clinical Research Associate who receives questions from sites regarding investigational product
- Designated CRO Document Management Associate who oversees the unblinded Trial Master File
- Designated Omeros Quality Assurance Associate who is the point of contact for investigational product temperature excursions and other quality issues
- The Independent Data Safety Monitoring Committee (IDMC) members will be unblinded for the interim data analysis

In a medical emergency, it may be necessary to identify a patient's assigned treatment before the study has been completed and treatments unblinded. The treatment blind should only be broken if this information is necessary to treat the patient for a medical condition. In this situation, it is important that the treatment blind be maintained for all other patients. The Omeros Medical Monitor should be contacted immediately if the treatment blind is broken. The date and reason for breaking the blind must be discussed with the Omeros Medical Monitor and recorded in the source documents.

Unblinding a patient's treatment assignment by the Investigator or study site personnel under any other circumstances (except as noted above) will be considered a protocol deviation.

9.4. Preparation of Study Drug

[redacted]

9.5. Storage and Handling of Study Drug

Narsoplimab vials must be stored refrigerated at 2° to 8°C. Allow narsoplimab to come to room temperature without manipulation (e.g., warming up in your hands or putting the vial in hot water is not allowed) for a minimum of 30 minutes following removal from refrigerated storage, and then use to prepare the appropriate dosing solution. Narsoplimab must be used to prepare the appropriate dosing solution within 4 hours following piercing of the vial septum.

Storage and handling of vehicle control is according to the manufacturer's instructions.

9.6. Study Drug Accountability

The Investigator will designate an unblinded pharmacist and/or designee who will be responsible for study drug accountability.

In compliance with FDA, European Medicines Agency (EMA), and other applicable regulations, records will be maintained by the Investigator and/or pharmacist designee for narsoplimab delivery to the site, the inventory at the site, the use of each vial, and the return/final disposition of used and unused drug product, including dates and quantities. The Investigator and/or pharmacist designee will maintain the investigative site's study drug accountability documentation. After the study has been completed, a copy of the drug accountability records will be provided to the Sponsor. The original drug accountability records will be retained by the site.

9.7. Return of Unused Drug Product

At the end of the study, the Sponsor will inform the site as to the disposition of unused drug product. If instructed, unused supplies may be destroyed at the site according to local laws, regulations, and the institution's standard operating procedures.

10. STUDY PROCEDURES

The Schedule of Events is summarized in Section 20.2.

10.1. Description of Study Procedures

The sections below describe the individual study procedures outlined in subsequent sections and in the Schedule of Events (Section 20.2).

For procedures that are impacted by COVID-19, please reference COVID Contingencies (Section 20.4).

10.1.1. Informed Consent

All patients must personally sign and date the IRB/IEC-approved informed consent form before any study-specific procedures are performed.

10.1.2. Medical History

A complete medical and surgical history will be obtained by the Investigator or designee prior to enrollment and recorded in the eCRF.

10.1.3. Prior/Concomitant Medications

All outpatient medications taken within the 6 months prior to Screening and during the Screening and Run-In Periods will be obtained prior to enrollment and recorded in the eCRF. At each study visit, the site will capture all medications taken by the patient since the last visit or during the visit (as applicable). Concomitant medications include prescription and non-prescription medications, vitamins, and minerals.

10.1.4. Physical Examination

This study requires complete physical examinations at specific study visits per the Schedule of Events (Section 20.2). At a minimum, the complete physical examination will include respiratory, abdomen, cardiovascular, central nervous system, head, ears, eyes, throat, skin, musculoskeletal system, neck, lower extremities, height, and weight (with the patient standing without shoes), and assessment of disease-related clinical signs and symptoms. Complete physical exams will not include breast, urogenital, or rectal examination unless clinically necessary. Complete physical examination findings during the Screening Period will be reported as medical history.

Complete physical examinations will also be performed at Screening, T12, Follow-Up 1 (Week 48) and Follow-Up 3/EOS (Week 96), 6-Week Relapse Retreatment Visit 6, 12-Week Relapse Retreatment Visit 12, and Open-Label Treatment Visit 12. Physical examinations at all other study timepoints will be symptom directed.

10.1.5. Blood Pressure Optimization

During the Run-In Period, patients will have appropriate lifestyle changes initiated and medications optimized as needed to attain/maintain a BP target of < 125/75 mmHg, in accordance with current KDIGO guidelines for patients with proteinuria of > 1 g/day and the Investigator's clinical judgment. Renin-angiotensin system blockade will be used for BP control with either ACEIs or ARBs. Additional BP medications may be added if maximally tolerated RAS blockade does not provide adequate BP control. For patients requiring RAS blockade adjustment during the Run-In Period, the BP will be optimized, and this optimized BP should be maintained.

10.1.6. Randomization

Patients may be randomized at the time of the Treatment 1 Visit (T1) or up to 24 hours prior to T1. Eligible patients will be randomized in the study via an electronic randomization system. Patients will be randomized in a ratio of 1:1 double-blind assignments to narsoplimab (active

treatment group) or placebo group. Randomization will be stratified by the baseline eGFR level (≥ 30 to ≤ 45 mL/min/1.73 m^2 and > 45 mL/min/1.73 m^2) and by baseline UPE (> 1 to < 2 g/day and ≥ 2 g/day).

10.1.7. Vital Signs

Vital signs will include pulse, systolic and diastolic BP, respiratory rate, and body temperature. Vital signs should be collected with the patient in a seated position for at least 5 minutes before taking any measurement.

On study drug treatment days, vital signs will be collected prior to dosing, approximately 5 minutes after the end of the 30-minute study drug infusion, and 30 minutes (± 5 minutes) following the end of the study drug infusion.

10.1.8. Electrocardiogram

A 12-lead ECG will be collected at specific study visits per the Schedule of Events (Section 20.2). The ECG will be collected after at least 5 minutes of rest in the supine position. The ECG parameters include heart rate, PR interval, QRS interval, QT interval, and QTc interval calculated by Fridericia's formula (QTcF), along with a clinical interpretation by the Investigator. The Investigator will review and sign all ECGs and retain the signed tracing with the source documents.

10.1.9. Laboratory Assessments

The central laboratory will be responsible for comprehensive metabolic panel (CMP), complete blood count with differential (CBC+diff), hemoglobin A1c (HgbA1c), urinalysis (UA), uPCR, uACR, 24-hour UPE, viral serology, and serum pregnancy testing per Table 2. Other tests listed in Table 2 will be performed by the Sponsor or a designated laboratory.

Specific instructions for processing, labeling, and shipping samples will be provided in the central laboratory manual. The date and time of sample collection will be reported to the central laboratory.

Table 2: Laboratory Analytes

Comprehensive Metabolic Panel	Complete Blood Count with Differential	Urinalysis	Other Analytes
Albumin Blood urea nitrogen Calcium Carbon dioxide (Bicarbonate) Chloride Creatinine Glucose Potassium Sodium Total Bilirubin Total Protein ALT Alkaline Phosphatase AST eGFR[1]	WBC RBC Hemoglobin Hematocrit MCV MCH MCHC RDW Platelet count MPV Absolute and percent neutrophils Absolute and percent lymphocytes Absolute and percent monocytes Absolute and percent eosinophils Absolute and percent basophils	Specific Gravity pH Protein Glucose Ketones Blood (hemoglobin) Leukocyte esterase Nitrite Bilirubin Urobilinogen Reflexive quantitative hematuria test when blood is present	PK PD ADA NAb Biomarkers 24-hour UPE uPCR uACR HIV Hepatitis B Hepatitis C Urine pregnancy test[2] Serum pregnancy test[2] HgbA1c

Abbreviations: ADA = anti-drug antibodies; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMP = comprehensive metabolic panel; eGFR = estimated glomerular filtration rate; HgbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MPV = mean platelet volume; NAb = neutralizing antibodies; PD = pharmacodynamics; PK = pharmacokinetics; RBC = red blood cells; RDW = red cell distribution width; uACR = urine albumin creatinine ratio; uPCR = urine protein creatinine ratio; UPE = urine protein excretion; WBC = white blood cells

1. eGFR will be calculated by the central laboratory
2. Pregnancy test for women of childbearing potential only. Test must be via serum for the final Run-In Visit and via urine for all other required visits.

10.1.9.1. 24-hour Urine Collection

Patients should be given specific instructions on the 24-hour urine collection. At a minimum, patients should be instructed to collect all urine over a 24-hour period, to keep the sample cold/refrigerated during the collection period, and to return the sample as soon as possible following its collection.

During the Run-In Period, patients will be instructed to collect two 24-hour urine collection samples, which must be collected no more than 14 days apart during the last 2 weeks of the Run-In Period. Investigative sites may use their discretion as to when to dispense the collection supplies for these two specimens.

Twenty-four-hour urine samples will be collected for specific study visits per the Schedule of Events (Section 20.2).

The 24-hour urine collection sample will be used to assess UPE, uPCR, and uACR. At some visits, spot urine will be used to assess uPCR and uACR per the Schedule of Events.

With patient consent, the 24-hour urine collection samples may be delivered from the patient's location to the study site by a specialty courier selected by the sponsor.

10.1.9.2. Pharmacokinetics and Pharmacodynamics

Blood samples will be collected for PK and PD assessments anytime at the final Run-In Visit (RI Visit, 15 minutes (± 5 minutes) after the end of the 30-minute infusion at T1, 168 hours (± 2 hours) after the start of the first dose (sample collected at Treatment 2 [T2]), and pre-dose at visits T4, T8, T10, and T12.

Blood samples will be collected for PK and PD 15 minutes (± 5 minutes) after the end of the 30-minute infusion at ExT1, 6RT1, 12RT1, and OLT12, and pre-dose at 6RT6, 12RT12, and OLT12.

10.1.9.3. Biomarkers

Serum, plasma, and urine will be collected for biomarkers at specific study visits, pre-dose, per the Schedule of Events (Section 20.2). Biomarkers assessed in this study may include but are not necessarily limited to: MBL (urine and serum), C4a (urine), C4d (urine), KIM-1 (urine), NGAL (urine), clusterin (urine), sMAC (urine), CL-11 (urine), and markers of tubular and glomerular damage. An exploratory evaluation of other relevant biomarkers may be conducted.

10.1.9.3.1. Serum and Urine Biomarkers and Antidrug Antibodies

Blood samples will be collected for ADA and NAb, and serum, plasma, and urine will be collected for biomarkers at specific study visits per the Schedule of Events (Section 20.2). In addition to these timepoints, prior to study drug retreatment, urine, serum, and plasma samples will be collected for assessment of biomarkers in patients who have relapsed.

10.1.9.3.2. Kidney Biomarkers

As an optional procedure, a block section of the original renal biopsy specimen used to confirm IgAN, if available, will be stained for MBL, or an unstained slide will be assessed for other biomarkers including C4, C3, IgA, galactose-deficient IgA, and/or sMAC (c5b-9). The sample will be sent to a specialty lab. Findings from this investigation will address the following issues and, potentially, others:

- Determine the proportion of patients in the study with MBL deposition
- Clarify whether MBL deposition is associated with disease severity and progression in IgAN
- Determine whether MBL deposition impacts response to narsoplimab

10.2. Study Schedule

The study visits described in this section will occur per the Schedule of Events (Section 20.2). The tests and procedures outlined in this section are further detailed in Section 10.1.

For procedures that are impacted by COVID-19, please reference COVID Contingencies (Section 20.4).

10.2.1. Screening Period (within 28 days prior to the Run-In Period)

The following tests and procedures are performed within the Screening Period at the timepoints indicated in the Schedule of Events (Section 20.2.1) to determine patient eligibility prior to the Run-In Period.

Before any of the screening procedures are performed for the specific purpose of this study, the patient must provide informed consent for this study in compliance with regulations and governing IRB/IEC requirements. A patient is considered entered into the study once they have provided informed consent and have been assigned a patient number.

All screening procedures will be completed within the 28 days prior to the patient proceeding into the Run-In Period. Screening procedures may take place on multiple days as long as they occur within the 28 days prior to the patient entering the Run-In Period.

The last clinical and laboratory evaluations performed during the Screening Period will provide the baseline for the Run-In Period.

10.2.1.1. Screening Period (within 28 days prior to the Run-In Period)

During the Screening Period, the procedures listed below will be performed and documented to determine patient eligibility prior to proceeding to the Run-In Period. The date on which the first study assessment occurs other than informed consent (e.g., medical history, complete physical exam, etc.) will be considered the official Screening Visit (SV):

- Obtain patient informed consent
- Review inclusion/exclusion criteria
- Register patient in the electronic data capture (EDC) system
- Assess medical history, including history of prior medication use
- Perform complete physical examination, including height and weight. Examination of breast, rectal, and genitourinary systems may be deferred unless clinically necessary
- Collect vital signs including BP, pulse rate, respiratory rate (RR) and temperature (after at least 5 minutes in a seated position)
- Complete ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, uACR/uPCR, and pregnancy test
- Complete urine pregnancy test
- Collect blood samples for CMP, CBC+diff, HgbA1c and serology for HIV, HBV, and HCV
- Adverse events will be collected beginning at the time of informed consent
- Assess concomitant medications/therapies
- At site discretion, dispense 24-hour urine collection supplies for collection of two 24-hour UPEs during the Run-In Period and provide patient with collection instructions. The urine collections should occur no more than 14 days apart during the

last two weeks of the Run-In Period. Patients should be instructed to return the 24-hour urine specimens to the clinic as soon as possible following their collection. Patients may collect both urine specimens in subsequent 24-hour periods if both collections are completed within three calendar days and the specimens returned to the study site within one calendar day following the 2nd collection.

Patients who meet all the study eligibility criteria during the Screening Period may proceed to the Run-In Period. Patients who do not meet the screening criteria may be rescreened a minimum of 30 days after Screen Failure. Patients may be rescreened once, with additional rescreening allowed based on Medical Monitor approval.

10.2.2. Run-In Period

The Run-In Period will follow the Screening Period and will last either 4 weeks or 12 weeks. During the Run-In Period, patients will have appropriate lifestyle changes initiated and medications optimized to attain/maintain a BP target of less than 125/75 mm Hg. Considering that some patients may not tolerate this target, there will be deference to the clinical judgment of the managing physician/Investigator regarding patients who have attained a stable maximum tolerable-dose regimen.

For patients who have been on documented, verifiable, maximally, or near-maximally tolerated doses of ACE inhibitors and/or ARBs for 8 weeks or more prior to Screening, the Run-In Period will be 4 weeks and will consist of two Run-In Visits occurring 4 weeks apart: Run-In Visit 1, and Run-In Visit 2 (which will serve as the final Run-In Visit). For all other patients, the Run-In Period will be 12 weeks and will consist of four Run-In Visits occurring every 4 weeks: Run-In Visits 1 through 4. In this case, Run-In Visit 4 will serve as the final Run-In Visit. The first Run-In Visit will occur no more than 28 days following the Screening Visit with the remainder of the visits occurring at 4-week intervals (± 7 days). Patients may return for additional, unscheduled visits during the Run-In Period as needed.

The maximum dose of RAS blockade will be determined as the dose tolerated by the patient or the country-approved maximum dose for hypertension. For patients who are not on stable, maximally tolerated doses of RAS blockade, RAS blockade will be optimized early in the Run-In Period, with the goal of attaining optimized BP control and maintaining it during the remainder of the Run-In Period. To progress to the Initial Treatment Period, the mean value of the two 24-hour UPE collections from the Run-In Period must be greater than 1 g/day. Baseline proteinuria will be the mean of two 24-hour UPE measurements performed at the end of the Run-In Period. During the Run-In Period and throughout the entire study, patients will be advised to avoid nonsteroidal anti-inflammatory drugs and any other nephrotoxic medicines. All patients must be stable on documented, verifiable, maximally tolerated RAS blockade prior to randomization.

If a patient does not meet the criteria to enter the Initial Treatment Period, the patient may be rescreened after a minimum of 30 days.

Data collected at the final Run-In Visit will serve as the study baseline. After completion of this period, patients who are eligible and who enroll in the Initial Treatment Period will be randomized in a double-blind manner into one of two groups: the placebo or active (narsoplimab) treatment group.

10.2.2.1. Run-In Visit 1 (RI1)

Run-In Visit 1 (RI1) must occur no more than 28 days following the SV and should be scheduled to occur as quickly as possible after all inclusion/exclusion criteria for Screening have been met.

Renin-angiotensin system blockade will be used for BP control with either ACEIs or ARBs. Additional BP medications may be added if maximally tolerated RAS blockade does not provide adequate BP control. All patients will continue to receive optimized RAS blockade throughout the study regardless of study timepoint or response status.

During the COVID-19 pandemic, RI1 may be conducted virtually (e.g. via telephone or video conference. All procedures noted below may be conducted over the phone with the exception of the collection of respiratory rate and the symptom-directed physical exam, which will be waived under these circumstances. If service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service, RI1 may be conducted at the patient's home.

During RI1, the procedures listed below will be performed and documented:

- Review inclusion/exclusion criteria
- Perform symptom-directed physical examination
- Blood pressure medication optimization, if additional adjustment needed
- Collect vital signs, including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- At site discretion, dispense 24-hour urine collection supplies for collection of two specimens and provide patient with collection instructions. The 24-hour urine collection supplies may be mailed to the patient at any point deemed convenient by the site and patient as long as the supplies are provided in time for the patient to collect the two 24-hour urine samples within the required timeframe. The urine collections should occur no more than 14 days apart during the two weeks prior to the final Run-In Visit. Patients should be instructed to return the 24-hour urine specimens to the clinic as soon as possible following their collection. The 24-hour urine collection specimens may be delivered to the study site by the specialty courier service selected by the sponsor, provided the patient has granted consent. Patients may collect both urine specimens in subsequent 24-hour periods if both collections are completed within three calendar days and the specimens returned to the study site within one calendar day following the 2nd collection.

10.2.2.2. Run-In Visit 2 (RI2, 4 weeks ± 7 days after RI1)

If the patient has been on documented, verifiable, maximally tolerated doses of RAS blockade for 12 or more weeks (8 or more weeks prior to Screening and 4 weeks during Run-In), per

Investigator discretion, RI2 may serve as the final study visit during the Run-In Period. These patients should have stable BP control (i.e., have had an unchanged dose regimen of BP medications for at least 4 weeks prior to Screening).

During Run-In Visit 2 (RI2), the procedures listed below will be performed and documented:

- Review inclusion/exclusion criteria
- Perform symptom-directed physical examination
- Blood pressure medication optimization, if additional adjustment needed
- Collect vital signs, including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position)
- Assess AEs
- Assess concomitant medications/therapies
- At site discretion, dispense 24-hour urine collection supplies for collection of two specimens and provide patient with collection instructions. The 24-hour urine collection supplies may be mailed to the patient at any point deemed convenient by the site and patient as long as the supplies are provided in time for the patient to collect the two 24-hour urine samples within the required timeframe. The urine collections should occur no more than 14 days apart during the two weeks prior to the final Run-In Visit. Patients should be instructed to return the 24-hour urine specimens to the clinic as soon as possible following their collection. The 24-hour urine collection specimens may be delivered to the study site by the specialty courier service selected by the sponsor, provided the patient has granted consent. Patients may collect both urine specimens in subsequent 24-hour periods if both collections are completed within three calendar days and the specimens returned to the study site within one calendar day following the 2nd collection.

The following procedures will be only performed if the patient has been on documented, verifiable, maximally tolerated doses of RAS blockade for 12 or more weeks and, per Investigator discretion, where RI2 is the final study visit during the Run-In Period.

- Complete ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, uACR/uPCR, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Collect blood samples for comprehensive metabolic panel, CBC+diff, HgbA1c, serum pregnancy test, PK, PD, ADA, NAb, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood)

The two 24-hour urine collections should occur during the two weeks prior to this visit that is, both collections should occur no more than 14 days apart during the last two weeks of the Run-In Period.

These procedures will be performed and documented when RI2 is the final study visit during the Run-In Period:

- Collect 24-hour urine samples from patient; collected twice, no more than 14 days apart
- Collect aliquots of urine from each 24-hour urine sample to be used for UPE, uPCR and uACR assessment; collected twice, no more than 14 days apart

Results of clinical and laboratory evaluations conducted during the final RI Visit will provide the baseline for the Initial Treatment Period of the study. After the final RI Visit, patients may proceed to the Initial Treatment Period if they continue to meet all inclusion criteria and do not meet any of the exclusion criteria.

10.2.2.3. Run-In Visit 3 (RI3, 8 weeks ± 7 days after RI1)

Run-In Visit 3 will occur for those patients who require a 12-week Run-In Period. If service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service, RI3 may be conducted at the patient's home.

During RI3, the procedures listed below will be performed and documented:

- Review inclusion/exclusion criteria
- Perform symptom-directed physical examination
- Blood pressure medication optimization, if additional adjustment needed
- Collect vital signs, including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position)
- Assess AEs
- Assess concomitant medications/therapies
- At site discretion, dispense 24-hour urine collection supplies for collection of two specimens and provide patient with collection instructions. The 24-hour urine collection supplies may be mailed to the patient at any point deemed convenient by the site and patient as long as the supplies are provided in time for the patient to collect the two 24-hour urine samples within the required timeframe. The urine collections should occur no more than 14 days apart during the two weeks prior to the final Run-In Visit. Patients should be instructed to return the 24-hour urine specimens to the clinic as soon as possible following their collection. The 24-hour urine collection specimens may be delivered to the study site by the specialty courier service selected by the sponsor, provided the patient has granted consent. Patients may collect both urine specimens in subsequent 24-hour periods if both collections are completed within three calendar days and the specimens returned to the study site within one calendar day following the 2nd collection.

10.2.2.4. Run-In Visit 4 (RI4, 12 weeks ± 7 days after RI1)

For patients who require a 12-week Run-In Period, RI4 will serve as the final RI Visit.

During RI4, the procedures listed below will be performed and documented:

- Review inclusion/exclusion criteria
- Perform symptom-directed physical examination
- Blood pressure medication optimization
- Collect vital signs, including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position)
- Complete ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, uACR/uPCR, and biomarkers (if consent granted by patient for optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Collect blood samples for comprehensive metabolic panel, CBC+diff, HgbA1c, serum pregnancy test, PK, PD, ADA, NAb, and biomarkers (if consent granted by patient for optional research biomarkers, collect additional blood)
- Assess AEs
- Assess concomitant medications/therapies

The two 24-hour urine collections should occur during the two weeks prior to the last Run-In Visit, that is, both collections should occur no more than 14 days apart during the last two weeks of the Run-In Period. Patients should be instructed to return the 24-hour urine specimens to the clinic as soon as possible following their collection. The 24-hour urine collection specimens may be delivered to the study site by the specialty courier service selected by the sponsor, provided the patient has granted consent.

These procedures will be performed and documented when RI4 is the final study visit during the Run-In Period:

- Collect 24-hour urine samples from patient; collected twice, no more than 14 days apart
- Collect aliquots of urine from each 24-hour urine sample to be used for UPE, uPCR and uACR assessment; collected twice, no more than 14 days apart

Results of clinical and laboratory evaluations conducted during the final RI Visit will provide the baseline for the Initial Treatment Period of the study. After the final RI Visit, patients may proceed to the Initial Treatment Period if they continue to meet all inclusion criteria and do not meet any of the exclusion criteria.

Treatment Visit 1 (T1) must be scheduled to occur no more than 7 days from receipt of all lab results, including both 24-hour UPEs, from the Central Lab.

10.2.3. Initial Treatment Period (Weeks 1-12)

During the Initial Treatment Period, the patients will be randomized to receive either narsoplimab (370 mg) or placebo, administered IV once weekly for 12 weeks. Treatment Visit 1 (T1) must occur no more than 7 days from receipt of all lab results, including both 24-hour UPEs, from the Central Lab. Target dates for subsequent Treatment Visits will be based on the Treatment Visit 1 date. Treatment Visit 2 (T2), T4, T8, T10, and T12 must occur within ± 2 days

of the target date due to the PK/PD blood draw; Treatment Visits 3, 5, 6, 7, 9, and 11 must be within ± 3 days of the target date. A minimum of two calendar days must separate each administration of study drug.

During the Initial Treatment Period, if the original kidney biopsy is available, an optional procedure will be to send specimens from the kidney biopsy to a specialty laboratory for analysis.

If service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service, Treatment Visits 4 through 11 may occur at the patient's home with the support of a home nursing vendor selected by the sponsor.

10.2.3.1. Method of Assigning Patients to Treatment Groups

On the day of or up to 24 hours prior to T1, eligible patients will be randomized in the study via the electronic randomization system. Computer-generated permuted block randomization will be created in a ratio of 1:1 double-blind assignment to narsoplimab (active treatment group) or placebo. Randomization will be stratified by the baseline eGFR level (≥ 30 to ≤ 45 mL/min/1.73 m^2 and > 45 mL/min/1.73 m^2) and by baseline UPE (> 1 to < 2 g/day and ≥ 2 g/day).

10.2.3.2. Treatment Visit 1 (T1, Week 1)

Treatment Visit 1 should be scheduled to occur as soon as possible from receipt of all laboratory results, and no more than 7 days from receipt of all laboratory results, including the second 24-hour UPE result from the final RI visit.

During T1, the procedures listed below will be performed and documented prior to treatment with study drug:

- Perform randomization in the electronic randomization system (if not previously completed in the 24 hours prior to the visit) (this procedure will not be repeated for patients who resume or reinitiate study treatment after a COVID-19 related interruption)
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position)
- Complete pre-dose ECG after patient has been supine for at least 5 minutes
- Collect urine sample and complete pregnancy test
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During T1, the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion
- Complete post-dose ECG at the end of the study drug infusion after at least 5 minutes of rest in a supine position; this should be obtained immediately before the post-dose PK/PD samples
- Collect PK/PD samples 15 minutes (± 5 minutes) after the end of the study drug infusion

At site discretion and for patient convenience, dispense 24-hour urine collection supplies to the patient at any time during T1 to T10 along with collection instructions. Patients will have the option to collect the 24-hour urine specimen at any point between T10 to T11. Patients should be instructed to return the 24-hour urine specimen to the clinic as soon as possible following its collection.

10.2.3.3. Treatment Visit 2 through Treatment Visit 11 (Weeks 2 through 11)

Treatment Visits 2, 4, 8, and 10 must occur within ± 2 days of the target date due to the PK/PD sample collection. Due to the timing of the PK/PD sample collection at Treatment Visit 2, whenever possible, patients should be encouraged to return for this visit on the target date. Treatment Visits 3, 5, 6, 7, 9, and 11 must occur within ± 3 days of their target date. For visits T2 through T11, the procedures listed below will be performed and documented prior to treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Collect PK/PD sample (**Visits T2 [at 168 ± 2 hours from start of dosing at T1], T4, T8, and T10 only**)
- Collect blood samples for CMP, CBC+diff, (**Visits T4 and T8 only**)
- Collect spot urine sample for uPCR, uACR, UA (**Visits T4 and T8 only**)
- Collect blood for ADA/ NAb and collect blood and urine samples for biomarkers **(Visit T4 only)** (if consent granted by patient for optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual and collect additional blood)
- Collect urine sample and complete pregnancy test (**Visits T4 and T8 only**)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

- Dispense 24-hour urine collection supplies along with collection instructions to patient
  - At site discretion and for the convenience of the patient, these may be dispensed to the patient at any time during T1 to T10. Patients will have the option to collect the 24-hour urine specimen at any point between T10 and T11. Patients should be instructed to return the 24-hour urine specimen to the site as soon as possible after its collection.

The study drug should be prepared and infused per Section 9.4.

During T2 through T11, the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

The procedures listed below may be performed and documented before, during or after the T11 visit:

- Collect 24-hour urine sample from patient
- Collect aliquot of urine from the 24-hour urine sample to be used for UPE, uPCR and uACR assessment

10.2.3.4. Treatment Visit 12/End-of-Initial Treatment (Week 12)

On completion of the Initial Treatment Period, the T12/End-of-Initial Treatment (EOT) evaluation will be conducted ± 2 days of the target date. For visit T12, the procedures listed below will be performed and documented prior to treatment with study drug:

- Perform complete physical examination including height and weight. Examination of breast, rectal, and genitourinary systems may be deferred unless clinically necessary
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Complete pre-dose ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, uPCR, uACR, pregnancy test, and biomarkers (if consent granted by patient for optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete urine pregnancy test
- Collect blood samples for CMP, CBC+diff, PK, PD, ADA, NAb, and biomarkers (if consent granted by patient for optional research biomarkers, collect additional blood)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential

- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During T12, the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

Once the 24-hour UPE results are available, assess the patients' response and the need for extended treatment with study drug as follows:

- Patients who are determined to have a 24-hour UPE > 1 g based upon the 24-hour urine specimen collected between T10 and T11 will receive 6 additional weeks of treatment (extended treatment) according to their originally assigned treatment group in a blinded fashion

Additional details surrounding study drug retreatment are provided in Section 10.2.7 and Section 20.3.

At site discretion, the 24-hour urine collection supplies for Weeks 24, 30, and 36 may be dispensed at this visit or at any point that is convenient to the patient and study site.

10.2.4. Extended Treatment Following Week 12

During the Extended Treatment Period, eligible patients will receive treatment with study drug according to the patient's originally assigned treatment group in a blinded fashion. Study drug treatment will be administered IV once weekly for 6 weeks. Extended Treatment Visit 1 should occur no later than 14 days from the date of T12.

Target dates for subsequent Extended Treatment Visits will be based on the Extended Treatment Visit 1 date. Extended Treatment Visits 2 through 6 must occur within ± 3 days of the target date. A minimum of two calendar days must separate each administration of study drug.

If service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service, Extended Treatment Visits 3, 4, and 5 may occur at the patient's home with the support of a home nursing vendor selected by the sponsor.

10.2.4.1. Extended Treatment Visit 1 (ExT1)

During ExT1, the procedures listed below will be performed and documented prior to treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position)
- Complete pre-dose ECG after patient has been supine for at least 5 minutes

- Collect urine sample for UA, pregnancy, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete urine pregnancy test
- Collect blood samples for ADA, NAb and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood samples)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade
- At site discretion and for patient convenience, dispense 24-hour urine collection supplies to the patient at any time during ExT1 to ExT5 along with collection instructions. Patients will have the option to collect the 24-hour urine specimen at any point between ExT5 to ExT6. Patients should be instructed to return the 24-hour urine specimen to the clinic as soon as possible following its collection.

The study drug should be prepared and infused per Section 9.4.

During ExT1, the procedures listed below will be performed and documented following treatment with study drug:

- Complete post-dose ECG at the end of the study drug infusion after at least 5 minutes of rest in a supine position, to be obtained immediately before the post-dose PK/PD samples
- Collect PK/PD samples 15 minutes (± 5 minutes) after the end of the study drug infusion
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

10.2.4.2. Extended Treatment Visits 2, 3, and 5 (ExT2, ExT3, and ExT5) ± 3 days

For ExT2, ExT3, and ExT5, the visits must occur within ± 3 days of their target date. The procedures listed below will be performed and documented prior to treatment with study drug.

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential

- Confirm and document stability of RAS blockade
- At site discretion and for patient convenience, dispense 24-hour urine collection supplies to the patient at any time during ExT1 to ExT5 along with collection instructions. Patients will have the option to collect the 24-hour urine specimen at any point between ExT5 to ExT6. Patients should be instructed to return the 24-hour urine specimen to the clinic as soon as possible following its collection.

The study drug should be prepared and infused per Section 9.4.

During ExT2, ExT3, and ExT5, the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

10.2.4.3. Extended Treatment Visit 4 (ExT4) ± 3 days

Extended Treatment Visit 4 must occur within ± 3 days of the target date. For visit ExT4 the procedures listed below will be performed and documented prior to treatment with study drug.

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Collect urine sample for uPCR, uACR, UA, and pregnancy test
- Perform pregnancy test
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade
- At site discretion and for patient convenience, dispense 24-hour urine collection supplies to the patient at any time during ExT1 to ExT5 along with collection instructions. Patients will have the option to collect the 24-hour urine specimen at any point between ExT5 to ExT6. Patients should be instructed to return the 24-hour urine specimen to the clinic as soon as possible following its collection.

The study drug should be prepared and infused per Section 9.4.

During ExT4, the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

10.2.4.4. Extended Treatment Visit 6 (ExT6) ± 3 days

For ExT6, the visit must occur within ± 3 days of the target date. The procedures listed below will be performed and documented prior to treatment with study drug.

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During ExT6, the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

The procedures listed below may be performed and documented before, during or after the ExT6 visit:

- Collect 24-hour urine sample from patient
- Collect aliquots of urine from the 24-hour urine sample to be used for UPE, uPCR and uACR assessment

After ExT6, the procedures listed below will be performed and documented:

- Once laboratory results are available, assess the response

10.2.5. Response Evaluation Period (Weeks 13-36)

Following the 12-week Initial Treatment Period, all patients enter the Response Evaluation Period.

The Response Evaluation Period will consist of one study visit at Week 36, where 24-hour UPE and other laboratory measurements will be taken, per the Schedule of Events (Section 20.2) and patients will be assessed for response. Phone calls will occur at Weeks 16, 20, 24, 30, and 34. At the Week 24, Week 30, and Week 36 timepoints, 24-hour UPEs will be collected to assess for response and need for retreatment for relapse, per the Schedule of Events (Section 20.2). Patients will only be retreated for relapse once during the Response Evaluation Period (Week 24, Week 30, or Week 36).

Patients will continue with BP medications for optimum BP control and other beneficial medication and lifestyle modifications.

At Week 36, the clinical and laboratory evaluations conducted represent the primary efficacy measures.

10.2.5.1. Response Evaluation Telephone Calls (Weeks 16, 20, 24, 30, and 34) ± 7 days

Five patient telephone calls will be made during the Response Evaluation Period at Weeks 16, 20, 24, 30, and 34. All telephone calls should occur within ± 7 days of the target date. Each patient telephone call will be documented in the patient's source documents and the CRF and will assess concomitant medications and AEs. Telephone calls do not need to be performed if they overlap with a scheduled extended treatment visit or scheduled relapse retreatment visit.

In addition to the telephone calls, to assess patient response and potential need for relapse retreatment, a 24-hour UPE will be performed at the Week 24 timepoint and again at the Week 30 timepoint. Patients will be required to collect one 24-hour urine specimen at each timepoint (Week 24 and Week 30).

The procedures below will be performed and documented for the Week 24 and Week 30 timepoints:

- Dispense 24-hour urine collection supplies along with collection instructions to patient
  - At site discretion and for the convenience of the patient, these may be dispensed at any time prior to or during the Response Evaluation Period along with collection instructions
  - To provide flexibility for patients, each 24-hour urine specimen may be collected within 7 days prior to or after the designated timepoint (Week 24 and Week 30)
  - Patients should be instructed to return each 24-hour urine specimen to the site as soon as possible after its collection. The 24-hour urine collection specimens may be delivered to the study site by the specialty courier service selected by the sponsor, provided the patient has granted consent.
- Collect 24-hour urine sample from patient
- Collect aliquots of urine from 24-hour urine sample to be used for UPE, uPCR and uACR assessment
- Once laboratory results are available, assess the response and the need for patient study drug retreatment as per Section 10.2.7 and Section 20.3
- Patients identified as relapsers at Week 24 or Week 30 will receive 6 additional weeks of treatment (6-week relapse retreatment) according to their originally assigned treatment group in a blinded fashion. Patients will only be retreated for relapse once during the Response Evaluation Period (Week 24, Week 30, or Week 36).

10.2.5.2. Response Evaluation Visit (Week 36) ± 7 days (Primary Endpoint)

For the Response Evaluation Visit at Week 36 the procedures listed below will be performed and documented:

- Perform symptom-directed physical examination

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position)
- Complete ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, uPCR, uACR, pregnancy test, and biomarkers (if consent granted by patient for optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete urine pregnancy test
- Collect blood samples for CMP, CBC+diff, ADA, NAb, biomarkers (if consent granted by patient for optional research biomarkers, collect additional blood)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The procedures below may be performed and documented before, during, or after the Response Evaluation Visit, Week 36:

- Dispense 24-hour urine collection supplies along with collection instructions to patient
- At site discretion and for the convenience of the patient, these may be dispensed to the patient at any time during the Response Evaluation Period. The 24-hour urine collection supplies may be mailed to the patient at any point deemed convenient by the site and patient as long as the supplies are provided in time for the patient to collect the 24-hour urine sample within the required timeframe.
  - Patients will have the option to collect the 24-hour urine specimen within 48 hours prior to the Response Evaluation Visit or within 48 hours after the Response Evaluation Visit. Patients should be instructed to return the 24-hour urine specimen to the site as soon as possible after its collection. The 24-hour urine collection specimens may be delivered to the study site by the specialty courier service selected by the sponsor, provided the patient has granted consent.
- Collect 24-hour urine sample from patient
- Collect aliquot of urine from 24-hour urine sample to be used for UPE, uPCR and uACR assessment
- Once laboratory results are available, assess the response as per Section 10.2.7. Additional details surrounding response assessment and study drug retreatment are provided in Section 10.2.7 and Section 20.3.

10.2.6. Follow-Up Period (Weeks 37-96)

Following the Response Evaluation Period, all patients will enter the Follow-Up Period from Week 37 through Week 96. Visits will occur at Weeks 48, 72 and 96/EOS. Between study visits, interim telephone calls will occur to monitor patient safety at Weeks 40, 44, 60, and 84. During this period, 24-hour UPE and other laboratory measurements will be collected, and patients will be assessed for response and offered retreatment according to their originally assigned treatment group in a blinded fashion if they relapse. Patients who relapse (as defined below) at Week 48 or Week 72 will be treated for 12 additional weeks following the relapse, then will be assessed for response. Retreatment for relapse may occur once during the Follow-Up Period.

All patients will continue optimized antihypertensive medication treatment and attempt to maintain optimized blood pressure throughout the study.

- **Relapsers**: Relapsers are patients who show a response to treatment of at least 30% reduction from baseline proteinuria at any post-treatment assessment timepoint but subsequently demonstrate an increase in 24-hour UPE by ≥ 30% from the value of their lowest measured post-treatment UPE and have a 24-hour UPE > 1 g. Patients who relapse will be retreated once.

10.2.6.1. Follow-Up Visit 1 (FU1) (Week 48) ± 14 days

Follow-Up Visit 1 (Week 48) must occur within ± 14 days of the target date. The procedures listed below will be performed and documented:

- Perform complete physical examination including height and weight. Examination of breast, rectal, and genitourinary systems may be deferred unless clinically necessary
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position)
- Complete ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, uPCR, uACR, pregnancy test and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete urine pregnancy test
- Collect blood samples for CMP, CBC+diff, ADA, NAb, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The procedures below will be performed and documented prior to, during, or after Follow-Up Visit 1:

- Dispense 24-hour urine collection supplies along with collection instructions to patient
  - At site discretion and for the convenience of the patient, these may be dispensed to the patient at any time during the Follow-Up Period. The 24-hour urine collection supplies may be mailed to the patient at any point deemed convenient by the site and patient as long as the supplies are provided in time for the patient to collect the 24-hour urine sample within the required timeframe. Patients will have the option to collect the 24-hour urine specimen within 48 hours prior to Follow-Up Visit 1 or within 48 hours after Follow-Up Visit 1. Patients should be instructed to return the 24-hour urine specimen to the site as soon as possible after its collection. The 24-hour urine collection specimens may be delivered to the study site by the specialty courier service selected by the sponsor, provided the patient has granted consent.
- Collect 24-hour urine sample from patient
- Collect aliquot of urine from 24-hour urine sample to be used for UPE, uPCR and uACR assessment
- Once all laboratory results are available, assess the response and the need for patient study drug retreatment as per Section 10.2.7.

Patients who have relapsed at the time of Follow-Up Visit 1 will receive an additional 12 weeks of study drug treatment. Study drug retreatment is limited to one 12-week course during the Follow-Up Period. Additional details surrounding response assessment and study drug retreatment are provided in Section 10.2.7 and Section 20.3.

10.2.6.2. Follow-Up Visit 2 (FU2) (Weeks 72) ± 14 days

Follow-Up Visit 2 (Weeks 72) must occur within ± 14 days of the respective target dates. The procedures listed below will be performed and documented for each visit:

- Perform symptom-directed physical examination
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position)
- Collect urine sample for UA, uPCR, uACR, and pregnancy
- Complete urine pregnancy test
- Collect blood samples for CMP and CBC+diff
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The procedures below will be performed and documented prior to, during, or after Follow-Up Visit 2:

- Dispense 24-hour urine collection supplies along with collection instructions to patient
  - At site discretion and for the convenience of the patient, these may be dispensed to the patient at any time during the Follow-Up Period. The 24-hour urine collection supplies may be mailed to the patient at any point deemed convenient by the site and patient as long as the supplies are provided in time for the patient to collect the 24-hour urine sample within the required timeframe. Patients will have the option to collect the 24-hour urine specimen within 48 hours prior to Follow-Up Visit 2 or within 48 hours after Follow-Up Visit 2. Patients should be instructed to return the 24-hour urine specimen to the site as soon as possible after its collection. The 24-hour urine collection specimens may be delivered to the study site by the specialty courier service selected by the sponsor, provided the patient has granted consent.
- Collect 24-hour urine sample from patient
- Collect aliquot of urine from 24-hour urine sample to be used for UPE, uPCR and uACR assessment
- Once all laboratory results are available, assess the response and the need for patient study drug retreatment as per Section 10.2.7

Patients who have relapsed at the time of Follow-Up Visit 2 receive an additional 12 weeks of study drug treatment. Study drug retreatment is limited to one 12-week course during the Follow-Up Period. Additional details surrounding response assessment and study drug retreatment are provided in Section 10.2.7 and Section 20.3.

10.2.6.3. Follow-Up Visit 3 (FU3/EOS) (Weeks 96) ± 14 days

Follow-Up Visit 3/EOS (Week 96) must occur within ± 14 days of the respective target date.

The procedures listed below will be performed and documented for this visit:

- Perform complete physical examination including height and weight. Examination of breast, rectal, and genitourinary systems may be deferred unless clinically necessary
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position)
- Complete ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, uPCR, uACR, pregnancy test, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete urine pregnancy test

- Collect blood samples for CMP, CBC+diff, ADA, NAb, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The procedures below will be performed and documented prior to, during, or after Follow-Up Visit 3/EOS:

- Dispense 24-hour urine collection supplies along with collection instructions to patient. The 24-hour urine collection supplies may be mailed to the patient at any point deemed convenient by the site and patient as long as the supplies are provided in time for the patient to collect the 24-hour urine sample within the required timeframe.
  - At site discretion and for the convenience of the patient, these may be dispensed to the patient at any time during the Follow-Up Period. Patients will have the option to collect the 24-hour urine specimen within 48 hours prior to Follow-Up 3/EOS or within 48 hours after Follow-Up 3/EOS. Patients should be instructed to return the 24-hour urine specimen to the site as soon as possible after its collection. The 24-hour urine collection specimens may be delivered to the study site by the specialty courier service selected by the sponsor, provided the patient has granted consent.
- Collect 24-hour urine sample
- Collect aliquot of urine from 24-hour urine sample to be used for UPE, uPCR and uACR assessment
- Once all laboratory results are available, assess the response

At such time the protocol amendment is approved and implemented, patients who have completed Week 96 should be asked to return to the site to complete their End of Study visit. All procedures will be completed as noted above for Follow Up 3 (Week 96/EOS) visit. However, if a patient is currently receiving treatment (12-Week Relapse Retreatment or any Open Label treatment per previous study design), they should continue to receive the full course of treatment before attending the End of Study visit.

10.2.6.4. Follow-Up Telephone Calls (Weeks 40, 44, 60, and 84) ± 14 days

A total of four patient telephone calls will be made during the Follow-Up Period. These calls will occur per the Schedule of Events (Section 20.2.3) at Weeks 40, 44, 60, and 84, within ± 14 days of the target date. Each patient telephone call will be documented in the patient's source documents and the CRF and will assess concomitant medications, compliance, and AEs.

Telephone calls do not need to be performed if they overlap with a scheduled relapse retreatment visit.

10.2.7. Study Drug Extended Treatment and Retreatment

Patients will be assessed for the need for 6-week extended treatment with study drug at the end of the Initial Treatment Period, for 6-week relapse retreatment at the Week 24, Week 30, and Week 36 Visits during the Response Evaluation Period, and for 12-week relapse retreatment during the Follow-Up Period (Week 48 and Week 72). The Week 96 Visit will be EOS; therefore, patients will be assessed for response but will not be re-treated.

All patients will continue to receive optimized antihypertensive medication treatment regardless of study timepoint or response status.

If a Retreatment Visit is scheduled to occur on the same day as a Response Evaluation (RE) or Follow-Up (FU) visit, refer to the Study Drug Retreatment Visit Overlap Guidelines for detailed instructions.

Based on the Treatment Visit 12 (Week 12) assessment, patients who have a 24-hour UPE > 1 g will receive 6 additional weeks of treatment (extended treatment) according to their originally assigned treatment group in a blinded fashion. During the Response Evaluation Period at Week 24, Week 30, or Week 36, patients who relapse will be treated for 6 additional weeks (6-Week relapse retreatment). Patients who relapse during the Response Evaluation Period will be retreated only once. During the Follow-Up Period at Week 48 or Week 72, patients who relapse will be treated for 12 additional weeks (12-Week relapse retreatment). Patient who relapse during the Follow-Up Period will only be offered retreatment once.

10.2.7.1. 6-Week Relapse Retreatment (Response Evaluation Period)

During the 6-Week Relapse Retreatment Period, relapsers will receive treatment with study drug according to the patient's originally assigned treatment group in a blinded fashion. Study drug treatment will be administered IV once weekly for 6 weeks. The first 6-Week Retreatment Visit must occur no more than 7 days from receipt of the 24-hour UPE results from the Central Lab and documentation of the patient's need for relapse retreatment. Target dates for subsequent 6-Week Relapse Retreatment Visits will be based on the 6-Week Relapse Retreatment Visit 1 date. Six-Week Relapse Retreatment Visits 2 through 6 must occur within ± 3 days of the target date. A minimum of two calendar days must separate each administration of study drug.

If service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service, 6-Week Relapse Retreatment Visits 3, 4 and 5 may occur at the patient's home with the support of a home nursing vendor selected by the sponsor.

10.2.7.1.1. 6-Week Relapse Retreatment Visit 1 (6RT1)

During visit 6RT1, the procedures listed below will be performed and documented prior to treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position)

- Complete pre-dose ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, pregnancy, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete urine pregnancy test
- Collect blood samples for ADA, NAb and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood samples)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During visit 6RT1, the procedures listed below will be performed and documented following treatment with study drug:

- Complete post-dose ECG at the end of the study drug infusion after at least 5 minutes of rest in a supine position, to be obtained immediately before the post-dose PK/PD samples
- Collect PK/PD samples 15 minutes (± 5 minutes) after the end of the study drug infusion
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and approximately 30 minutes (± 5 minutes) after the end of the study drug infusion

10.2.7.1.2. 6-Week Relapse Retreatment Visits 2, 3, and 5 (6RT2, 6RT3, and 6RT5) ± 3 days

For 6RT2, 6RT3, and 6RT5 the visits must occur within ± 3 days of their target date. The procedures listed below will be performed and documented prior to treatment with study drug.

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During 6RT2, 6RT3, and 6RT5 the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

10.2.7.1.3. 6-Week Relapse Retreatment Visit 4 (6RT4) ± 3 days

For 6RT4, the visit must occur within ± 3 days of the target date. For visit 6RT4 the procedures listed below will be performed and documented prior to treatment with study drug.

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Collect urine sample for uPCR, uACR, UA, and pregnancy test
- Perform pregnancy test
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During visit 6RT4, the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

10.2.7.1.4. 6-Week Relapse Retreatment Visit 6 (6RT6) ± 3 days

For visit 6RT6, the procedures listed below will be performed and documented prior to treatment with study drug.

- Perform complete physical examination including height and weight. Examination of breast, rectal, and genitourinary systems may be deferred unless clinically necessary
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Complete pre-dose ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, uPCR, uACR, pregnancy test, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete pregnancy test

- Collect blood samples for CMP, CBC+diff, PK, PD, ADA, NAb, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood samples)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During 6RT6, the procedures listed below will be performed and documented following treatment with study drug:

- Complete post-dose ECG at the end of the study drug infusion after at least 5 minutes of rest in a supine position
- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

The procedures listed below will be performed and documented prior to, during or after 6RT6:

- Dispense 24-hour urine collection supplies along with collection instructions to patient
  - At site discretion and for the convenience of the patient, these may be dispensed to the patient at any time during the 6-Week Retreatment Period. Patients will have the option to collect the 24-hour urine specimen within 48 hours prior to 6RT6 or within 48 hours after 6RT6. Patients should be instructed to return the 24-hour urine specimen to the site as soon as possible after its collection
- After patient returns 24-hour urine specimen, collect aliquot of urine from the 24-hour urine specimen to be used for UPE, uPCR and uACR assessment. Once all laboratory results are available, assess the response.

10.2.7.2. 12-Week Relapse Retreatment (Follow-Up Period)

During the 12-Week Relapse Retreatment Period, relapsers will receive treatment with study drug according to the patient's originally assigned treatment group in a blinded fashion. Study drug treatment will be administered IV once weekly for 12 weeks. The first 12-Week Relapse Retreatment Visit must occur no more than 7 days from receipt of the 24-hour UPE results from the Central Lab and documentation of the patient's need for relapse retreatment. Target dates for subsequent 12-Week Relapse Retreatment Visits will be based on the 12-Week Relapse Retreatment Visit 1 date. Twelve-Week Relapse Retreatment Visits 2 through 12 must occur within ± 3 days of the target date. A minimum of two calendar days must separate each administration of study drug.

If service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service, 12-Week Relapse Retreatment Visits 4 through 11 may occur at the patient's home with the support of a home nursing vendor selected by the sponsor.

10.2.7.2.1. 12-Week Relapse Retreatment Visit 1 (12RT1)

During visit 12RT1, the procedures listed below will be performed and documented prior to treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position)
- Complete pre-dose ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, pregnancy, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete urine pregnancy test
- Collect blood samples for ADA, NAb and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood samples)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During visit 12RT1, the procedures listed below will be performed and documented following treatment with study drug:

- Complete post-dose ECG at the end of the study drug infusion after at least 5 minutes of rest in a supine position, to be obtained immediately before the post-dose PK/PD samples
- Collect PK/PD samples 15 minutes (± 5 minutes) after the end of the study drug infusion
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

10.2.7.2.2. 12-Week Relapse Retreatment Visits 2, 3, 5, 6, 7, 9, 10, and 11 (12RT2, 12RT3, 12RT5, 12RT6, 12RT7, 12RT9, 12RT10, and 12RT11) ± 3 days

For 12RT2, 12RT3, 12RT5, 12RT6, 12RT7, 12RT9, 12RT10, and 12RT11 the visits must occur within ± 3 days of their target date. The procedures listed below will be performed and documented prior to treatment with study drug.

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During 12RT2, 12RT3, 12RT5, 12RT6, 12RT7, 12RT9, 12RT10, and 12RT11, the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

10.2.7.2.3. 12-Week Relapse Retreatment Visits 4 and 8 (12RT4 and 12RT8) ± 3 days

12-Week Retreatment Visits 4 and 8 must occur within ± 3 days of their target date. For visits 12RT4 and 12RT8 the procedures listed below will be performed and documented prior to treatment with study drug.

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Collect urine sample for uPCR, uACR, UA, and pregnancy test
- Perform pregnancy test
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During visit 12RT4 and visit 12RT8, the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

10.2.7.2.4. 12-Week Relapse Retreatment Visit 12 (12RT12) ± 3 days

For visit 12RT12, the procedures listed below will be performed and documented prior to treatment with study drug.

Perform complete physical examination including height and weight. Examination of breast, rectal, and genitourinary systems may be deferred unless clinically necessary

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Complete pre-dose ECG after patient has been supine for at least 5 minutes
- Collect urine sample for uPCR, uACR, UA, pregnancy test, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete pregnancy test
- Collect blood samples for CMP, CBC+diff, PK, PD, ADA, NAb, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood samples)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

The study drug should be prepared and infused per Section 9.4.

During visit 12RT12, the procedures listed below will be performed and documented following treatment with study drug:

- Complete post-dose ECG at the end of the study drug infusion after at least 5 minutes of rest in a supine position
- Collect vital signs approximately 5 minutes after the end of the study drug infusion and 30 minutes (± 5 minutes) after the end of the study drug infusion

The procedures listed below will be performed and documented prior to, during or after 12RT12:

- Dispense 24-hour urine collection supplies along with collection instructions to patient
  - At site discretion and for the convenience of the patient, these may be dispensed to the patient at any time during the 12-Week Relapse Retreatment Period. Patients will have the option to collect the 24-hour urine specimen within

48 hours prior to 12RT12 or within 48 hours after 12RT12. Patients should be instructed to return the 24-hour urine specimen to the site as soon as possible after its collection.

After patient returns 24-hour urine specimen, collect aliquot of urine from the 24-hour urine specimen to be used for UPE, uPCR and uACR assessment.

- Once all laboratory results are available, assess the response.

The retreatment algorithm for guiding retreatment based on patient status and study timepoint is provided in Table 1 and in Section 20.3.

10.2.8. Open-Label Option for High-Risk Patients

Patients with 24-hour UPE > 2 g at baseline will be allowed to receive 12-weeks of open-label active drug (narsoplimab) at Week 72 (18 months post randomization) per protocol, provided they meet the conditions stipulated below:

- Patient has < 30% reduction in UPE at the OL assessment visit when compared to baseline UPE, and
- Proteinuria is ≥ 3.0 g/day 72 weeks post randomization, as confirmed by two measurements at least 2 weeks apart (but no more than 3 weeks apart), and
- Patient has worsening renal function, defined as a decline in eGFR of > 5 mL/min/m^2 from baseline.

The Investigator is encouraged to contact the Omeros Medical Monitor to discuss the use of open-label treatment. Open-label treatment with narsoplimab will be administered IV once weekly for 12 weeks. Patients who receive treatment with open-label narsoplimab should continue to attend all study visits and complete all required study procedures. Neither the Investigator nor the patient who receives open-label treatment will be unblinded to the patient's original treatment assignment. Following the 12 weeks of open-label treatment, patients with 24-hour UPE > 1 g/day can receive 6 additional weeks of open-label treatment with narsoplimab (open-label extended treatment) as described in Section 10.2.8.2

10.2.8.1. Open-Label Treatment (Week 72)

Patients who meet the eligibility criteria noted in Section 0 may receive one course of treatment with open-label narsoplimab at Week 72.

Open-Label Treatment Visit 1 should occur no more than 7 days from the date of receipt of all laboratory results (two 24-hour UPEs and eGFR) and documentation of the patient's eligibility for open-label treatment.

Target dates for subsequent Open-Label Treatment Visits will be based on the Open-Label Treatment Visit 1 date. Open-Label Treatment Visits 2 through 12 must occur within ± 3 days of the target date. A minimum of two calendar days must separate each administration of narsoplimab.

If service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service,

Open-Label Treatment Visits 4 through 11 may occur at the patient's home with the support of a home nursing vendor selected by the sponsor.

10.2.8.1.1. Open-Label Treatment Visit 1 (OLT1)

During OLT1, the procedures listed below will be performed and documented prior to treatment with open-label narsoplimab:

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position)
- Complete pre-dose ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, pregnancy, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete urine pregnancy test
- Collect blood samples for ADA, NAb and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood samples)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

Narsoplimab should be prepared and infused per Section 9.4.

During OLT1, the procedures listed below will be performed and documented following treatment with open-label narsoplimab:

- Complete post-dose ECG at the end of the narsoplimab infusion after at least 5 minutes of rest in a supine position, to be obtained immediately before the post-dose PK/PD samples
- Collect PK/PD samples 15 minutes (± 5 minutes) after the end of the narsoplimab infusion
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) approximately 5 minutes after the end of the narsoplimab infusion and 30 minutes (± 5 minutes) after the end of the narsoplimab infusion

10.2.8.1.2. Open-Label Treatment Visits 2, 3, 5, 6, 7, 9, 10, and 11 (OLT2, OLT3, OLT5, OLT6, OLT7, OLT9, OLT10, and OLT11) ± 3 days

For OLT2, OLT3, OLT5, OLT6, OLT7, OLT9, OLT10, and OLT11 the visits must occur within ± 3 days of their target date. The procedures listed below will be performed and documented prior to treatment with open-label narsoplimab:

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

Narsoplimab should be prepared and infused per Section 9.4.

During OLT2, OLT3, OLT5, OLT6, OLT7, OLT9, OLT10, and OLT11, the procedures listed below will be performed and documented following treatment with narsoplimab:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the narsoplimab infusion and 30 minutes (± 5 minutes) after the end of the narsoplimab infusion

10.2.8.1.3. Open-Label Treatment Visits 4 and 8 (OLT4 and OLT8) ± 3 days

Open-label Treatment Visits 4 and 8 must occur within ± 3 days of their target date. For OLT4 and OLT8 the procedures listed below will be performed and documented prior to treatment with narsoplimab:

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Collect urine sample for uPCR, uACR, UA, and pregnancy test
- Perform pregnancy test
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

Narsoplimab should be prepared and infused per Section 9.4.

During OLT4 and OLT8, the procedures listed below will be performed and documented following treatment with narsoplimab:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the narsoplimab infusion and 30 minutes (± 5 minutes) after the end of the narsoplimab infusion

10.2.8.1.4. Open-Label Treatment Visit 12 (OLT12) ± 3 days

For OLT12, the procedures listed below will be performed and documented prior to treatment with narsoplimab:

- Perform complete physical examination including height and weight. Examination of breast, rectal, and genitourinary systems may be deferred unless clinically necessary
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Complete pre-dose ECG after patient has been supine for at least 5 minutes
- Collect urine sample for uPCR, uACR, UA, pregnancy test, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete pregnancy test
- Collect blood samples for CMP, CBC+diff, PK, PD, ADA, NAb, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood samples)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

Narsoplimab should be prepared and infused per Section 9.4.

During OLT12, the procedures listed below will be performed and documented following treatment with narsoplimab:

- Complete post-dose ECG at the end of the narsoplimab infusion after at least 5 minutes of rest in a supine position
- Collect vital signs approximately 5 minutes after the end of the narsoplimab infusion and 30 minutes (± 5 minutes) after the end of the narsoplimab infusion

The procedures listed below will be performed and documented prior to, during or after OLT12:

- Dispense 24-hour urine collection supplies along with collection instructions to patient
  - At site discretion and for the convenience of the patient, these may be dispensed to the patient at any time during the 12-Week Open-Label Treatment Period. Patients will have the option to collect the 24-hour urine specimen within 48 hours prior to OLT12 or within 48 hours after OLT12. Patients should be instructed to return the 24-hour urine specimen to the site as soon as possible after its collection

After patient returns 24-hour urine specimen, collect aliquot of urine from the 24-hour urine specimen to be used for uPCR and uACR assessment

- Once all laboratory results are available, assess the response
- Patients who have a 24-hour UPE > 1 g at Open-Label Treatment Visit 12 (OLT12) can receive 6 additional weeks of open-label treatment (open-label extended treatment)

10.2.8.2. Open-Label Extended Treatment

Patients who have a 24-hour UPE > 1 g at Open-Label Treatment Visit 12 (OLT12) can receive 6 additional weeks of open-label extended treatment with narsoplimab (open-label extended treatment). Treatment with open-label narsoplimab will be administered IV once weekly for 6 weeks. Open-Label Extended Treatment Visit 1 should occur no later than 14 days from the date of OLT12.

Target dates for subsequent Open-Label Extended Treatment Visits will be based on the Open-Label Extended Treatment Visit 1 date. Open-Label Extended Treatment Visits 2 through 6 must occur within ± 3 days of the target date. A minimum of two calendar days must separate each administration of narsoplimab.

If service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service, Open-Label Extended Treatment Visits 3, 4, and 5 may occur at the patient's home with the support of a home nursing vendor selected by the sponsor.

10.2.8.2.1. Open-Label Extended Treatment Visit 1 (OLExT1)

During OLExT1, the procedures listed below will be performed and documented prior to treatment with narsoplimab:

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position)
- Complete pre-dose ECG after patient has been supine for at least 5 minutes
- Collect urine sample for UA, pregnancy, and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, aliquot the urine sample as per instructions in the Lab Manual)
- Complete urine pregnancy test
- Collect blood samples for ADA, NAb and biomarkers (if consent granted by patient for evaluation of optional research biomarkers, collect additional blood samples)
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

- At site discretion and for patient convenience, dispense 24-hour urine collection supplies to the patient at any time during OLExT1 to OLExT5 along with collection instructions. Patients will have the option to collect the 24-hour urine specimen at any point between OLExT5 to OLExT6. Patients should be instructed to return the 24-hour urine specimen to the clinic as soon as possible following its collection.

Narsoplimab should be prepared and infused per Section 9.4.

During OLExT1, the procedures listed below will be performed and documented following treatment with narsoplimab:

- Complete post-dose ECG at the end of the narsoplimab infusion after at least 5 minutes of rest in a supine position, to be obtained immediately before the post-dose PK/PD samples
- Collect PK/PD samples 15 minutes (± 5 minutes) after the end of the narsoplimab infusion
- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) approximately 5 minutes after the end of the narsoplimab infusion and 30 minutes (± 5 minutes) after the end of the narsoplimab infusion

10.2.8.2.2. Open-Label Extended Treatment Visits 2, 3, and 5 (OLExT2, OLExT3, and OLExT5) ± 3 days

For OLExT2, OLExT3, and OLExT5, the visits must occur within ± 3 days of their target date. The procedures listed below will be performed and documented prior to treatment with narsoplimab.

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade
- At site discretion and for patient convenience, dispense 24-hour urine collection supplies to the patient at any time during OLExT1 to OLExT5 along with collection instructions. Patients will have the option to collect the 24-hour urine specimen at any point between OLExT5 to OLExT6. Patients should be instructed to return the 24-hour urine specimen to the clinic as soon as possible following its collection.

Narsoplimab should be prepared and infused per Section 9.4.

During OLExT2, OLExT3, and OLExT5, the procedures listed below will be performed and documented following treatment with study drug:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the end of the narsoplimab infusion and 30 minutes (± 5 minutes) after the end of the narsoplimab infusion

10.2.8.2.3. Open-Label Extended Treatment Visit 4 (OLExT4) ± 3 days

Open-Label Extended Treatment Visit 4 must occur within ± 3 days of the target date. For visit OLExT4 the procedures listed below will be performed and documented prior to treatment with narsoplimab.

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Collect urine sample for uPCR, uACR, UA, and pregnancy test
- Perform pregnancy test
- Assess AEs
- Assess concomitant medications/therapies
- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade
- At site discretion and for patient convenience, dispense 24-hour urine collection supplies to the patient at any time during OLExT1 to OLExT5 along with collection instructions. Patients will have the option to collect the 24-hour urine specimen at any point between OLExT5 to OLExT6. Patients should be instructed to return the 24-hour urine specimen to the clinic as soon as possible following its collection.

Narsoplimab should be prepared and infused per Section 9.4.

During OLExT4, the procedures listed below will be performed and documented following treatment with narsoplimab:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the narsoplimab infusion and 30 minutes (± 5 minutes) after the end of the narsoplimab infusion

10.2.8.2.4. Open-Label Extended Treatment Visit 6 (OLExT6) ± 3 days

For OLExT6, the visit must occur within ± 3 days of the target date. The procedures listed below will be performed and documented prior to treatment with narsoplimab.

- Collect vital signs including BP, pulse rate, RR, and temperature (all after at least 5 minutes in a seated position) prior to dosing
- Assess AEs
- Assess concomitant medications/therapies

- Confirm and document ongoing use of medically acceptable birth control method for patients of childbearing or reproductive potential
- Confirm and document stability of RAS blockade

Narsoplimab should be prepared and infused per Section 9.4.

During OLExT6, the procedures listed below will be performed and documented following treatment with narsoplimab:

- Collect vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes in a seated position) approximately 5 minutes after the end of the narsoplimab infusion and 30 minutes (± 5 minutes) after the end of the narsoplimab infusion

The procedures listed below may be performed and documented before, during or after the OLExT6 visit:

- Collect 24-hour urine sample for UPE from patient
- Collect aliquot of urine from the 24-hour urine sample to be used for uPCR and uACR assessment

After OLExT6, the procedures listed below will be performed and documented:

- Once laboratory results are available, assess the response only

10.2.9. Early Termination

Reasons that patients may discontinue study treatment or withdraw from study participation are detailed in Sections 8.3.1 and 8.3.2, respectively.

Patients will be encouraged to complete all evaluations. However, provided written consent to do so has not been withdrawn, patients who prematurely discontinue study drug treatment should complete all scheduled study visits, and patients who prematurely discontinue study participation should complete the evaluations scheduled for the FU3/EOS (Week 96) visit. Patients with ongoing SAEs at the time of early termination from the study should be followed for resolution (as possible) or Investigator confirmation that the event is believed to be stable.

10.2.10. Unscheduled Visits

Unscheduled visits and assessments for patient safety should be documented and recorded in the patient's source documentation and eCRF.

10.2.11. Timing of Study Procedures

Procedures with a specified time frame will be considered per protocol if they are performed within the following windows: vital signs and ECGs on dosing days prior to drug administration; vital signs on dosing days after the end of the study drug infusion ± 5 minutes and 30 minutes after end of IP infusion ± 5 minutes; PK/PD draw at T1 ± 5 minutes; PK/PD draw at T2 (168 hours after the start of the first dose) ± 2 hours. If multiple procedures are specified at one timepoint, they should be performed in the following order: vital signs, ECG, and then blood draw.

At site discretion and for the convenience of the patient, the 24-hour urine collection supplies may be dispensed to the patient at any time during the applicable study periods (Run-In Period, Extended Treatment Period, Response Evaluation Period, Relapse Retreatment Period, Open Label Treatment, and Follow-Up Period) along with collection instructions. Patients should be instructed to return the 24-hour urine specimen to the site as soon as possible after its collection.

During the Run-In Period, two 24-hour urine samples will be collected no more than 14 days apart during the last 2 weeks of the Run-In Period. During the Response Evaluation Period, to assess patient response and potential need for relapse retreatment, a 24-hour UPE will be performed at the Week 24 timepoint and again at the Week 30 timepoint. Patients will be required to collect one 24-hour urine specimen at each timepoint. To provide flexibility for patients, each 24-hour urine may be collected within 7 days prior to or after each designated timepoint (Week 24 and Week 30).

10.2.12. Timing of Study Visits

10.2.12.1. Visit Windows

Treatment Visit 2 (T2), T4, T8, T10, and T12 must occur within ± 2 days of the target date due to the PK/PD blood draw. The PK/PD sample collection at T2 should occur 168 ± 2 hours from the start of the first dose administered at T1. Therefore, patients should be encouraged, whenever possible, to return for T2 on the target date. All other treatment visits (Initial Treatment, Extended Treatment, or 6- and 12-Week Relapse Retreatment, Open-Label Treatment) must be within ± 3 days of the target date. At a minimum, two calendar days must separate each administration of study drug. Telephone Calls at Week 16 through Week 34 must occur within ± 7 days of the target date. The Response Evaluation Visit at Week 36 must occur within ± 7 days of the target date. Telephone Calls at Week 40 through FU3/EOS (Week 96) must occur within ± 14 days of the target date.

10.2.12.2. Timing Between Assessments

Run-In Period: This period includes two urine collection timepoints conducted no more than 14 days apart during the last 2 weeks of the Run-In Period.

Treatment 1: T1 visit should be scheduled to occur as soon as possible from receipt of all lab results, and no more than 7 days from receipt of the 2nd 24-hour UPE result from the final RI Visit.

Study drug retreatment: Patients who will receive study drug retreatment, either Extended or 6- or 12-Week Relapse Retreatment, should receive the first retreatment within 7 days of receipt of the 24-hour UPE result that demonstrates need for retreatment.

Open-Label Option for High-Risk Patients: Patients who meet the eligibility criteria for open-label treatment should receive the first open-label treatment within 7 days of the receipt of all lab results that demonstrate eligibility (two 24-hour UPEs at least 2 weeks apart but no more than 3 weeks apart, eGFR).

At a minimum, two calendar days must separate each administration of study drug.

10.3. Unblinding

In a medical emergency, it may be necessary to identify a patient's assigned treatment before the study has been unblinded. In this situation, it is important that the blind be maintained for all other patients. If a patient's treatment is unblinded, study drug may continue at the discretion of the Investigator. The patient will be followed through the Follow-Up Period.

Emergency unblinding instructions, including any manual backup processes, are provided in the Pharmacy Manual. Unblinding may be performed only if the patient's wellbeing requires knowledge of the patient's treatment assignment. All unblinding events are recorded and reported by the randomization system. Emergency unblinding must also be documented at the investigative site.

The sponsor medical monitor must be immediately notified if an unblinding occurs.

10.4. Concomitant Therapy

In a controlled study, fish oil reduced the rate of decline in renal function [Donadio 1994]. However, this finding was not confirmed in another clinical trial [Bennett 1989]. Intake of fish oil will be restricted during this study. Patients already on fish oil who meet all inclusion criteria will be allowed to remain on fish oil. However, patients not previously taking fish oil should not start taking fish oil while in this study. The STOP-IgAN study also revealed that immunosuppressive therapy did not improve outcome in IgAN patients with proteinuria of > 0.75 g/day and they had more AEs compared to the control arm of supportive care [Rauen 2015]. Patients on immunosuppressive therapy will be excluded from this trial, except for those receiving immunosuppressants for indications other than IgAN and the patient continues to meet study eligibility criteria.

Treatment with immunosuppressants, cytotoxic drugs, or eculizumab is prohibited within 8 weeks prior to the SV and throughout a patient's study participation, except as allowed for treatment of indications other than IgAN or for rescue therapy described in Section 10.4.1.

Treatment with systemic corticosteroids is prohibited for 8 weeks prior to the SV and during the Run-In Period and any time after Randomization except short-term use (3 weeks or less) of non-systemic corticosteroids that are not being used for the management of IgAN, except as allowed for rescue therapy as described in Section 10.4.1.

Use of Chinese traditional medicine to treat IgAN is prohibited for 8 weeks prior to the SV and throughout a patient's study participation.

Initiation of treatment with sodium glucose co-transporter 2 inhibitors (SGLT2i) are prohibited from screening onward. However, a stable unchanged dose regimen established at least 8 weeks prior to screening is acceptable.

Treatment with Tarpeyo™ (budesonide) or other approved treatments for IgAN are prohibited within 6 months prior to screening and throughout the study.

Treatment with Kerendia® (finerenone) is prohibited within 6 months prior to screening and throughout the study.

Initiation of treatment with Filspari™ (sparsentan), a dual Endothelin Angiotensin Receptor Antagonist (dEARA) or similar medication within three months prior to screening. A stable dose initiated at minimum 3 months before screening is acceptable.

During the Run-In Period and throughout the entire study, patients should be advised to avoid nonsteroidal anti-inflammatory drugs and any other nephrotoxic medicines.

All other medications for the health and wellbeing of the patient are permitted and are to be recorded in the source documents and eCRF.

10.4.1. Rescue Therapy

A patient may be considered for rescue therapy treatment by the Investigator according to local practice (which may include corticosteroids or immunosuppressants) if the following conditions are met:

- It is recommended that the patient is in the study for over one year. However, rescue therapy may be administered at less than one year if clinically warranted
- Patient meets study eligibility criteria (other than eGFR ≥ 30), including 24-hour UPE > 1 g or 24-hour uPCR > 0.75, twice over an 8-week period
- Patient has 100% increase in 24-hour UPE from baseline and patient has a 30% decrease in eGFR from baseline, as measured twice over an 8-week period
- Use of rescue therapy is discussed with the sponsor's medical monitor

The Investigator is encouraged to contact the sponsor Medical Monitor to discuss the use of rescue therapy, although it is not mandatory.

Rescue therapy for study patients is not encouraged given that there is no specific medication or treatment regimen approved for IgAN. However, if the Investigator feels that rescue therapy is required, and the patient meets the above criteria, the patient may be managed per local guidelines at the Investigator's discretion, however the patient must be withdrawn from study treatment. Patients requiring rescue treatment will be followed per protocol through the Follow-Up Period.

10.5. Treatment Compliance

The study drug will be administered by study personnel. Administration dates and times must be recorded in both the patient's medical record and the eCRF. If any portion of a dose of study drug is not administered during a study visit, an explanation must be provided in the medical chart and on the eCRF.

11. ASSESSMENT OF EFFICACY

11.1. Primary Efficacy Measure

The primary efficacy measure is 24-hour UPE. Proteinuria has been reported to predict renal outcomes, and remission of proteinuria is associated with improved renal prognosis [Coppo 2014, Reich 2007]. Improvements in proteinuria following treatment are associated with

improved renal outcomes [Inker 2021, Inker 2016]. Therefore, 24-hour UPE will be used as the primary efficacy measurement in this study.

11.2. Secondary Efficacy Measures

Secondary efficacy measures include other measures of renal function. These include other measures of proteinuria (e.g., uPCR) and measures of glomerular filtration rate. Categorical achievement of treatment response and different levels of proteinuria will also be assessed. The persistence of these proteinuria milestones will also be evaluated.

Secondary efficacy measures include:

- 24-hour UPE (achievement of complete or partial proteinuria remission defined as 24-hour UPE of < 0.3 g or < 0.6 g, respectively)
- uPCR and 24-hour uPCR
- eGFR
- Use of rescue therapy

11.3. Pharmacokinetic/Pharmacodynamic/Immunogenicity Measures

Pharmacokinetic (PK), PD, and immunogenicity measures in this study include:

- PK
- PD
- Anti-drug antibodies (ADA) and NAb

Samples will be collected at the timepoints detailed in the Schedule of Events (Section 20.2) and collection and processing procedures will be provided in the study laboratory manual.

11.4. Biomarker Measures

Biomarker samples, including urine, serum, and plasma samples, will be collected at the time points detailed in the Schedule of Events (Section 20.2).

In addition, if available, the original renal biopsy specimen will be evaluated for biomarkers. Findings from this investigation will address the following and, potentially, other issues:

- Determine the proportion of study patients with MBL deposition
- Clarify whether MBL deposition is associated with disease severity and progression in IgAN
- Determine whether MBL deposition impacts response to narsoplimab

An exploratory evaluation of other relevant biomarkers may be conducted.

12. ASSESSMENT OF SAFETY

The Investigator and clinical facility staff are responsible for detection, recording, and reporting of events that meet the criteria and definition of Adverse Events as listed below. Adverse events will be recorded from time of signed informed consent through the last study visit. Serious Adverse Events will be recorded from time of signed informed consent through 30 days post last study visit. In addition, the Investigator and clinical facility staff are responsible for detection, recording, and reporting of pregnancies of study participants and of participants' partners as well as appropriate follow-up.

12.1. Safety Parameters

Safety will be evaluated by assessing AEs, clinical laboratory tests, vital signs, and ECGs per the Schedule of Events (Section 20.2) and on an as-needed basis. Only clinically significant (per Investigator opinion) changes in vital signs, ECGs, or laboratory tests or that require medical intervention will be reported as AEs.

12.2. Definition and Assessment of Adverse Events

12.2.1. Adverse Events

An AE is any untoward medical occurrence in a patient during his or her participation in this clinical trial and which does not necessarily have to have a causal relationship with the treatment. Treatment emergent AEs will be defined as AEs with an onset after administration of the study drug or when a preexisting medical condition increases in severity or frequency after study drug administration.

Adverse events will include:

- Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether or not related to this product (Refer to International Conference on Harmonisation [ICH] E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, 27 October 1994).
- Any new undesirable medical experience or an unfavorable and unintended change of an existing condition, including exacerbation of existing disease or disease progression, that occurs between the time of informed consent and the study duration required by the protocol, whether or not considered related to study drug
- Abnormal laboratory findings considered by the Investigator to be clinically significant, i.e., those that are unusual for the population being studied or individual patient
- Abnormal laboratory findings are not necessarily Adverse Events. An abnormal laboratory value can be considered an AE if it results in the following criteria:
  - Development of symptoms
  - Necessitates treatment

- Hospitalization
- Prolongation of the hospital stay

Adverse events will not include:

- A medical or surgical procedure such as surgery, endoscopy, tooth extraction, or transfusion (although the condition that leads to the procedure may be an AE)
- A pre-existing disease or condition present at the start of the study that does not worsen during the study
- Any situation where an untoward medical occurrence has not occurred (for example, hospitalizations for cosmetic elective surgery or social admissions)
- An overdose of either the investigational product or a concurrent medication without any resulting signs or symptoms

Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis into a single event term or diagnosis. For example, cough, rhinitis, and sneezing might be grouped together as *upper respiratory tract infection*.

12.2.2. Serious Adverse Event (SAE):

A SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening
  - The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect, or
- Is a medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that may not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require medical or surgical intervention to prevent one of the other serious outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.2.3. Severity

The Investigator will assess the severity of the AE reported during the study.

All AEs will be graded according to the following definitions:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

A severe event should not be confused with a serious event. See additional clarification in Section 12.3.2.

12.2.4. Relationship to Study Drug

The Investigator is obligated to assess the relationship between investigational product and the occurrence of each AE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, plus the temporal relationship of the event to the investigational product should be considered and investigated. It is recommended that the Investigator contact the sponsor Medical Monitor to discuss the relationship between investigational product and AEs.

The relationship of AEs to study drug is categorized as probable, possible, unlikely, or not related. An alternative etiology must be provided for all AEs for which the relationship to study drug is considered "possible," "unlikely," or "not related".

Definitions of each of these terms are below:

Probable: The AE has a timely relationship to administration of the study drug and when there are facts, evidence, or arguments to suggest that the event is related to the product under investigation.

Possible: The AE has a timely relationship to administration of the study drug and there is a reasonable possibility that the AE may have been caused by the product under investigation.

Unlikely: The AE is likely related to an etiology other than administration of study drug.

Not Related: An unreasonable temporal relationship between administration of the product and the onset of the AE (e.g., the event occurred either before, or too long after administration of the product for it to be considered product-related); a causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident); a clearly alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event).

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial SAE report, required within 24 hours of initial awareness.

However, it is very important that the Investigator always assess causality for every event prior to transmission of the SAE report form. The Investigator may change his/her opinion of causality considering follow-up information, amending the SAE report form accordingly. The causality assessment is one of the criteria used when determining global regulatory reporting requirements.

12.2.5. Clinical Outcome of Adverse Events

The Investigator or medical designee will report the clinical outcome of the AE as follows:

Recovered Completely: The patient has fully recovered from the event with no residual effects observable.

Recovered with Sequelae: Effects of the event remain. The likelihood of these effects changing (improving or worsening) is low.

Not Yet Recovered: Effects of the event are still present and changing. The event is considered ongoing.

Unknown; Lost to Follow-up: Not known, not observed, not recorded, or patient refused to provide information.

Died: The event may or may not be the immediate or primary cause of death.

12.3. Reporting Adverse Events

12.3.1. Adverse Event Reporting

Beginning at the time of informed consent, all AEs, whether observed by the Investigator or reported by the patient, and whether or not thought to be related to the study drug, will be recorded on the appropriate AE CRF by the Investigator (or designee). In describing AEs on the CRF, standard, medically accepted terminology will be used. The description of each AE will identify the date of onset, duration, severity (see Section 12.2.3 for Definitions of Severity), action taken (including any diagnostic procedures or laboratory tests performed and all treatments administered), relationship to the study drug, and clinical outcome of the event. Any AEs that are related to the COVID-19 pandemic should be clearly noted as such in the patient source documents and the AE eCRF.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not recorded as an AE, but rather recorded as medical history. However, if the medical condition increases in frequency or severity after the time of informed consent, it will be recorded as an AE on the appropriate CRF.

12.3.2. Serious Adverse Event Reporting

Serious Adverse Events will be collected from the signing of informed consent until 30 days after the last study visit. Ongoing SAEs at the time of study completion or discontinuation will be monitored until event resolution, the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up (see Section 12.4 below). The study site is required to report any SAE directly to the Omeros' pharmacovigilance (PVG) designee on an SAE report form within 24 hours of becoming aware of the event, whether or not the SAE is

deemed drug-related (see Section 1.2 for contact information). The SAE report form will always be completed as thoroughly as possible with all available details of the event and signed by the Investigator (or designee). If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before reporting the event. The SAE report form will be updated when additional information is received.

The Investigator (or medically qualified designee) will provide an assessment of causality relationship of study drug with SAE at the time of the initial report as described in Section 12.2.4.

Other supporting documentation of the event may be requested by Omeros' PVG designee and should be provided as soon as possible.

Death is an outcome of an event and not an event per se (sudden death or death of unexplainable causes can be reported, but follow-up will be required until cause of death is determined).

Serious and Severe are not synonymous and should not be confused. Severity is a category utilized for rating the intensity of an event (Grade 1 - 5); and both AEs and SAEs can be assessed as severe. Seriousness is based on a regulatory definition, as noted in Section 12.2.2. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE, if serious criteria are not met. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but it would be considered an SAE as an important medical event.

[redacted]

12.3.3. Reporting of Serious Adverse Events to Regulatory Agencies and to IRB/IECs

Omeros or its designee will submit the SAEs requiring expedited reporting to regulatory agencies. Prompt notification of SAEs by the Investigator is essential so that Omeros can comply with its global regulatory obligations.

The Investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC.

12.3.4. Pregnancy and Overdose Reporting

If a patient becomes pregnant during the study, Omeros' PVG designee must be notified by fax or email within 24 hours of site awareness and the patient must be discontinued from study drug. Cases of pregnancy must be reported on a pregnancy report form. Pregnancy itself is not considered an AE. Additional instructions for reporting of the pregnancy and outcome will be provided by Omeros at the time of notification. Pregnancies of partners of male patients will also be followed provided the patient's partner provides informed consent for follow-up of the pregnancy.

Occurrences of overdose, with or without clinical sequelae, should be reported to Omeros' PVG designee within 24 hours of awareness. Overdose is defined as any dosing above the protocol-defined dosing instructions. Additional instructions for reporting overdose information will be provided by Omeros at the time of notification. There is no specific antidote to narsoplimab overdose. Treatment is generally supportive care as medically necessary and indicated.

12.4. Type and Duration of the Follow-Up of Patients After Adverse Events

All AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up. Once resolved, the appropriate AE CRF page and SAE report form (if event is serious) will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE.

If an SAE persists at the last study visit or the time of early termination after study treatment, it will be marked as "ongoing" and "not yet recovered" in the CRF and on the SAE report form. An SAE will be followed by the Investigator until such time that it is deemed to be resolved or at a stable condition, or for as long as feasible. Patients with ongoing SAEs at the time of early termination from the study should be followed for resolution (as possible) or Investigator confirmation that the event is believed to be stable.

Investigators are not obligated to actively seek AEs in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the Investigator will promptly notify Omeros.

12.5. Independent Data Safety Monitoring Committee

An IDMC is established to oversee all aspects of the safety on this study. The IDMC will operate in accordance with the IDMC charter and have regular meetings in person or by teleconference.

13. APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety measurements used in this study followed standard medical practice guidelines and are acceptable measurements that provided health assessments for this study

population. These measurements are generally recognized as reliable, accurate, relevant, and appropriate.

Standard PK assessments will be conducted that are appropriate for the study. The number, frequency, and timing of blood samples collected for PK analysis are based on the concentration time profile of the study drug.

Proteinuria is being used as a primary endpoint based on several clinical and scientific studies. Proteinuria is a known adverse prognostic indicator in IgAN [Geddes 2003], and the degree of proteinuria is an independent risk factor for persistent proteinuria [Kamei 2015]. Furthermore, improvement in proteinuria has been shown to be the most important predictor of the rate of GFR decline and disease progression in IgAN [Reich 2007]. Analysis of individual-level associations indicates that greater reductions in proteinuria are consistently associated with slower IgAN progression [Inker 2021, Inker 2016]. Early reduction in proteinuria at 9 months was associated with a reduction in the composite clinical outcome of time to doubling of serum creatinine (SCr), ESRD, and death [Inker 2021, Inker 2016]. This publication provided evidence in support of proteinuria as a surrogate of clinical endpoint in IgAN patients.

In this study, uPCR and uACR will be measured from an aliquot of urine obtained from the 24-hour urine collection and have been shown to be reflective of protein excretion in a timed urine collection [KDIGO Work Group 2012]. Spot urine samples will be used to assess uPCR and uACR at visits where 24-hour urine collection is not required. Since ratios are measured, spot urine samples tend not to be affected by hydration [KDIGO Work Group 2012].

Historically the FDA has accepted doubling of serum creatinine or 57% decline in eGFR as a surrogate endpoint of renal failure. This approach requires large sample sizes and longer duration of clinical trials. To address this, a committee of the FDA, National Kidney Foundation and academicians met in December 2012. During that meeting, it was proposed that declines in eGFR over a 2- or 3-year period can provide an early surrogate for the development of ESRD [Levey 2014] in chronic kidney diseases trials. In this study therefore, the slope of eGFR in the two treatment groups will be evaluated over the duration of the trial.

14. STATISTICS

14.1. Determination of Sample Size

The planned sample size is determined using the primary endpoint (change in log-transformed 24-hour UPE from baseline to 36 weeks) in the high-risk proteinuria group and the two key secondary endpoints: the rate of change in eGFR for high-risk proteinuria patients and the rate of change in eGFR for the all-patients population. The planned sample size for the primary endpoint is 180 patients for the high-risk proteinuria group, 280 patients for the eGFR rate of change endpoint in the high-risk proteinuria group, and 450 patients for the eGFR rate of change in the all-patients population.

14.1.1. Sample Size for Primary Efficacy Endpoint

The statistical hypotheses are:

H_0: $\mu_d = \mu_p$,
H_1: $\mu_d \neq \mu_p$,

where μ_d and μ_p are the mean change in log-transformed 24-hour UPE from baseline to 36 weeks for narsoplimab and placebo, respectively.

Based on IgAN patient registry data from University Hospital Leicester, UK, the log scale standard deviation for the change in UPE from baseline to 9 months in IgAN patients with ≥ 2 g/day is estimated to be 0.80. Hypothesizing a treatment effect on UPE of 35% (-0.393 on the log scale), a total N of 180 patients with a baseline UPE ≥ 2g/day need to be randomized on a 1:1 basis to narsoplimab or placebo to provide 95% power to test the stated hypotheses, at the 2-sided 5% alpha level. Data from the preplanned blinded sample size reassessment for UPE at 9 months in the high-risk proteinuria population (baseline UPE ≥ 2 g/day) gave blinded logscale SD estimates of 0.63, hence the sample size of N = 180 is supported.

14.1.2. Sample Size for Key Secondary Rate of Change in eGFR Endpoints

Data from IgAN database from the University of Leicester, UK, provides the basis for the power calculation for eGFR Rate of Decline over 2 years in patients with a baseline UPE ≥ 2 g/day. Patients on ACE/ARBs with a baseline UPCR of ≥ 2 g/day were identified and their eGFR values over 3 to 24 months were assigned to 3 monthly windows to reflect the intended sampling schedule in the OMS721-IGA-001 protocol.

The annualized eGFR rate of decline was thus estimated to be -5.44 mL/min/m^2 (SE 0.1869 mL/min/m^2), the between slope variance component σ_β^2 was estimated to be 6.4932^2 mL/min/m^2 annually ($= 0.7356^2$ mL/min/m^2 monthly), and the residual error variance σ_ε^2 was estimated to be $= 6.5077^2$ mL/min/m^2.

Thus, hypothesizing that the 2-year annualized eGFR rate of decline for narsoplimab relative to placebo in the high-risk proteinuria group (baseline UPE ≥ 2 g/day) is 3.48 mL/min/1.73 m^2, a sample size of 280 patients (i.e., 140 per treatment group) followed for 2 years post randomization will provide at least 85% power at the 2-sided 5% level to test this hypothesis.

Similarly, data from the University of Leicester registry provide an estimate of the annualized eGFR rate of decline in patients with a baseline UPCR of > 1 g/day of –4.40 mL/min/m^2 (SE 1.716 mL/min/m^2), and the between-slope variance component σ_β^2 was estimated to be 7.8469^2 mL/min/m^2 annually ($= 0.6539^2$ mL/min/m^2 monthly) with the residual-error variance σ_ε^2 estimated to be $= 5.9517^2$ mL/min/m^2.

Hypothesizing that the 2-year annualized eGFR rate of decline for narsoplimab relative to placebo in the all-patients population is 2.45 mL/min/1.73 m^2, a sample size of 450 patients (i.e., 225 per treatment group) followed for 2 years post randomization will provide at least 85% power at the 2-sided 5% level to test this hypothesis.

14.1.3. Blinded Sample Size Re-estimation for UPE Endpoint

A pre-planned blinded sample size re-estimation for UPE endpoint in the all-patients population was performed when 168 patients completed the Week 36 visit. The independent IDMC statistician re-calculated the sample size using an adjusted variance. A bias-adjusted variance of the log-transformed 24-hour UPE change from baseline to Week 36 was calculated using the pooled variance from the available data and the assumed treatment effect size in a blinded fashion. The bias-adjusted variance was expressed as [Kieser 2003]:

$$VV^2_{aaaaaa} = VV^2_{ppppppppeeaa} - \frac{mm}{4(mm-1)}\Delta^2,$$

where $VV^2_{ppppppppeeaa}$ is the pooled variance, n is half of the number of patients with UPE at Week 36 at the time of the sample size re-estimation (i.e., m = 168), and Δ is the assumed treatment effect size in the sample size calculation.

The log scale SD was estimated to be lower than anticipated and, hence, no change to sample size was made.

14.1.4. Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to the interim database snapshot. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

14.1.5. Conditional Power-Based Sample Size Re-Estimation for Key Secondary eGFR Rate-of-Change Endpoint in the High-Risk Proteinuria Group (i.e., Patients with Baseline Proteinuria ≥ 2g/day)

A CP-based sample size re-estimation for the key secondary eGFR Rate-of-Change endpoint in patients in the high-risk proteinuria group is planned at the time of the formal interim analysis of the primary UPE endpoint in the same population. The method will be described in the final SAP.

14.1.6. General Considerations

Summary statistics for continuous variables will include number of patients, mean, median, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be provided. When required for the statistical analysis of a particular variable, the baseline value will be the last recorded value prior to randomization. The exception is the baseline 24-hour UPE, uPCR and uACR, which are defined as the average of the two pre-dose values collected during the last two weeks of the Run-In Period before randomization. In addition, study week is defined from study Day 1 and will be determined by analysis visit windows which are defined approximately equally over adjacent scheduled visits. A study endpoint at a particular study week (e.g., 24-hour UPE at 36 weeks) is the value collected during that analysis visit window. All statistical tests will be performed at the two-sided significance level of 5%. All confidence intervals will be constructed at the two-sided 95% confidence level.

14.1.6.1. Adjustments for Covariates

Efficacy analyses will adjust for randomization strata. Some potential baseline patient and disease characteristics may affect the interpretation of the efficacy results. Subgroup analyses and regression analyses may be performed to adjust for the potential covariate effects. These analyses will be considered exploratory and, if performed, will be discussed in the clinical study report.

14.1.6.2. Multicenter Study

This is a multicenter study. Descriptive statistics of the primary efficacy endpoint will be provided for each site to evaluate potential site differences.

14.1.6.3. Multiple Comparisons and Multiplicity

The primary efficacy endpoint (change in log-transformed 24-hour UPE from baseline to 36 weeks) in the high-risk proteinuria group and, if positive, the two key secondary endpoints will be tested sequentially to preserve the overall type I error rate of 5%.

Key Secondary Efficacy Endpoints:

i. the rate of change in eGFR over 2 years in the high-risk proteinuria group

ii. the rate of change in eGFR over 2 years in the all-patients population

If the primary efficacy endpoint is statistically significant at 5% level in a 2-sided test, then key secondary endpoint (i), the rate of change in eGFR over 2 years in the high-risk proteinuria group, will be tested in a two-sided test at 5% level of significance. If the key secondary eGFR endpoint for the high-risk proteinuria group is statistically significant in a two-sided test at 5% level, then the key secondary eGFR endpoint (ii), the rate of change in eGFR over 2 years in the all-patients population, will be tested in a two-sided test at 5% level.

Testing of other efficacy endpoints will not be subject to type-1 error control and, therefore, will be viewed as supportive.

In the blinded SSRE for the key secondary UPE endpoint (primary endpoint in the original protocol), no alpha level penalty was applied.

A conditional power-based SSRE for the key secondary endpoint of eGFR is planned in the high-risk proteinuria group (at least N = 180) at the time of the primary endpoint analysis. At this SSRE, no formal statistical testing will be performed on eGFR data.

14.1.6.4. Handling of Missing Data

The following general methods will be used for producing the data summaries and documenting missing data:

- Available clinical data at each visit will be presented and the sample size displayed will reflect the number of patients with available data. Patient listing data will be provided as recorded on the case report form, indicating partial dates and missing data

- Generally, if data are missing or incomplete, the missing or incomplete values will be presented in the data listings. Data summaries will be based on the observed data without imputation, unless otherwise specified
- If there are 2 or more assessments in the same analysis visit, the closest one to the target day will be used in the analysis. If there are 2 assessments that are equally spaced from the target day, the latest one will be used in the analysis, unless otherwise specified

14.1.6.5. Analysis Populations

The primary efficacy analysis population will be the Full Analysis Set (FAS) population, defined as all randomized patients in the high-risk proteinuria group. Patients will be grouped by their assigned treatment. When considering the all-patients population (baseline 24-hour UPE > 1 g/day), the same principal applies, i.e. the FAS for this population is defined as all randomized patients.

The supporting efficacy analysis populations will be the Per-Protocol Analysis Set population, which includes all randomized high-risk proteinuria patients who receive at least 10 doses of study drug in the Initial Treatment Period and have non-missing primary endpoint data (24-hour UPE at baseline and Week 36). Patients will be grouped by their assigned treatment.

Safety analyses will be based on the Safety Analysis Set, which includes all patients who receive any positive amount of study drug. Patients will be grouped by their actual treatment received. Supportive safety summaries will also be made in the population of all patients who receive any positive amount of study drug.

14.1.7. Patient Disposition

An accounting of study patients by disposition will be tabulated by treatment group. The number of patients in each analysis population will be summarized by treatment group. Patients who discontinued study drug prematurely or withdrew from the study will be summarized and listed with reason for early termination/withdrawal. Patients who re-initiated study treatment will be summarized by treatment group.

Furthermore, the number of patients who receive open-label treatment of narsoplimab will be summarized by treatment group for the FAS population. Time from randomization to the date of the first dose of open-label narsoplimab will be analyzed by Kaplan-Meier (KM) method for each treatment group for the FAS population. Patients who have not received open-label narsoplimab-treatment will be censored at the last known date on study. Median time with 95% confidence interval will be provided by treatment group.

14.1.8. Patient Characteristics

Demographic and other baseline characteristics and concomitant medications will be listed and summarized by treatment group.

14.1.9. Treatment Compliance

Because all dosing will be under direct supervision of study personnel, treatment compliance will not be analyzed. Dosing information will be summarized and listed.

14.1.10. Efficacy Analyses

14.1.10.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint will be based on the natural logarithm transformed 24-hour UPE. Descriptive statistics for the log-transformed 24-hour UPE change from baseline to 36 weeks, the geometric mean ratio (GMR) relative to the study baseline, and the coefficient of variation in percentage will be provided by treatment group for the FAS population.

The primary analysis will be a MMRM analysis on the change from baseline in log-transformed 24-hour UPE at Week 12, Week 24, Week 30, and Week 36. The model will fitted in SAS via the PROC MIXED procedure. Terms will be included for treatment, time (as a categorical variable for the four timepoints), treatment by time interaction, and randomization strata as fixed effects. Within patient error will be modeled using an unstructured covariance matrix. Log baseline UPE will be included as a covariate in the model. Restricted maximum likelihood method will be used to estimate the model parameters. If the estimation of the model fails, an autoregressive (1) [AR(1)] covariance structure will be used. The difference in least squares (LS) means at Week 36 between the treatment groups and its 95% confidence interval (CI) will be estimated. Two-sided p-value will be calculated. The LS mean at Week 36 will be estimated with 95% CI for each treatment group. The ratio of the GMR between the treatment groups will also be estimated with 95% CI.

Sensitivity analysis of the primary efficacy endpoint relate to the handling of missing data.

Jump to Placebo Multiple Imputation

The first approach will employ a control-based multiple imputation [Ratitch 2011] whereby missing observations in both the narsoplimab and placebo groups are imputed using only data observed in the placebo group; as such, this approach reflects a 'jump to placebo (or reference)' analysis. Imputation of values in the placebo arm will assume missing at random (MAR) while imputation of values in the narsoplimab arm will assume missing not at random (MNAR), i.e. as if the patient had been a member of the placebo arm. This approach does not assume a sustained benefit of narsoplimab treatment after discontinuation and limits a post-discontinuation effect to that of placebo.

Tipping Point Multiple Imputation

The second approach analysis will be a tipping point analysis. This will assess the robustness of the primary endpoint analysis by determining the penalty that, when applied to narsoplimab patients with missing data, renders the primary endpoint p-value non-significant. This analysis requires that the data has a monotone missingness pattern, thus, and as necessary, a partial-imputation method using the MCMC method will be employed as described above for Jump to Placebo.

COVID-19

Statistical analysis using the primary analysis method will be performed by excluding the data collected from patients re-initiating study treatment due to the COVID-19 pandemic.

14.1.10.2. Analysis of Rate of Change in eGFR

The analysis of the key secondary efficacy eGFR endpoints (1) the rate of change in eGFR over 2 years in the high-risk proteinuria group and (2) the rate of change in eGFR over 2 years in the all-patients population will be performed only if the primary UPE efficacy endpoint in the high-risk proteinuria group is significant at 5% level of significance in a 2-sided test. If the primary endpoint is significant then key secondary endpoints (1) and (2) will each be sequentially tested at 5% level of significance in a 2-sided test.

The key secondary rate of change in eGFR over 2 years in patients in the high-risk proteinuria group (baseline UPE ≥ 2g/day) and in the all-patients population will be analyzed by a random coefficients model for the FAS population. This analysis will be performed after the final database lock.

The random coefficients model is specified as follows:

$$yy_{iiaa} = (\beta\beta_0 + bb_{0ii}) + \beta\beta_1 \cdot GG + (\beta\beta_2 + bb_{2ii})xx_{iiaa} + \beta\beta_3 \cdot GG \cdot xx_{iiaa} + ee_{iiaa}$$

where

- yy_{iiaa} is the eGFR value for patient ii at assessment time jj;
- xx_{iiaa} is the time of the jj^{tth} assessment for patient ii;
- $GG = 0, 1$ for placebo and narsoplimab
- $\beta\beta_0 =$ intercept fixed placebo effect, $\beta\beta_0 + \beta\beta_1 =$ intercept fixed narsoplimab effect and $\beta\beta_1 =$ the fixed treatment effect on the intercept;
- $\beta\beta_2 =$ slope fixed placebo effect, $\beta\beta_2 + \beta\beta_3 =$ slope fixed narsoplimab effect and $\beta\beta_3 =$ the fixed treatment effect on slope;
- bb_{0ii} and bb_{2ii} are the random intercept and slope effects associated with patient ii;
- ee_{iiaa} are the residual error for patient ii at time jj, with ee_{iiaa};

The random effects, bb_{0ii} and bb_{2ii} are assumed $ii.ii.dd$ Normally distributed with variance components $\sigma\sigma_0^2$ and $\sigma\sigma_2^2$ and, independently, the random error ee_{iiaa} is Normally distributed with variance $\sigma\sigma^2$.

The restricted maximum likelihood (REML) method in SAS PROC MIXED will be used to fit the model. The treatment difference in the rate of change in eGFR over 2 years will be estimated from the model along with its standard error, 2-sided confidence interval and p-value. The applicable alpha level will be 5% in a 2-sided test.

Sensitivity analyses for both key secondary efficacy eGFR endpoints will include:

- Jump to Placebo Multiple Imputation
- Tipping Point Multiple Imputation
- COVID-19

These analyses will be executed in the same fashion as described for the primary UPE endpoint.

14.1.10.3. Analyses of Secondary and Exploratory Efficacy Endpoints

Proteinuria durability will be evaluated by the time adjusted AUC change from baseline in the log-transformed 24-hour UPE between 36 and 48 weeks, and between 36 and 72 weeks. The time adjusted AUC will be calculated as the AUC of the change in the log-transformed 24-hour UPE from baseline over the said time period divided by the time between the first observation and the last observation over the said time period. Patients who are on study and have not reached the Week-36 visit will be excluded from the analysis. The time adjusted AUC will be summarized descriptively. The geometric mean ratio relative to the study baseline, and the coefficient of variation in percentage will be provided by treatment group for the FAS population. A MI with FCS regression method will be used to impute missing log-transformed 24-hour UPE at the scheduled visits from Week 12 to Week 72. The FCS regression method will include the treatment group and the randomization strata as covariates. The time adjusted AUC will be calculated using the imputed values. The treatment difference will be estimated by an analysis of variance (ANOVA) model with treatment and randomization strata as covariates using Rubin method with 30 imputations.

Proteinuria responder durability will be evaluated by the time adjusted AUC 24-hour UPE from 36 weeks to 48 weeks where this time adjusted AUC is < 1 g/day or at least 50% reduced from the baseline 24-hour UPE for the high proteinuria group in the FAS population. Patients who are on study and have not reached the Week-36 visit will be excluded from the analysis. The time adjusted AUC will be calculated using AUC similar to the above. Patients with missing time average will be considered as non-responders (non-responder imputation). Percentage of proteinuria responder durability will be summarized by treatment group. A CMH test stratified by the baseline eGFR level (≥ 30 to ≤ 45 mL/min/1.73 m^2 and > 45 mL/min/1.73 m^2) will be performed. Proteinuria responder durability will also be evaluated similarly by the time adjusted AUC 24-hour UPE from 36 weeks to 72 weeks.

Natural logarithm transformation will be used to analyze 24-hour UPE, 24-hour uPCR, 24-hour uACR, spot-urine uPCR and spot-urine uACR. Geometric-mean ratio relative to the study baseline will be presented by treatment group and visit for the FAS population. A repeated measures model for the change in the log-transformed value from baseline will be used for analysis. The model will include treatment, time (as a categorical variable for the scheduled timepoints), treatment by time interaction, randomization strata as fixed effects and a time-dependent covariate for open-label treatment of narsoplimab as fixed effects, and an AR (1) covariance matrix. The time-dependent covariate is a binary variable that has a value of 0 before the initiation of the open-label treatment and 1 afterwards. It is defined for the placebo group only. The REML method will be used to estimate the model parameters. The difference in least squares (LS) means between the treatment groups and its 95% CI will be estimated for each post-baseline scheduled visit. The LS mean will be estimated with 95% CI for each treatment group. The ratio of the GMR between the treatment groups will also be estimated with 95% CI. It is noted that the primary analysis of 24-hour UPE is based on the 24-hour UPE up to Week 36 and the time-dependent covariate is not applicable to the primary analysis.

Time adjusted AUC change from baseline in spot-urine uPCR through 36 weeks will be calculated as the AUC of the change from baseline in spot-urine uPCR divided by the time from

baseline to the last observation on or before Week 36. Time average of change in spot-urine uPCR will be summarized descriptively. An ANOVA model with treatment and randomization strata as covariates will be performed.

The binary endpoints will be summarized descriptively. Non-responder imputation will be used to impute missing data. Exact 95% confidence intervals for the crude rate will be calculated and a CMH test stratified by the randomization stratum will be performed for the FAS population.

The time-to-event endpoints will be analyzed by Kaplan-Meier (KM) method for each treatment group for the FAS population. Median time with 95% confidence interval will be provided by treatment group. Log-rank test stratified by the randomization stratum will be performed.

Change from baseline in RBC/HPF will be summarized descriptively by treatment group and scheduled visit.

14.1.11. Pharmacokinetic, Pharmacodynamic and Biomarker Analyses

Blood samples will be collected from patients at intervals using sparse sampling to enable population PK analyses. Biomarker, ADA, NAb, and PD data will be summarized descriptively. An exploratory evaluation of other relevant biomarkers may be conducted.

14.1.12. Safety Analyses

14.1.12.1. Extent of Exposure

The following exposure items will be summarized with descriptive statistics by treatment group for the safety analysis set:

- Cumulative doses in milligrams taken by blinded treatment period (the Initial Treatment Period, the extended treatment period, the retreatment period, and the entire treatment period)
- Cumulative narsoplimab doses in milligrams during the open-label treatment period for the placebo group
- Duration of treatment in weeks by blinded treatment period, which is defined as (the last dose date of the treatment period – the first dose date of the treatment period + 7)/7
- Duration of open-label treatment period in weeks
- Absolute dose intensity (ADI), which is defined as the actual dose taken in milligrams per week by blinded treatment period. (ADI = Cumulative doses taken in milligrams /Duration of blinded treatment in weeks)
- Relative dose intensity (RDI), which is defined as the ADI as a percentage of the intended dose intensity (IDI) by blinded treatment period, RDI = ADI/IDI × 100, where IDI = 370 mg/week.

14.1.12.2. Adverse Events

The incidence of all reported AEs and treatment-related AEs before the initiation of the open-label treatment of narsoplimab will be tabulated by treatment group. AE data collected during the

open-label period will be summarized separately. AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

The focus of AE summarization for this study will be on treatment-emergent AEs (TEAEs). A TEAE is defined as an event that first occurs or worsens in severity after the first dose of study drug.

AEs will be listed and summarized by treatment group, MedDRA PT, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same PT in one patient, the AE will be counted once as the worst occurrence. The incidence of AEs will be tabulated by SOC and treatment group. AEs leading to premature discontinuation of study drug or withdrawal from the study will be summarized and listed in the same manner.

14.1.12.3. Serious Adverse Events

Serious adverse events will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

14.1.12.4. Clinical Laboratory Results

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by treatment group and scheduled visit. Patients with laboratory values outside of the normal reference range at any post-baseline assessment will be listed by treatment group.

Shifts from baseline laboratory values will be tabulated as appropriate by treatment group.

14.1.12.5. Other Safety Analyses

Summary statistics for actual values and change from baseline will be tabulated for vital signs by treatment group and scheduled visit.

14.1.13. Interim Analyses

The IDMC will operate in accordance with the IDMC charter and have regular meetings in person or by teleconference. A description of the frequency and nature of IDMC data monitoring and any operating procedures to maintain study blinding are detailed in the IDMC charter.

A pre-planned blinded sample size re-estimation for UPE endpoint in the all-patients population was performed when 168 patients completed the Week 36 visit. The independent IDMC statistician re-calculated the sample size using an adjusted variance. A bias-adjusted variance of the log-transformed 24-hour UPE change from baseline to Week 36 was calculated using the pooled variance from the available data and the assumed treatment effect size in a blinded fashion. The bias-adjusted variance was expressed as [Kieser 2003]:

$$VV^2_{aaaaaa} = VV^2_{ppppppppeeaa} - \frac{mm}{4(mm-1)}\Delta^2,$$

where $VV^2_{ppppppppeeaa}$ is the pooled variance, n is half of the number of patients with UPE at Week 36 at the time of the sample size re-estimation (i.e., m = 168), and Δ is the assumed treatment effect size in the sample size calculation.

The log scale SD was estimated to be lower than anticipated and, hence, no change to sample size was made.

An interim analysis is planned for the primary efficacy UPE endpoint. The interim database will include at least 180 patients in the high proteinuria group. The primary efficacy UPE endpoint will be analyzed and formally tested for treatment comparison. Other efficacy endpoints will also be descriptively summarized. No formal statistical tests will be performed for the other efficacy endpoints based on the interim database. Safety analysis will be performed. The study sites and patients will remain blinded to the treatment. The study will be unblinded at the study level only so that statistical analyses can be performed.

The final database lock will occur when all randomized patients have completed the study. The rate of change in eGFR will be estimated and formally tested for treatment comparison if the primary efficacy endpoint is statistically significant at the interim analysis. Other efficacy endpoints will also be descriptively summarized. Safety analysis will be performed.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will maintain appropriate medical and research records for this study in accordance with the IRB/IEC, regulatory, and ICH requirements for the protection of confidentiality of patients. The Investigator and his/her study site(s) will permit authorized representatives of the Sponsor, the governing IRB/IEC, competent authority, FDA, EMA, and/or other regulatory agencies to examine clinical records for the purposes of monitoring the study, including verifying the accuracy and completeness of data, evaluating study safety, assessing protocol and regulatory adherence, and quality assurance reviews, audits, and inspections.

15.1. Study Monitoring

The Investigator and his/her study site(s) agree to allow Omeros and its designees to have direct access to the source data/documents during the monitoring visits. The monitoring visits provide Omeros with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records, as well as assuring that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled.

The study monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator.

15.2. Audits and Inspections

The study site will allow representatives of Omeros to periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each patient. Case report forms will be reviewed by Omeros or its representative for adherence to protocol, completeness, and acceptability. Portions of the patient’s medical and hospital records pertinent to the study will be reviewed at the study site to assure accuracy. It is important that the Investigator and/or other staff are available at these visits. If contacted by a regulatory agency for an inspection, please call the Sponsor’s study monitor immediately. Contact information for the Sponsor’s study monitor is included in the investigator study file.

16. QUALITY CONTROL AND QUALITY ASSURANCE

Following written standard operating procedures, the monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Data Management will implement quality-control procedures and generate data logic checks that will be run on the data. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. Data quality-control measures are outlined in the Data Management Plan for the study.

16.1. Monitoring

To ensure accurate, complete, and reliable data, Omeros or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate
- Provide start-up training and continuing training (if applicable) to the Investigators and study personnel on the protocol, the completion of the CRFs, and study procedures
- Make periodic monitoring visits to the investigational site
- Be available for consultation and stay in contact with the investigational site personnel by mail, telephone, electronic mail, and/or fax
- Use an accredited local laboratory and combine laboratory data across study sites
- Monitor the patient data recorded in the CRF against source documents at the investigational site

Review and evaluate CRF data and use standard computer edits to detect anomalies in data collection, which will be forwarded to the Investigator for resolution

During the COVID-19 pandemic, study monitoring activities may be impacted due to the restrictions established by each institution and the respective local authorities. As on-site monitoring visits may not be permitted or may be substantially restricted due to local and national legislation and the availability of investigative staff, Omeros or its representatives will implement the following alternate monitoring activities, which are consistent with FDA and EMA guidelines:

- Extending the interval between on-site monitoring visits
- Canceling or postponing on-site monitoring
- Implementation of phone and video monitoring visits while ensuring compliance with the applicable legislation on protection of patient privacy (most EU member states do not allow remote source data verification)
- Modification of the on-site monitoring plan to include additional centralized review of data

When the COVID-19 pandemic stabilizes, on-site monitoring activities will resume at more frequent intervals in order to ensure any impact of reduced monitoring is mitigated and all issues are appropriately documented.

16.2. Auditing

The study may be audited by the Sponsor or its representatives at any time.

17. ETHICS

17.1. Ethics Review

Each participating institution must provide for the review and approval of this protocol, the associated informed consent documents, and any patient-directed materials (e.g. patient diary) by a properly constituted IEC or IRB. Any amendments to the protocol, consent, or patient-directed materials must also be approved prior to implementation. The Investigator will provide Omeros or its designee with documentation of the IRB or IEC approval of the protocol, informed consent document, and patient-directed materials before the study may begin at the investigative site(s).

In addition, the Investigator or designee will submit for review to the investigative site's IRB/IEC:

- Clinical IB and updates
- Required safety and SAE reports
- Deviations from the protocol and applicable FDA or other regulatory agency regulations (as required by the IRB/IEC)
- Any additional submissions (e.g. continuing review reports or new information) required by the site's IRB/IEC

The IRB/IEC will provide initial and continuing review. The continuing review will be performed at least once per year.

The Investigator must provide Omeros or its designee all IRB/IEC related submission decisions, approvals and/or acknowledgement of receipts, as appropriate.

17.2. Ethical Conduct of the Study

17.2.1. Regulatory Considerations

This study will be conducted in compliance with the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (1996), GCP, Health Insurance Portability and Accountability Act (HIPAA), 21 CFR Part 11, and any additional applicable national, state, and local rules and regulations.

After reading the protocol, the Investigator will sign the Investigator Agreement and return it to Omeros or its designee.

17.2.2. Investigator Information

The contact information and qualifications of the Principal Investigator (PI) and Sub-Investigators, and the name and address of the research facilities are included in the Investigator file.

17.2.3. Protocol Amendments and Study Termination

Any Investigator-initiated changes to the protocol (except for changes to eliminate an immediate hazard to a study patient) must be approved by Omeros prior to seeking approval from the IRB/IEC, and prior to implementing. The Investigator is responsible for enrolling patients who have met protocol eligibility criteria. Protocol violations must be reported to Omeros and to the local IRB/IEC in accordance with IRB/IEC policies.

Omeros may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

17.2.4. Participant Confidentiality

All reports and communications relating to patients in the study will identify each patient only by the patient's initials and/or patient number.

17.2.5. Clinical Trial Agreement

Payments by Omeros to Investigators and institutions conducting the trial, requirements for Investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the Clinical Trial Agreement.

17.3. Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Any procedures specifically for the study cannot be started until the informed consent form is signed by the patient and the person conducting the consent. Discussion of risks and possible benefits of this therapy will be provided to the patients. Consent forms describing in detail the Study Agent(s)/Intervention(s), study procedures, and risks are given to the patient and written documentation of informed consent is required prior to starting study agent/intervention. Consent forms will be IRB/IEC approved and the patient will be asked to read and review the document. Upon reviewing the document, the Investigator will explain the research study to the patient and answer any questions that may arise. The patients should have sufficient opportunity to discuss the study and process the information in the consent form prior to agreeing to participate. The patients may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

In addition, patients will provide written permission for use and disclosure of protected health information collected in connection with participation in this study through an authorization that satisfies the HIPAA Privacy Rule (see 45 CFR 164.508). The authorization will be provided to

patients in accordance with IRB/IEC procedures. The authorization may either be combined with the informed consent or provided as a separate document.

17.4. Investigator Reports

During the conduct of the study and at its completion, the Investigator will report to the IRB/IEC as required by the applicable IRB/IEC requirement and regulations. In addition, the Investigator will report to Omeros in accordance with regulation 21 CFR 312.64.

18. DATA HANDLING AND RECORDKEEPING

18.1. Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the Investigator's site staff to ensure that they are accurate and complete. Adverse Events must be graded, assessed for severity and causality, and reviewed by the site PI or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study.

18.2. Data Capture Methods

Electronic case report forms (eCRFs) are used to transmit the information collected in the performance of this study to Omeros and applicable regulatory agencies. For EDC-based studies, data is captured electronically and stored by the vendor during the study. At the end of the study, the Investigator will be provided with an electronic file of all the eCRFs for their patients.

The Investigator and study personnel will ensure that proper data for the clinical study are collected and accurately documented in the appropriate sections of the eCRFs. The Investigator will review each eCRF for completeness and accuracy and sign and date the forms where indicated. In addition, it will be the Investigator's responsibility to provide signatures where requested indicating concurrence with data in the eCRF.

eCRFs will be reviewed by monitors from Omeros or its representative for adherence to protocol, completeness, and acceptability. Portions of the patient's medical and hospital records pertinent to the study will be reviewed at the study site to assure accuracy.

18.3. Source Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP, regulatory, and institutional requirements for the protection of confidentiality of participants.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, source document worksheets, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from

automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial. FDA regulations require that the Investigator prepares and maintains adequate and accurate records for each patient treated with study drug.

18.4. Retention of Records

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the Investigator until notified by Omeros in writing that retention is no longer necessary.

The Sponsor will archive the EDC data, including associated queries and audit trail.

FDA regulations require that the Investigator prepares and maintains adequate and accurate records for each patient treated with study drug. Source documents such as hospital, clinic or office charts, laboratory reports, ECGs, operative reports, anesthesia records, consultation reports, history and physical examination reports, study worksheets, and the signed informed consent will be included in the Investigator's files with the patient's study records.

Records containing patient medical information must be handled in accordance with the requirements of the HIPAA Privacy Rule and consistent with the terms of the patient authorization contained in the informed consent document for the study (the authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the authorization. Furthermore, CRFs and other documents to be transferred to Omeros should be completed in strict accordance with the instructions provided by Omeros, including the instructions regarding the coding of patient identities.

No study document should be destroyed without prior written agreement between Omeros and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from Omeros.

18.5. Protocol Deviations

A protocol deviation is defined as any non-adherence to study procedures or schedules, as specified by the protocol, and applies to the reporting of emergency and non-emergency departures from the protocol.

A protocol deviation includes any noncompliance with the clinical trial protocol, GCP, or manual of procedures requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study-site staff. As a result of deviations, corrective actions are to be developed by the Investigator and/or his/her staff and implemented promptly. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site Investigator/study staff is responsible for knowing and adhering to their IRB/IEC requirements. Deviations that occur due to the COVID-19 pandemic should be clearly identified as such in the patient source documents and communicated to the site's CRA for entry into CTMS.

Definitions of major and minor protocol deviations are as follows:

Major Deviation – A deviation that *has* a substantive adverse effect on the safety, rights or well-being of subjects, data integrity, or the quality of investigational products or placebos (e.g.,

storage condition). Minor deviations may be considered major, if the frequency or duration is deemed excessive.

Minor Deviation – A deviation that *does not* have a substantive adverse effect on the safety, rights or well-being of subjects, data integrity, or the quality of investigational products or placebos.

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20. APPENDICES

20.1. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation

The CKD-EPI equation will be used when calculating eGFR:

eGFR (mL/min/1.73 m^2) = 141 × min (SCr/κ, 1)$^{\alpha}$ × max (SCr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black]

κ = 0.7 if female
κ = 0.9 if male

α = –0.329 if female
α = –0.411 if male

min = The minimum of SCr/κ or 1
max = The maximum of SCr/κ or 1

SCr = serum creatinine (mg/dL)

20.2. Study Schedule of Events

20.2.1. Study Schedule of Events – Screening, Run-In, and Initial Treatment Periods

Study Period	**Screening Period**[1]	**Run-In Period**[2, 3]				**Initial Treatment Period**[4]		
Visit	**SV**	**RI1**[5]	**RI2**[5, 6] **(±7 days)**	**RI3**[5] **(±7 days)**	**RI4**[6] **(±7 days)**	**T1**[7, 8, 9]	**T2 to T11**[10]	**T12 (±2 days)**
Week	**Screening Days 1 to 28**	**Run-In Weeks 1 to 4 or 12**				**1**	**2 to 11**	**12**
Informed consent[11], medical history	X							
Review of inclusion/exclusion criteria	X	X	X	X	X			
Perform complete physical examination	X							X
Symptom-directed physical examination		X[12]	X[12]	X[12]	X			
BP medication optimization including BP and pulse[13]		X	X	X	X			
Randomization[14]						X		
Vital signs[15]	X	X	X	X	X	X	X	X
ECG	X		X[16]		X	X[17]		X[17]
Dispense 24-hour urine collection supplies[18]	X	X	X	X	X		X	
Collect 24-hour urine sample(s) for UPE, uPCR and uACR[19]			X[16]		X		X[20]	
uPCR and uACR from spot urine	X		X		X		X[22]	X
Urinalysis[21]	X		X[16]		X		X[22]	X
Comprehensive metabolic panel[21]	X		X[16]		X		X[22]	X
Complete blood count with differential[21]	X		X[16]		X		X[22]	X
HgbA1c[21]	X		X[16]		X			
Serology for HIV, HBV, and HCV	X							
Pregnancy test[23]	X		X[16]		X	X	X[24]	X
Study drug administration						X	X	X
Assess response and need for retreatment[25]								X
PK and PD sampling[26]			X[16]		X	X	X[10]	X
Biomarker[27], ADA, and NAb sampling			X[16]		X		X[28]	X
If available, send kidney biopsy to central reader						X[29]	X[29]	X[29]
Adverse events	X	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X	X	X
Confirm and document stability of RAS blockade					X	X	X	X

Abbreviations: ADA = anti-drug antibody; BP = blood pressure; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CMP = comprehensive metabolic panel; CBC+diff = complete blood count with differential; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HgbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; NAb = neutralizing antibody; PD = pharmacodynamics; PK = pharmacokinetics; RAS = renin-angiotensin system; RE = Response Evaluation Visit; RI = Run-In Visit; SV = Screening Visit; T = Treatment Visit; TC = telephone call; UA = urinalysis; uACR = urine albumin-to-creatinine ratio; uPCR = urine protein-to-creatinine ratio; UPE = urine protein excretion

[1] During the COVID-19 pandemic: Investigators may request re-consideration of patients who fail the Screening Period due to COVID-19 restrictions, based on case-by-case discussion with the Medical Monitor. Patients for whom the Screening Period is interrupted due to COVID-19 restrictions may re-screen when the study site has re-opened for study visits.

[2] During the COVID-19 pandemic: Upon case-by-case discussion with the Medical Monitor, investigators may request an extension of the Run-In Period for patients who, due to COVID-19 restrictions, are unable to attend in-person Run-In Visits. During the extended Run-In Period, telephone calls to the patient should occur every 4 weeks (+/- 7 days) to check for adverse events, changes in medications and confirm patient safety. During the telephone calls, patients will collect their own pulse, systolic and diastolic BP, and body temperature using calibrated equipment. Patients will record pulse, systolic and diastolic BP, and temperature on a patient diary and provide this diary to the study site at the first available opportunity. Telephone calls may occur more frequently if needed. These calls must be documented in the patient source documents and in the eCRF.

[3] Two 24-hour urine specimens will be collected during the last two weeks of the Run-In Period. The following samples will be collected from each of the two urine collection samples: 24-hour UPE, uPCR, and uACR. During the COVID-19 pandemic: The two 24-hour urine collection specimens may be delivered to the study site or the central lab by the specialty courier service selected by the sponsor, provided the patient has granted consent.

[4] During the COVID-19 pandemic: Instructions on how to handle COVID-19 related treatment interruptions are covered in Section 20.4.2. All patients who experience a treatment interruption due to COVID-19 restrictions will have blood and urine collected for safety testing and the site must confirm the results meet study entrance criteria, with the exception of uPCR and eGFR (see Section 8) prior to the patient resuming or reinitiating Initial Treatment. For complete details on resumption or re-initiation of Initial Treatment, refer to Section 10.2.3. If a patient misses more than two study treatment visits, a 24-hour UPE will be completed to guide next steps. The patient will be contacted by phone every 4 weeks (+/- 7 days) to check on safety, AEs, and Con Meds. These telephone calls may occur more frequently if needed. During the calls, patients will collect their own pulse, systolic and diastolic BP, and body temperature using calibrated equipment and record these values on a patient diary, which they will provide to the study site at the first available opportunity. These calls must be documented in the patient source documents and in the eCRF. Patients who miss more than two consecutive study treatment visits due to COVID-19 restrictions and are administered rescue therapy as a result, may reinitiate Initial Treatment at T1 after an 8-week wash-out period.

[5] During the COVID-19 pandemic: Run-In Visit 1 (RI1), and Run-In Visit 3 (RI3) may be conducted virtually (e.g. via telephone or video conference) or at patient's home. RI2 may occur at the patient's home or, if it is not the final Run-In Visit, it may be completed virtually. All visit procedures may be conducted virtually, except for collection of respiratory rate and performance of the symptom-directed physical exam, which will be waived under these circumstances.

[6] During the COVID-19 pandemic: The final Run-In Visit (RI2 or RI4) should be conducted at the study site, or, if permitted by site/institution, may be conducted at the patient's home.

[7] During the COVID-19 pandemic: Randomization of eligible patients to study treatment at Treatment Visit 1 (T1) will be allowed at the investigator's discretion and should align with guidance from local authorities and site/institution.

[8] Visit T1 must occur within 7 days from receipt of the lab results from the final Run-In Visit.

[9] During the COVID-19 pandemic: Before T1 is repeated due to treatment interruptions from COVID-19, a 24-hr UPE will be obtained to guide investigator on next steps. Blood and urine will be collected for safety testing beforehand and must be confirmed as meeting study entrance criteria, with the exception of uPCR and eGFR (see Section 8) prior to resuming study treatment. Patients who choose to continue without reinitiating study treatment will provide a 24-hr urine sample at the time of study continuation

[10] Visit T2 PK/PD collection must be done 168 hours ± 2 hours after the start of the first dose at T1. Visits T4, T8, and T10 require PK/PD collection and must occur within ± 2 days due to PK/PD collection, and Visits T3, T5, T6, T7, T9, and T11 do not require PK/PD collection and must occur within ± 3 days.

[11] During the COVID-19 pandemic, it may not be possible for sites to obtain in-person consent. While considering alternate consent methods as per FDA and EMA guidance, investigators should at all times adhere to institution/IRB/IEC guidance on appropriate re-consenting methods (see Section 10.1.1).

[12] During the COVID-19 pandemic: If Run-In Visits 1 and 3 are conducted virtually (e.g. telephone or video conference) physical exams will not be performed at those visits. If Run-In Visit 2 is done virtually and as long as it is not the final Run-In Visit, the physical exam will not be performed.

[13] During the COVID-19 pandemic: Blood pressure optimization may be performed during a virtual study visit (e.g. over the phone or via video conferencing).

[14] Randomization: patients who meet all eligibility criteria will be randomized at T1 or within 24 hours prior to T1

[15] Vital signs: to be collected prior to dosing, approximately 5 minutes after the end of the 30-minute study drug infusion, and 30 minutes (± 5 minutes) following the end of the study drug infusion on study drug treatment days. During the COVID-19 pandemic: For study visits conducted virtually, it may be necessary for patient to collect his or her own pulse, systolic and diastolic BP, and body temperature. Patients will record pulse, systolic and diastolic BP and temperature on a patient diary and provide this diary to the study site. In the case of a thermometer shortage due to the COVID-19 pandemic, sites may allow a patient to collect body temperature with the patient's own thermometer.
[16] During the Run-In visits, these assessments will only be performed if the patient is on stable BP medication and the visit is considered the final Run-In visit
[17] During the Initial Treatment Period ECGs will be collected: pre-dose and at the end of the 30-minute infusion at T1 (to be obtained immediately before the 15-minute post-dose PK/PD samples), and pre-dose at T12
[18] Patients should be instructed to return the 24-hour urine sample to the clinic as soon as possible following its collection. With patient consent, the 24-hour urine collection samples may be delivered from the patient's location to the study site or the central lab by a specialty courier selected by the sponsor.
[19] Due to COVID-19 restrictions, it may be allowable for a local commercial laboratory to assess 24-hour UPE, uPCR, and uACR if neither the study site nor the local commercial lab is able to process and prepare the samples for delivery to the central lab. In this case only, the local commercial lab may assess 24-hour UPE, uPCR and uACR.
[20] To be done either before, during, or after T11
[21] During the COVID-19 pandemic, it may be allowable for CMP, CBC+diff, HgbA1c, UA, uACR, and uPCR to be performed by a local commercial laboratory in cases where the patient is unable to travel to the study site or the study site is unable to receive or process the samples for delivery to the central laboratory.
[22] During the Initial Treatment Period between T2 and T11, collection of the following laboratory samples occurs only at T4 and T8: blood for CMP, CBC + diff., spot urine for uPCR, uACR, and UA.
[23] Pregnancy test for women of childbearing potential only. Test must be via serum for the final RI visit, and must be via urine for all other visits. Due to COVID-19 restrictions, it may be allowable for a patient to perform the urine pregnancy test at home at selected visits, using an approved urine pregnancy test. Patients will be provided with pregnancy test instructions and a diary in which to record the test result. The patient should verbally provide the pregnancy test result to the study site during a telephone call. If there is any doubt regarding the test result, the site should attempt to visually confirm the result over a webcam or via a video conference. The patient must provide the completed diary showing the pregnancy test result to the site at the first available opportunity.
[24] Collection of urine pregnancy at T4 and T8 only
[25] The patient's need for study drug retreatment should be assessed beginning at T12 as detailed in Section 10.2.4 and Section 10.2.7.
[26] PK and PD samples to be collected: any time at the final RI visit, 15 minutes (± 5 minutes) after the end of the study drug infusion at T1, 168 hours ± 2 hours after the start of the first dose (sample collected at T2), and pre-dose at visits T4, T8, T10, and T12
[27] Biomarker samples include urine, serum, and plasma samples, and are always collected pre-dose
[28] Collection of ADA, NAb, and biomarker samples at T4 only
[29] Biopsy specimens may be sent to the central reader at any time during the Initial Treatment Period

Note: If multiple procedures are specified at one timepoint they should be performed in the following order: vital signs, ECG, and then blood draw. The Screening Period and Run-In Period may be of variable length depending on the patient status.

20.2.2. Schedule of Events – Extended Treatment Following Initial Treatment

Study Visit	Extended Treatment[10, 11]					
Weekly Visit	**ExT1**[1]	**ExT2 (±3 days)**	**ExT3 (±3 days)**	**ExT4 (±3 days)**	**ExT5 (±3 days)**	**ExT6 (±3 days)**
Perform complete physical examination						
Vital signs[2]	X	X	X	X	X	X
ECG[3]	X					
Dispense 24-hour urine sample supplies[4]	X	X	X	X	X	X[5]
Collect 24-hour urine sample(s) for UPE, uPCR and uACR[6]						X
uPCR and uACR from spot urine				X		
Urinalysis	X			X		
Comprehensive metabolic panel						
Complete blood count with differential						
Urine pregnancy test[7]	X			X		
Study drug administration	X	X	X	X	X	X
PK and PD sampling[8]	X					
Biomarker[9], ADA, and NAb sampling	X					
Assess response						X
Adverse events	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X
Confirm and document stability of RAS blockade	X	X	X	X	X	X

Abbreviations: AE = adverse event ADA = anti-drug antibody; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; NAb = neutralizing antibody; PD = pharmacodynamics; PK = pharmacokinetics; RAS = renin angiotensin system; uACR = urine albumin/creatinine ratio; uPCR = urine protein-to-creatinine ratio; UPE urine protein excretion

[1] Extended Treatment Visit 1 should occur no later than 14 days from the date of T12

[2] Vital signs: to be collected prior to dosing, approximately 5 minutes after the end of the 30-minute study drug infusion, and 30 minutes (± 5 minutes) following the end of the study drug infusion on study drug treatment days

[3] During extended treatment, ECGs will be collected: pre-dose and at the end of the 30-minute study drug infusion at ExT1

[4] Supplies can be dispensed at any time during the Extended Treatment Period

[5] The 24-hour UPE sample may be collected at any time between ExT5 and ExT6

[6] Patients should be instructed to return the 24-hour urine sample to the clinic following its collection, which should occur within 48 hours following the visit.

[7] Pregnancy test for women of childbearing potential only

[8] PK and PD samples to be collected: 15 minutes (± 5 minutes) after the end of the study drug infusion at ExT1

[9] Biomarker samples include urine, serum, and plasma samples, and are always collected pre-dose

[10] During the COVID-19 pandemic: Instructions on how to handle COVID-19 related treatment interruptions are covered in Section 10.2. All patients who experience a treatment interruption due to COVID-19 restrictions will have blood and urine collected for safety testing and the site must confirm the results meet study entrance criteria, with the exception of uPCR and eGFR (see Section 8) prior to the patient resuming Extended Treatment or reinitiating Initial Treatment. For complete details on resuming Extended

Treatment or reinitiating Initial Treatment, refer to Section 10.2.4. If a patient misses more than two study treatment visits, a 24-hour UPE will be completed to guide next steps. The patient will be contacted by phone every 4 weeks (+/- 7 days) to check on safety, AEs, and Con Meds. These telephone calls may occur more frequently if needed. During the calls, patients will collect their own pulse, systolic and diastolic BP, and body temperature using calibrated equipment and record these values on a patient diary, which they will provide to the study site at the first available opportunity. These calls must be documented in the patient source documents and in the eCRF. Patients who miss more than two consecutive study treatment visits due to COVID-19 restrictions and are administered rescue therapy as a result, may reinitiate study treatment at T1 after an 8-week wash-out period. Patients who choose to continue without reinitiating study treatment will provide a 24-hr urine sample at the time of study continuation.

[11] During the COVID-19 pandemic: Patients who meet eligibility criteria for Extended Treatment will be allowed to commence study treatment at EXT1 at the investigator's discretion, based on guidance from local authorities, the IRB/IEC and site/institution. Eligible patients who experience delays of > 28 days from T12 in initiating Extended Treatment will provide another 24-hr UPE specimen and if the results are > 1 g/day, the patient will reinitiate Initial Treatment at T1. If the results are < or = 1 g/day, the patient will continue in the Response Evaluation Period and may receive relapse retreatment if relapse criteria are met at protocol specified timepoints.

20.2.3. Study Schedule of Events – Response Evaluation and Follow-Up Periods

Period		**Response Evaluation Period (Week 13-36)**			**Follow-Up Period**[4]		
Visit	**TC**[1]	**Week 24**	**Week 30**	**Week 36**[2, 3]	**FU1**[4] **Week 48**	**FU2**[4] **Week 72**	**FU3/EOS**[5] **Week 96**
Visit window		**±7 days**	**±7 days**	**±7 days**	**±14 days**	**±14 days**	**±14 days**
		TC	**TC**	**9-month visit**	**1-year visit**	**1.5-year visit**	**2-year visit**
Complete physical examination[6]					X		X
Symptom-directed physical examination[6]				X		X	
Vital signs[7]				X	X	X	X
ECG[6]				X	X		X
Dispense 24-hour urine sample supplies[8]		X	X	X	X	X	X
Collect 24-hour urine sample for UPE, uPCR and uACR[9]		X	X	X	X	X	X
uPCR and uACR from spot urine[10]				X	X	X	X
Urinalysis[10]				X	X	X	X
Complete blood count with differential[10]				X	X	X	X
Comprehensive metabolic panel[10]				X	X	X	X
Urine pregnancy test[11]				X	X	X	X
Biomarker, ADA, and NAb sampling[10, 12]				X	X		X
Assess response and need for study drug retreatment[13]		X	X	X	X	X	X[14]
Adverse events	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X	X
Confirm and document stability of RAS blockade				X	X	X	X

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; NAb = neutralizing antibody; PD = pharmacodynamics; PK = pharmacokinetics; RAS = renin-angiotensin system; uACR = urine albumin/creatinine ratio; uPCR = urine protein-to-creatinine ratio; UPE = urine protein excretion

[1] Telephone Calls 1 occur at the following timepoints relative to baseline: Weeks 16, 20, 24, 30, 34, 40, 44, 60, and 84. Assessments for telephone calls for Week 16 through Week 34 must occur within ± 7 days of the target date. Assessments for Telephone Calls for Week 40 through 84 must occur within ± 14 days of the target date.

[2] RE Week 36 – 9-month visit is the Primary Endpoint

[3] During the COVID-19 pandemic: The Response Evaluation Visit/Week 36 (RE/W36) should be conducted at the study site. If this is not possible due to COVID-19 restrictions, the visit may be conducted at the patient's home, or virtually via telephone or video conference if available in the region, if approval has been granted by study site/institution, and if patient provides consent for the service. For specific guidance on how to conduct the RE/W36 visit during the COVID-19 pandemic, refer to Section 10.2.5.

[4] During the COVID-19 pandemic: If it is not possible to conduct Follow-Up Visits 1 and/or 2 at the study site, due to COVID-19 restrictions, these visits may be conducted virtually (e.g. via telephone or web-cam) or at the patient's home if service is available in the region, if approval has been granted by study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service. FU3/EOS should be conducted at the study site in order to ensure completion of all required end of study assessments. If it is not possible to conduct this visit within the protocol-specified window due to COVID-19 restrictions, the study site should notify the Medical Monitor

of the deviation to the study visit schedule. This must be clearly documented as a deviation due to COVID-19 restrictions in the patient's source documents and in the eCRF. For guidance on how to conduct the Follow-Up Visits during the COVID-19 pandemic, refer to Section 10.2.6.

[5] FU3/EOS should be conducted at the study site in order to ensure completion of all required end of study assessments. If it is not possible to conduct this visit within the protocol -specified window due to COVID-19 restrictions, the study site should notify the Medical Monitor of the deviation to the study visit schedule. This must be clearly documented as a deviation due to COVID-19 restrictions in the patient's source documents and in the eCRF

[6] During the COVID-19 pandemic: If visits RE/Week 36 and Follow Up 1 are allowed to be conducted virtually, physical exam and ECG will not be performed.

[7] During the COVID-19 pandemic: If visits RE/Week 36 and Follow Up 1 - 2 are allowed to be conducted virtually, collection of blood pressure, pulse, and temperature may be performed with calibrated equipment by the patient.

[8] Patients should be instructed to return the 24-hour urine sample to the clinic as soon as possible following its collection. The 24-hour urine collection specimen may be delivered to the study site or central lab by the specialty courier service selected by the sponsor, provided the patient has granted consent.

[9] Due to COVID-19 restrictions, it may be allowable for a local commercial laboratory to assess 24-hour UPE, uPCR, and uACR if neither the study site nor the local commercial lab is able to process and prepare the samples for delivery to the central lab. In this case only, the local commercial lab may assess 24-hour UPE, uPCR and uACR.

[10] During the COVID-19 pandemic: If visits RE/W36, Follow Up 1 - 2 are allowed to be conducted virtually (e.g., by telephone or video conference), the collection, processing, and testing of blood and urine for safety may be completed at a local commercial lab convenient to the patient.

[11] Pregnancy test for women of childbearing potential only. During the COVID-19 pandemic: If allowable, the patient may perform the urine pregnancy test at home using an approved urine pregnancy test. Patients will be provided with pregnancy test instructions and a diary in which to record the test result. The patient should verbally provide the pregnancy test result to the study site. If there is any doubt regarding the test result, the site should attempt to visually confirm the result over a webcam or via a video conference. The patient must provide the completed diary showing the pregnancy test result to the site at the first available opportunity.

[12] Biomarker samples include urine, serum, and plasma samples.

[13] The patient's need for study drug retreatment should be assessed and retreatment provided for relapse as detailed in Section 10.2.7.

[14] At FU3/EOS response will be assessed but no retreatment will be given.

20.2.4. Schedule of Events – 6-Week Relapse Retreatment (During Response Evaluation Period)

Study Visit	6-Week Relapse Retreatment[8, 9]					
Weekly Visit	**6RT1[1]**	**6RT2 (±3 days)**	**6RT3 (±3 days)**	**6RT4 (±3 days)**	**6RT5 (±3 days)**	**6RT6 (±3 days)**
Perform complete physical examination						X
Vital signs[2]	X	X	X	X	X	X
ECG[3]	X					X
Dispense 24-hour urine sample supplies[4]						X
Collect 24-hour urine sample(s) for UPE, uPCR and uACR						X
uPCR and uACR from spot urine				X		X
Urinalysis	X			X		X
Comprehensive metabolic panel						X
Complete blood count with differential						X
Urine pregnancy test[5]	X			X		X
Study drug administration	X	X	X	X	X	X
PK and PD sampling[6]	X					X
Biomarker[7], ADA, and NAb sampling	X					X
Assess response						X
Adverse events	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X
Confirm and document stability of RAS blockade	X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; NAb = neutralizing antibody; PD = pharmacodynamics; PK = pharmacokinetics; RAS = renin angiotensin system; uACR = urine albumin/creatinine ratio; uPCR = urine protein-to-creatinine ratio; UPE = urine protein excretion

[1] Visit 6RT1 must occur no more than 7 days from receipt of the 24-hour UPE results from the Central Lab and documentation of the patient's need for relapse retreatment.

[2] Vital signs: to be collected prior to dosing, approximately 5 minutes after the end of the 30-minute study drug infusion, and 30 minutes (± 5 minutes) following the end of the study drug infusion on study drug treatment days

[3] During the relapse retreatment visits, ECGs will be collected: pre-dose and at the end of the 30-minute infusion at 6RT1 and 6RT6

[4] Patients should be instructed to return the 24-hour urine sample to the clinic following its collection.

[5] Pregnancy test for women of childbearing potential only

[6] PK and PD samples to be collected: 15 minutes (+/- 5 minutes) after the end of the study drug infusion at 6RT1 and pre-dose at visit 6RT6

[7] Biomarker samples include urine, serum, and plasma samples, and are always collected pre-dose.

[8] During the COVID-19 pandemic: Instructions on how to handle COVID-19 related treatment interruptions are covered in Section 10.2. All patients who experience a treatment interruption due to COVID-19 restrictions will have blood and urine collected for safety testing and the site must confirm the results meet study entrance criteria, with the exception of uPCR and eGFR (see Section 8) prior to the patient resuming or reinitiating 6-Week Relapse Retreatment. For details on resuming or reinitiating 6-Week Relapse Retreatment, refer to Section 10.2.7.1. If a patient misses more than two study treatment visits, a 24-hour UPE will be completed to guide next steps. The patient will be contacted by phone every 4 weeks (+/- 7 days) to check on safety, AEs, and Con Meds. These telephone calls may occur more frequently if needed. During the calls, patients will collect their own pulse, systolic and diastolic BP, and body temperature using calibrated equipment and record these values on a patient diary, which they will provide to the study site at the first available opportunity. These calls must be documented in the patient source documents and in the eCRF. Patients who miss more than two consecutive

study treatment visits due to COVID-19 restrictions and are administered rescue therapy as a result, may reinitiate study treatment at 6-RT1 after an 8-week wash-out period. Patients who choose to continue without reinitiating study treatment will provide a 24-hr urine sample at the time of study continuation.

[9] During the COVID-19 pandemic: Patients who meet eligibility criteria for 6-Week Relapse Retreatment will be allowed to commence study treatment at 6RT1 at the investigator's discretion, based on guidance from local authorities, the IRB/IEC and site/institution.

20.2.5. Schedule of Events – 12-Week Relapse Retreatment (During Follow-Up Period)

Study Visit	12-Week Relapse Retreatment[8, 9]											
Weekly Visit	**12 RT1** [1]	**12 RT2 (±3 days)**	**12 RT3 (±3 days)**	**12 RT4 (±3 days)**	**12 RT5 (±3 days)**	**12 RT6 (±3 days)**	**12 RT7 (±3 days)**	**12 RT8 (±3 days)**	**12 RT9 (±3 days)**	**12 RT10 (±3 days)**	**12 RT11 (±3 days)**	**12 RT12 (±3 days)**
Perform complete physical examination												X
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X
ECG[3]	X											X
Dispense 24-hour urine sample supplies[4]												X
Collect 24-hour urine sample(s) for UPE, uPCR and uACR												X
uPCR and uACR from spot urine				X				X				X
Urinalysis	X			X				X				X
Comprehensive metabolic panel												X
Complete blood count with differential												X
Urine pregnancy test[5]	X			X				X				X
Study drug administration	X	X	X	X	X	X	X	X	X	X	X	X
Assess response												X
PK and PD sampling[6]	X											X
Biomarker, ADA, and NAb sampling[7]	X											X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X	X	X
Confirm and document stability of RAS blockade	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; NAb = neutralizing antibody; PD = pharmacodynamics; PK = pharmacokinetics; RAS = renin angiotensin system; uACR = urine albumin/creatinine ratio; uPCR = urine protein-to-creatinine ratio; UPE = urine protein excretion

[1] The first 12-Week Relapse Retreatment Visit must occur no more than 7 days from receipt of the 24-hour UPE results from the Central Lab and documentation of the patient's need for relapse retreatment.

[2] Vital signs: to be collected prior to dosing, approximately 5 minutes after the end of the 30-minute study drug infusion, and 30 minutes (± 5 minutes) following the end of the study drug infusion on study drug treatment days.

[3] During the Retreatment Visits, ECGs will be collected: pre-dose and at the end of the 30-minute infusion at 12RT1 and 12RT12.

[4] Patients should be instructed to return the 24-hour urine sample to the clinic following its collection.

[5] Pregnancy test for women of childbearing potential only.

[6] PK and PD samples to be collected: 15 minutes (± 5 minutes) after the end of the study drug infusion at 12RT1and pre-dose at visit 12RT12.

[7] Biomarker samples include urine, serum, and plasma samples, and are always collected pre-dose.

[8] During the COVID-19 pandemic: Instructions on how to handle COVID-19 related treatment interruptions are covered in Section 10.2. All patients who experience a treatment interruption due to COVID-19 restrictions will have blood and urine collected for safety testing and the site must confirm the results meet study entrance criteria, with the exception of uPCR and eGFR (see Section 8) prior to the patient resuming or reinitiating 12-Week Relapse Retreatment. For details on resuming or reinitiating 12-Week Relapse Retreatment, refer to Section 10.2.7.2. If a patient misses more than two study treatment visits, a 24-hour UPE will be completed to guide next steps. The patient will be

contacted by phone every 4 weeks (+/- 7 days) to check on safety, AEs, and Con Meds. These telephone calls may occur more frequently if needed. During the calls, patients will collect their own pulse, systolic and diastolic BP, and body temperature using calibrated equipment and record these values on a patient diary, which they will provide to the study site at the first available opportunity. These calls must be documented in the patient source documents and in the eCRF. Patients who miss more than two consecutive study treatment visits due to COVID-19 restrictions and are administered rescue therapy as a result, may reinitiate study treatment at 12-RT1 after an 8-week wash-out period. Patients who choose to continue without reinitiating study treatment will provide a 24-hr urine sample at the time of study continuation.

[9] During the COVID-19 pandemic: Patients who meet eligibility criteria for 12-Week Relapse Retreatment will be allowed to commence study treatment at 12RT1 at the investigator's discretion, based on guidance from local authorities, the IRB/IEC and site/institution.

20.2.6. Schedule of Events – Open-Label Treatment

Study Visit	12-Week Open-Label Treatment[7, 8]											
Weekly Visit	**OLT1 (±7 days)**	**OLT2 (±3 days)**	**OLT3 (±3 days)**	**OLT4 (±3 days)**	**OLT5 (±3 days)**	**OLT6 (±3 days)**	**OLT7 (±3 days)**	**OLT8 (±3 days)**	**OLT9 (±3 days)**	**OLT 10 (±3 days)**	**OLT 11 (±3 days)**	**OLT 12[9] (±3 days)**
Perform complete physical examination												X
Vital signs[1]	X	X	X	X	X	X	X	X	X	X	X	X
ECG[2]	X											X
Dispense 24-hour urine sample supplies[3]												X
Collect 24-hour urine sample(s) for UPE, uPCR and uACR												X
uPCR and uACR from spot urine				X				X				X
Urinalysis	X			X				X				X
Comprehensive metabolic panel												X
Complete blood count with differential												X
Urine pregnancy test[4]	X			X				X				X
Study drug administration	X	X	X	X	X	X	X	X	X	X	X	X
Assess response												X
PK and PD sampling[5]	X											X
Biomarker, ADA, and NAb sampling[6]	X											X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X	X	X
Confirm and document stability of RAS blockade	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; NAb = neutralizing antibody; PD = pharmacodynamics; PK = pharmacokinetics; RAS = renin angiotensin system; uACR = urine albumin/creatinine ratio; uPCR = urine protein-to-creatinine ratio

[1] Vital signs: to be collected prior to dosing, approximately 5 minutes after the end of the 30-minute study drug infusion, and 30 minutes (± 5 minutes) following the end of the study drug infusion on study drug treatment days.

[2] During the Retreatment Visits, ECGs will be collected: pre-dose and at the end of the 30-minute infusion at OLT1 and OLT12.

[3] Patients should be instructed to return the 24-hour urine sample to the clinic following its collection.

[4] Pregnancy test for women of childbearing potential only.

[5] PK and PD samples to be collected: 15 minutes (± 5 minutes) after the end of the study drug infusion at OLT1and pre-dose at visit OLT12.

[6] Biomarker samples include urine, serum, and plasma samples, and are always collected pre-dose.

[7] During the COVID-19 pandemic: All patients who experience an OL treatment interruption due to COVID-19 restrictions will have blood and urine collected for safety testing and the site must confirm the results meet study entrance criteria, with the exception of uPCR and eGFR (see Section 8) prior to the patient resuming or reinitiating Open-Label (OL) Treatment. For details on resuming or reinitiating OL Treatment, refer to Section 10.2.8. If a patient misses more than two OL treatment visits, a 24-hour UPE will be

completed to guide next steps. The patient will be contacted by phone every 4 weeks (+/- 7 days) to check on safety, AEs, and Con Meds. These telephone calls may occur more frequently if needed. During the calls, patients will collect their own pulse, systolic and diastolic BP, and body temperature using calibrated equipment and record these values on a patient diary, which they will provide to the study site at the first available opportunity. These calls must be documented in the patient source documents and in the eCRF. Patients who miss more than two consecutive OL Treatment visits due to COVID-19 restrictions and are administered rescue therapy as a result, may reinitiate study treatment at OLT1 after an 8-week wash-out period. Patients who miss more than two consecutive OL treatment visits due to COVID-19 restrictions may reinitiate OL treatment per the instructions provided in Section 10.2.8, after the site/institution allows study visits. Patients who choose to continue without reinitiating OL treatment will provide a 24-hr urine sample at the time of study continuation.

[8] During the COVID-19 pandemic: Patients who meet eligibility criteria for OL Treatment will be allowed to commence study treatment at OLT1 at the investigator's discretion, based on guidance from local authorities, the IRB/IEC and site/institution.

[9] Patients who have a 24-hour UPE > 1 g at Open-Label Treatment Visit 12 (OLT12) can receive 6 additional weeks of open-label extended treatment with narsoplimab (open-label extended treatment). Treatment with open-label narsoplimab will be administered IV once weekly for 6 weeks. Open-Label Extended Treatment Visit 1 should occur no later than 14 days from the date of OLT12.

20.2.7. Schedule of Events – Open-Label Extended Treatment

Study Visit	Open-Label Extended Treatment[8, 9]					
Weekly Visit	**OLExT1[1]**	**OLExT2 (±3 days)**	**OLExT3 (±3 days)**	**OLExT4 (±3 days)**	**OLExT5 (±3 days)**	**OLExT6 (±3 days)**
Vital signs[2]	X	X	X	X	X	X
ECG[3]	X					
Dispense 24-hour urine sample supplies					X	
Collect 24-hour urine sample(s) for UPE, uPCR and uACR[4]						X
uPCR and uACR from spot urine				X		
Urinalysis	X			X		
Comprehensive metabolic panel						
Complete blood count with differential						
Urine pregnancy test[5]	X			X		
Study drug administration	X	X	X	X	X	X
PK and PD sampling[6]	X					
Biomarker[7], ADA, and NAb sampling	X					
Assess response						X
Adverse events	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X
Confirm and document stability of RAS blockade	X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; NAb = neutralizing antibody; RE = Response Evaluation Visit; TC = telephone call; uACR = urine albumin-to-creatinine ratio; uPCR = urine protein-to-creatinine ratio

[1] OLExT1 should occur no later than 14 days from the date of OLT12.

[2] Vital signs: to be collected prior to dosing, approximately 5 minutes after the end of the 30-minute study drug infusion, and 30 minutes (± 5 minutes) following the end of the study drug infusion on study drug treatment days

[3] During Open Label Extended Treatment, ECGs will be collected: pre-dose and at the end of the 30-minute infusion at OLExT1

[4] Patients should be instructed to return the 24-hour urine sample to the clinic following its collection, which should occur within 48 hours following the visit

[5] Pregnancy test for women of childbearing potential only

[6] PK and PD samples to be collected: 15 minutes (± 5 minutes) after the end of the study drug infusion at OLExT1

[7] Biomarker samples include urine, serum, and plasma samples, and are always collected pre-dose

[8] During the COVID-19 pandemic: For detailed guidance regarding how to handle missed Open Label Extended Treatment Visits during the COVID-19 pandemic, refer to Section 10.2.8, Open-Label Option for High-Risk Patients.

[9] During the COVID-19 pandemic: Patients who meet eligibility criteria for Open Label Extended Treatment will be allowed to commence study treatment at OLExT1 at the investigator's discretion, based on guidance from local authorities, the IRB/IEC and site/institution.

20.3. Patient Retreatment Quick Reference

Assessment Timepoint	Criteria	Treatment
Week 12	24-hour UPE > 1 g	6-Week Extended Treatment in a blinded fashion
Week 24, 30, or 36	Relapser	6-Week Relapse Retreatment in a blinded fashion
Week 48 or 72	Relapser	12-Week Relapse Retreatment in a blinded fashion
Week 72	Patients with 24-hour UPE > 2 g at baseline who: • Have less than 30% reduction in UPE at the OL assessment visit when compared to baseline UPE, and • Proteinuria is ≥ 3.0 g/day at 72 weeks from randomization, as confirmed by two measurements at least 2 weeks apart, and • Patient has worsening renal function, defined as a decline in eGFR of > 5 mL/min/m^2 from baseline	12-Week Open-Label Treatment Note: Patients who are eligible for and receive 12-Week Open-Label Treatment may be eligible for an additional 6 weeks of Open-Label Extended Treatment if their 24-hour UPE at OLT12 is > 1 g
Week 96/EOS	Final response assessment	No study treatment required

Abbreviations: eGFR = estimated glomerular filtration rate; UPE = urine protein excretion

Relapsers are patients who show a response to treatment of at least 30% reduction from baseline proteinuria at any post-treatment assessment timepoint but subsequently demonstrate an increase in 24-hour UPE by ≥ 30% from the value of their lowest measured post-treatment UPE and have a 24-hour UPE > 1 g. Retreatment for relapse can occur once during the Response Evaluation Period (either Week 24, Week 30, or Week 36) and once during the Follow-Up Period.

20.4. COVID-19 Considerations

20.4.1. 20.4.1 COVID-19 General Considerations and Guidance

When considering how to handle ongoing participation of patients in this clinical trial during the COVID-19 pandemic, patient safety is the highest priority. Study visit activities should be conducted in an environment that protects the patient from potential COVID-19 exposure. All study activities must be conducted in compliance with the advice and restrictions established by each institution, the IRB/IEC, and the respective local authorities.

Restrictions imposed during this time may result in study procedures, study visits, and/or study treatment being unavoidably canceled, skipped, or delayed. Some study visits may be conducted remotely at the patient's home (if service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service) or virtually via telephone or video conference (if allowed by local regulations). Each patient currently in study treatment should be evaluated for risk vs. benefit of continuing treatment within the framework of institutional guidelines and local regulations. If permitted by local authorities, the IRB/IEC, and the site/institution, and if the patient agrees, a patient in study treatment may complete the full treatment course.

Protocol deviations related to such delays or cancelations will be clearly identified in source documents and reported to site CRA for entry into CTMS as related to COVID-19.

Any AEs that are related to the COVID-19 pandemic should be clearly noted as such in the patient source documents and the AE eCRF.

20.4.2. Treatment Guidance for Missed Visits Due to COVID-19

20.4.2.1. Patients Who Miss One or Two Consecutive Study Treatment Visits Due To COVID-19:

Patients who miss 2 or fewer consecutive study treatment visits due to COVID-19 restrictions may continue their treatment period after the site/institution allows study visits to re-commence. Prior to resuming study treatment, patients will have blood and urine collected for safety testing and the site must confirm the results meet study entrance criteria, with the exception of uPCR and eGFR (see Section 8).

Patients whose safety labs do not meet study entrance criteria will be individually assessed by the Medical Monitor and a determination made if further testing or evaluation may be necessary to allow the patient to continue in the study. To minimize patient burden and/or the risk to patient safety, if desirable, these laboratory tests may be performed by a local commercial laboratory. Safety testing will consist of the following procedures:

- Collect urine sample for UA, uACR/uPCR
- Collect blood samples for comprehensive metabolic panel, CBC+diff, serum pregnancy test, PK, PD, ADA, and NAb

20.4.2.2. Patients Who Miss Three or More Study Treatment Visits Due To COVID-19:

Patients who miss more than 2 consecutive study treatment visits due to COVID-19 restrictions will be contacted by the site via telephone to check for adverse events and changes in medications and to confirm patient safety. These telephone calls will occur every 4 weeks (+/- 7 days) or more frequently if needed. During the calls, patients will collect their own pulse, systolic and diastolic BP, and body temperature using calibrated equipment provided to them. Patients will record pulse, systolic and diastolic BP, and temperature on a patient diary and provide this diary to the study site at the first available opportunity. These calls must be documented in the patient source documents and in the eCRF.

After the site/institution allows study visits to re-commence, these patients who missed three or more consecutive treatment visits may reinitiate study treatment. Prior to reinitiating treatment, patients will collect a 24-hour urine specimen. The 24-hour UPE results will be used to determine the next steps for the patient, as per the instructions below:

- If the 24-hour UPE result is > 1 g/day, the patient will be given the option to reinitiate treatment in the same treatment arm to which they were originally assigned. Before treatment is repeated, blood and urine will be collected for safety testing
- If the 24-hour UPE result is ≤ 1 g/day, the patient will not reinitiate treatment, but will continue in the protocol defined timepoints for further treatment assessments

Prior to reinitiated treatment, blood and urine will be collected for safety testing. Results from the safety labs must be received and the site must confirm the results meet study entrance criteria, with exception of uPCR and eGFR (see Section 8) prior to resuming study treatment. Patients whose safety labs do not meet study entrance criteria will be individually assessed by the Medical Monitor and a determination made if further testing or evaluation may be necessary to allow the patient to continue in the study. To minimize patient burden and/or the risk to patient safety, if desirable, these laboratory tests may be performed by a local commercial laboratory. Safety testing will consist of the following procedures:

- Collect urine sample for UA, uACR/uPCR
- Collect blood samples for comprehensive metabolic panel, CBC+diff, serum pregnancy test, PK, PD, ADA, and NAb

The original study baseline UPE value will continue to be used for further evaluations and to determine eligibility for retreatment.

If patient reinitiates at the beginning of Initial Treatment Visit 1 (T1), their visit schedule should be re-calculated from the re-initiated T1 date.

Patients may choose to not resume or reinitiate a treatment period after a COVID-19 interruption. If they wish to not resume/reinitiate treatment, they may remain in the study to attend required study visits through Week 96/EOS, and will be evaluated for relapse at the protocol defined timepoints and may receive relapse retreatment if relapse criteria are met.

20.4.3. Study Schedule Contingencies and Guidance if Visits are Impacted by COVID-19

The following contingencies for the study schedule may be followed during COVID-19 provided that the patient has granted consent for any additional vendors/service providers/laboratories/couriers to receive their information (where applicable), the contingencies are allowable by local regulations, and alternative services are available in the region.

Screening Period (within 28 days prior to the Run-In Period)

During the COVID-19 pandemic, if recommended by the investigator's institution, IRB/IEC and the local authorities, screening of new patients should be halted. Investigators may request re-consideration of patients who fail the Screening Period due to COVID-19 restrictions, based on case-by-case discussion with the Medical Monitor. Patients for whom the Screening Period is interrupted due to COVID-19 restrictions may re-screen when the study site has re-opened for study visits.

Run-In Period

During the Run-In Period, patients should be assessed case by case via a discussion with the Medical Monitor. Run-In Visit 1 (RI1), and Run-In Visit 3 (RI3) may be conducted virtually (e.g. via telephone or video conference) or at the patient's home (if service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service). All visit procedures may be conducted virtually, except for collection of respiratory rate and performance of the symptom-directed physical exam, which will be waived in these circumstances. Run-In Visit 2 (RI2) may be conducted virtually, except when this visit is the final Run-In Visit. The final Run-In Visit (RI2 or RI4) should be conducted at the study site or, if permitted by site/institution, may be conducted at the patient's home (if service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service).

The two 24-hour urine collection specimens may be delivered to the study site or directly to the central laboratory by the specialty courier service selected by the sponsor, provided the patient has granted consent.

Upon case-by-case discussion with the Medical Monitor, investigators may request an extension of the Run-In Period for patients who, due to COVID-19 restrictions, are unable to attend in-person Run-In Visits. During the extended Run-In Period, telephone calls to the patient should occur every 4 weeks (+/- 7 days) to check for adverse events, changes in medications and confirm patient safety. During the telephone calls, patients will collect their own pulse, systolic and diastolic BP, and body temperature using calibrated equipment provided to them. Patients will record pulse, systolic and diastolic BP, and temperature on a patient diary and provide this diary to the study site at the first available opportunity. Telephone calls may occur more frequently if needed. These calls must be documented in the patient source documents and in the eCRF.

Initial Treatment Period (Weeks 1-12)

Randomization of eligible patients to study treatment at Treatment Visit 1 (T1) will be allowed at the investigator's discretion and should align with guidance from local authorities and site/institution.

Guidelines for how to handle missed visits during COVID-19 should be followed as noted above in Section 20.4.2.

Extended Treatment Following Week 12

During COVID-19 restrictions, patients who meet eligibility criteria for Extended Treatment will be allowed to commence study treatment at EXT1 at the investigator's discretion, based on guidance from local authorities, the IRB/IEC and site/institution.

Patients who were deemed eligible to begin Extended Treatment but who, due to COVID-19 restrictions, experience a delay in starting this treatment of more than 28 days from T12, will provide another 24-hour urine specimen. The 24-hour UPE results will be obtained and used to determine the next steps for the patient, as per the instructions noted in Section 20.4.2

If Extended Treatment is interrupted by COVID-19 and patient misses 3 or more visits, once they reinitiate after collecting all necessary labs and meeting the re-initiation criteria, they will resume the study at Initial Treatment 1. This is the only treatment period where patient would not resume at the beginning of the treatment period that was interrupted by COVID-19.

All other guidelines for how to handle missed visits during COVID-19 should be followed as noted above in Section 20.4.2.

Response Evaluation Period (Weeks 13-36)

If permitted by site/institution, the IRB/IEC and, if the patient agrees, the Response Evaluation Visit/Week 36 (RE/W36) should be conducted at the study site. If this is not possible, the visit may be conducted at the patient's home (if service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service) or virtually via a telephone or video conference.

If RE/W36 is conducted virtually (e.g., by telephone or video conference), the collection, processing, and testing of blood and urine for safety may be completed at a local commercial lab convenient to the patient. Collection of blood pressure, pulse, and temperature may be performed by the patient using calibrated equipment provided to them. The urine pregnancy test may be performed by the patient using the urine pregnancy test and instructions provided by the site. The patient should verbally provide the pregnancy test result to the study site during the virtual visit. If there is any doubt regarding the test result, the site should attempt to visually confirm the result over a webcam or via a video conference. The patient must provide the completed diary showing the pregnancy test result to the site at the first available opportunity. The physical exam, ECG and collection of respiratory rate will not be performed. All other study procedures may be performed virtually (e.g. by telephone, video conference, etc.). The 24-hour urine collection specimen may be delivered to the study site or central lab by the specialty courier service selected by the sponsor, provided the patient has granted consent.

6-Week Relapse Retreatment (Response Evaluation Period)

During COVID-19 restrictions, patients who meet eligibility criteria for 6-Week Relapse Retreatment during the Response Evaluation Period will be allowed to commence study

treatment at 6RT1 at the investigator's discretion, based on guidance from local authorities, the IRB/IEC and site/institution.

Guidelines for how to handle missed visits during COVID-19 should be followed as noted above in Section 20.4.2.

Follow-Up Period (Weeks 37-96)

If it is not possible to conduct Follow-Up Visits 1 (Week 48) and 2 (Week 72) at the study site due to COVID-19 restrictions, these visits may be conducted virtually (e.g. via telephone or video conference) or at the patient's home (if service is available in the region, if approval has been granted by the study site/institution as well as the relevant Ethics Committee or IRB, and if patient provides consent for the service).

For Follow-Up Visits conducted virtually, the collection, processing, and testing of blood and urine for safety may be completed at a local commercial lab convenient to the patient. Collection of blood pressure, pulse and temperature may be performed by the patient using calibrated equipment provided to them. The urine pregnancy test may be performed by the patient using the urine pregnancy test and instructions provided by the site. The patient should verbally provide the pregnancy test result to the study site during the virtual visit. If there is any doubt regarding the test result, the site should attempt to visually confirm the result over a webcam or via a video conference. The patient must provide the completed diary showing the pregnancy test result to the site at the first available opportunity. The physical exam, ECG and the collection of respiratory rate will not be completed. All other study procedures may be performed virtually. The 24-hour urine specimen may be delivered to the study site or central lab by the specialty courier service selected by the sponsor, provided the patient has granted consent for this service.

During the COVID-19 pandemic, FU3 (Week 96)/EOS should be conducted at the study site in order to ensure completion of all required end of study assessments. If it is not possible to conduct this visit within the protocol-specified window due to COVID-19 restrictions, the study site should notify the Medical Monitor of the deviation to the study visit schedule. This must be clearly documented as a deviation due to COVID-19 restrictions in the patient's source documents and in the eCRF.

12-Week Relapse Retreatment (Follow-Up Period)

During COVID-19 restrictions, patients who meet eligibility criteria for 12-Week Relapse Retreatment during the Follow-Up Period will be allowed to commence study treatment at 12RT1 at the investigator's discretion, based on guidance from local authorities, the IRB/IEC and site/institution.

Guidelines for how to handle missed visits during COVID-19 should be followed as noted above in Section 20.4.2.

Open-Label Option for High-Risk Patients

During COVID-19 restrictions, patients who meet eligibility criteria for treatment with open-label narsoplimab at Week 72 will be allowed to commence treatment at Open-Label Treatment Visit 1 (OLT1) at the investigator's discretion, based on guidance from local authorities, the IRB/IEC and site/institution. Eligible patients who choose not to resume or reinitiate study treatment during the Initial Treatment or Response Evaluation Periods and who wish to continue

in the study will be allowed to commence OL treatment at Week 72 if they meet all OL treatment criteria.

Guidelines for how to handle missed visits during COVID-19 should be followed as noted above in Section 20.4.2.

20.4.4. Rescue Therapy

Patients who miss three or more consecutive Initial Treatment, 6- or 12-Week Relapse Retreatment, or OL treatment visits due to COVID-19 restrictions and are administered rescue therapy as a result, may, after an 8-week wash-out period, reinitiate study treatment at the first visit of the treatment period the patient was in at the time of the interruption. Patients who are in the Extended Treatment Period at the time of the interruption may reinitiate study treatment at T1 after an 8-week wash-out period.

20.4.5. Study Procedure Contingencies and Guidance if Visits are Impacted by COVID-19

The following contingencies for study procedures may be followed during COVID-19 provided that the patient has granted consent for any additional vendors/service providers/laboratories/couriers to receive their information (where applicable), the contingencies are allowable by local regulations, and alternative services are available in the region.

Informed Consent

During the COVID-19 pandemic, it may not be possible for sites to obtain in-person consent. FDA and EMA guidance provide examples of alternative methods of obtaining patient consent. These include 1) using a validated and secure electronic system to obtain consent that is in compliance with national legislation or 2) conducting the consent discussion with the patient along with an impartial witness over the telephone or during a video teleconference. During this conversation, the patient signs the informed consent form after all questions are addressed and faxes or sends back the signed form via secure email. When considering alternative methods of obtaining consent during the COVID-19 pandemic, investigators should at all times adhere to the guidance issued by their institution/IRB/IEC on appropriate re-consenting procedures.

Physical Examination

During the COVID-19 pandemic, Run-In Visits 1 and 3, Response Evaluation Visit (Week 36), and Follow-Up Visit 1 may be conducted virtually (e.g. telephone or video conference); if virtual visits are conducted, physical exams (either complete physical examinations or symptom-directed physical examinations) will not be performed at those visits. Run-In Visit 2 may be performed virtually as long as it is not the final Run-In Visit; in this case, the symptom-directed physical exam will not be performed.

Blood Pressure Optimization

During the COVID-19 pandemic, blood pressure optimization may be performed during a virtual study visit (e.g. over the telephone or via video conference).

Vital Signs

During the COVID-19 pandemic, it may be necessary for the patient to collect his or her own pulse, systolic and diastolic BP, and body temperature using calibrated equipment provided to them for study visits conducted virtually (over the telephone or via video conference). Patients will obtain their own vital signs during telephone calls that occur during an extension of the Run-In Period or during study treatment interruptions of more than two infusions, due to COVID-19 restrictions. Patients will be provided with instructions and will record pulse, systolic and diastolic BP and body temperature on a patient diary and provide this diary to the study site. In the case of a thermometer shortage due to the COVID-19 pandemic, sites may allow a patient to collect body temperature with the patient's own thermometer.

Electrocardiogram

ECGs will not be collected during virtual study visits that are conducted as a result of COVID-19 restrictions.

Laboratory Assessments

During the COVID-19 pandemic, it may be allowable for CMP, CBC+diff, HgbA1c, UA, uACR, and uPCR to be performed by a local commercial laboratory in cases where the patient is unable to travel to the study site or the study site is unable to receive or process the samples for delivery to the central laboratory.

Due to COVID-19 restrictions, it may be allowable for a patient to perform the urine pregnancy test at home at selected visits, using an approved urine pregnancy test. Patients will be provided with pregnancy test instructions and a diary in which to record the test result. The patient should verbally provide the pregnancy test result to the study site during a telephone call. If there is any doubt regarding the test result, the site should attempt to visually confirm the result over a webcam or via a video conference. The patient must provide the completed diary showing the pregnancy test result to the site at the first available opportunity.

24-hour Urine Collection

During the COVID-19 pandemic, if the study site is not able to receive or process 24-hour urine specimens, it may be allowable for the patient to prepare and process the 24-hour urine specimen for delivery directly to the central laboratory by a specialty courier selected by the sponsor, provided the patient has granted consent for this service. The patient will receive training and instructions from the study site on the proper preparation and processing of 24-hour urine specimens.

Due to COVID-19 restrictions, it may be allowable for a local commercial laboratory to assess 24-hour UPE, uPCR, and uACR if neither the study site nor the local commercial lab is able to process and prepare the samples for delivery to the central lab. In this case only, the local commercial lab may assess 24-hour UPE, uPCR and uACR.

Serum and Urine Biomarkers and Antidrug Antibodies

During the COVID-19 pandemic, it may be allowable for a commercial lab to prepare and ship protocol-specified biomarker samples, and, if applicable, optional research biomarker samples, to the central laboratory.

20.4.6. Patients Who Test Positive for COVID-19:

Patients who test positive for COVID-19 must immediately discontinue infusions of study treatment. Re-initiation of study treatment will be considered on a case-by-case basis by the sponsor. No patients will be allowed to resume study treatment or attend any in-person study visits until at least 1 week after all COVID-19-related symptoms have resolved and the patient is allowed by applicable health authorities and the site/institution to attend in-person study visits.

At the investigator's discretion, infusions may be resumed, provided the full panel of safety labs below is completed and the site has confirmed the results meet study entrance criteria, with the exception of uPCR and eGFR. Patients whose safety labs do not meet study entrance criteria will be individually assessed by the Medical Monitor and a determination made if further testing or evaluation may be necessary to allow the patient to continue in the study. To minimize patient burden and/or the risk to patient safety, if desirable, these laboratory tests may be performed by a local commercial laboratory. A repeat COVID-19 test is recommended before resuming study treatment.

Safety Labs to be Completed Prior to Patient Resuming Treatment After Testing Positive for COVID-19:

- Collect urine sample for UA, uACR/uPCR
- Collect blood samples for comprehensive metabolic panel, CBC+diff, serum pregnancy test, PK, PD, ADA, and NAb
- Collect 24-hour urine specimen for UPE, uPCR, and uACR assessment

20.4.7. Information on COVID-19 Vaccinations/Boosters

For patients who receive COVID-19 vaccinations/boosters during the study, there are no known contraindications or foreseen interactions between vaccines/boosters and narsoplimab. It is recommended that patients wait at least 7 days after a patient receives a COVID-19 vaccine/booster before administering infusion of narsoplimab/placebo. Before receiving infusions, patients should be free from any potential side effects from vaccine/booster. After completing the 7 day waiting period, patients can resume infusions at the treatment visit where they left off. If treatment visits are out of window due to patient receiving COVID-19 vaccine/booster, this should be documented in the patient's source documents/medical records as a protocol deviation related to COVID-19 and reported to the site's CRA to be entered into CTMS. All COVID-19 vaccinations/boosters should be documented in the Concomitant Medications log in EDC with the indication noted as prophylaxis, as per the Case Report Form Completion Guidelines.