Statistical Analysis Plan

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)

Protocol: OMS721-IGA-001

Sponsored by:

Omeros Corporation

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Confidentiality Statement

Approval Signatures

Product:	OMS721 (narsoplimab)
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this statistical analysis plan.

Abbreviation or Specialist Term	Explanation
ADA	anti-drug antibodies
ADI	absolute dose intensity
AE	adverse event
AUC	area-under-the-curve
BCI	Bayesian credible interval
CI	confidence interval
CP	conditional power
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
FAS	Full Analysis Set
FCS	fully conditional specification
GMR	geometric-mean ratio
IDI	intended dose intensity
IDMC	Independent Data Monitoring Committee
IgAN	immunoglobulin A nephropathy
KM	Kaplan-Meier
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
Nab	neutralizing antibodies
PD	Pharmacodynamics
PK	Pharmacokinetics
RBC/HPF	red blood cells per high-powered field
RDI	relative dose intensity
REML	restricted maximum likelihood
SOC	system organ class
SSRE	sample size re-estimation
TEAE	treatment-emergent adverse event
uACR	urine albumin/creatinine ratio
uPCR	urine protein/creatinine ratio
UPE	urine protein excretion
WHO	World Health Organization

1. STUDY DESCRIPTION

1.1. Study Objectives

The primary objective of this study is to evaluate the effect of narsoplimab in immunoglobulin A 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.

The secondary objectives of this study are 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) at up to 96 weeks from baseline in patients with high baseline proteinuria (high-risk proteinuria group; 24-hour urine protein excretion [UPE] ≥ 2 g/day)
- Proteinuria assessed by 24-hour UPE at 36 weeks from baseline in all patients (the all-patients population; 24-hour UPE > 1 g/day)
- 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 in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day) and the all-patients population (baseline 24-hour UPE > 1 g/day)
- Safety and tolerability in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day) and in the all-patients population (baseline 24-hour UPE > 1 g/day)
- Pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of narsoplimab in patients with IgAN

1.2. 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/day at baseline. During the study, all patients will continue optimized renin angiotensin system blockade. The study consists of 5 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.

Eligible patients will be randomized equally to one of the study treatments (placebo or narsoplimab 370 mg). 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 24-hour UPE (> 1 to < 2 g/day and ≥ 2 g/day). All randomized patients are to receive 12 weekly doses of initial study treatment. Following treatment completion, the proteinuria response will be evaluated at several timepoints, and additional study treatment will be given to patients as specified in Section 7.1 of the protocol.

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

- Patient has < 30% decrease in 24-hour UPE from baseline, and
- Proteinuria is ≥ 3.0 g/day at any time on or after 72 weeks from randomization, as confirmed by 2 24-hour UPE measurements at least 2 weeks apart, and
- Patient has worsening renal function, defined as a decline in eGFR of > 5 mL/min/1.73 m^2 from baseline

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.

The primary efficacy endpoint of this study is the change from baseline in log-transformed 24-hour UPE in g/day at 36 weeks from baseline in patients in the high-risk proteinuria group (24-hour UPE ≥ 2 g/day). A sample size of 180 patients is planned for the primary endpoint.

The key secondary efficacy endpoints of this study are:

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

A sample size of 280 patients is planned for the key secondary eGFR endpoint, the rate of change in eGFR at up to 96 weeks from baseline in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day).

A sample size of 450 patients is planned for the key secondary eGFR endpoint, the rate of change in eGFR at up to 96 weeks from baseline in patients in the all-patients population (baseline 24-hour UPE > 1 g/day).

An Independent Data Monitoring Committee (IDMC) has been established to oversee all aspects of the safety of this study. The IDMC will operate in accordance with the IDMC charter and have regular meetings in person or by teleconference.

Special considerations to be taken during the COVID-19 pandemic:

Patients who miss two or fewer study treatment visits during the Initial Treatment period or the Extended Treatment Visits due to COVID-19 restrictions may continue their Initial/Extended Treatment after the site/institution allows study visits to re-commence. The Initial/Extended Treatment will resume at the first visit that the patient missed.

Patients who miss more than two consecutive study treatment visits (Initial or Extended) due to COVID-19 restrictions will be contacted by the site via telephone to check for adverse events and/or changes in medications and to confirm patient safety. Patients will record pulse, systolic and diastolic blood pressure, and temperature on a patient diary and provide this diary to the study site at the first available opportunity. After the site/institution allows study visits to re-commence, these patients may reinitiate the originally assigned study treatment at treatment visit 1 (T1). Prior to reinitiating Initial Treatment, these patients will collect a 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 below:

- If the 24-hour UPE result is > 1 g/day, the patient will be given the option to reinitiate treatment
- 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

If the patient reinitiates Initial Treatment:

- The patient will re-start infusions at T1 in the same treatment arm to which they were originally assigned, irrespective of which study visit they had completed when infusions stopped
- Before T1 is repeated, blood and urine will be collected for safety testing. 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

1.3. 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 2 key secondary endpoints: the rate of change in eGFR for high-risk proteinuria group and the rate of change in eGFR for the all-patients population. The planned sample size for the primary endpoint is 180 patients, 280 patients for the eGFR rate of change endpoint in high-risk proteinuria patients, and 450 patients for the eGFR rate of change in the all-patients population. A blinded sample size re-estimation (SSRE) for the UPE endpoint was conducted in the trial after N = 168 patients had been randomized to provide a blinded estimate of the log scale SD in both the all patient and ≥ 2 g/day populations, results are outlined below. A conditional power (CP) based SSRE for the eGFR key secondary endpoint in the high-risk proteinuria group is planned at the time of the primary endpoint analysis in the same population with N = 180 patients.

1.3.1. Sample Size for Primary UPE Endpoints

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.

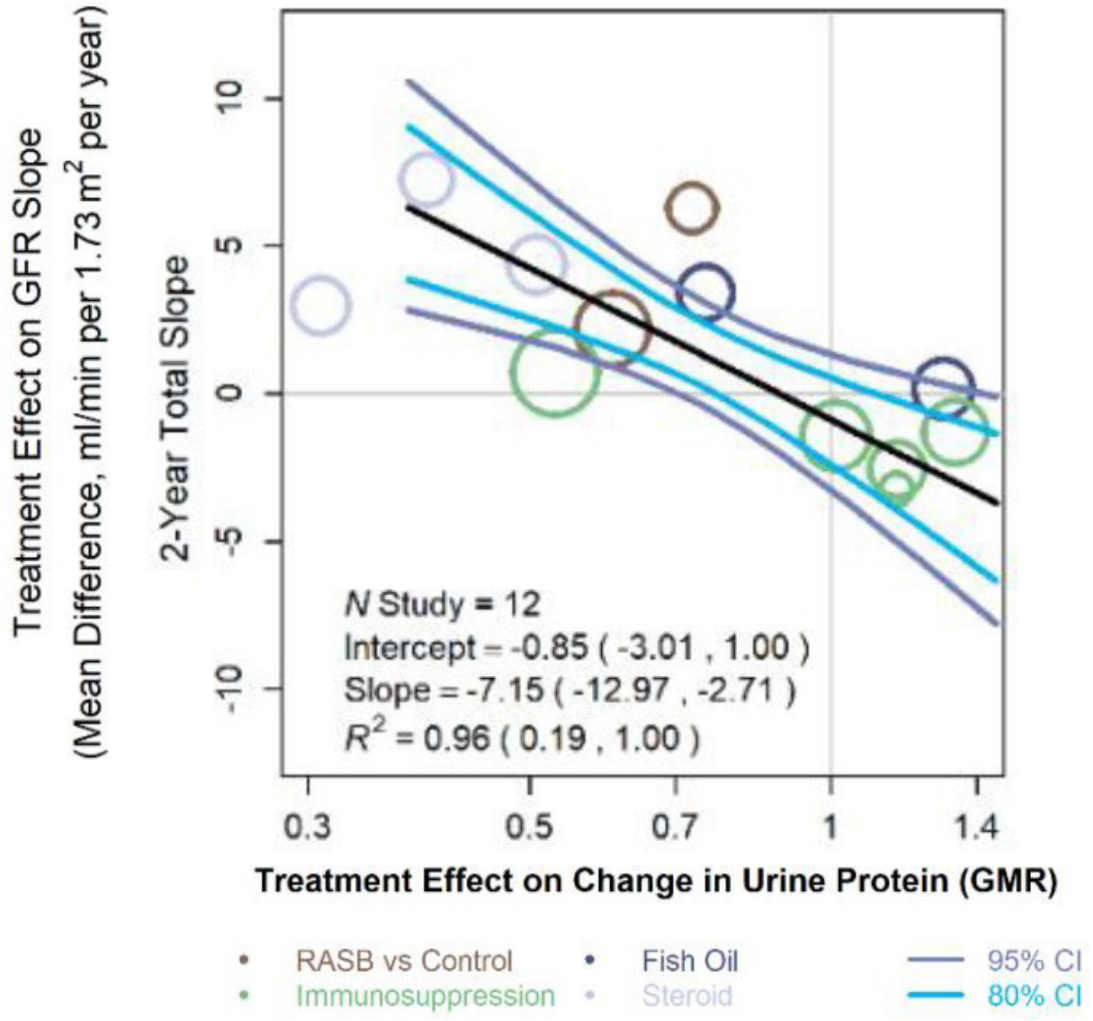
Based on IgAN patient registry data from University Hospital Leicester, UK, the log scale standard deviation for the change in UPE from baseline to 9 months in IgAN patients with ≥ 2 g/day is estimated to be 0.80. Hypothesizing a treatment effect on UPE of 35% (-0.393 on the log scale), a total N = 180 patients with a baseline UPE ≥ 2 g/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. Further, with N = 180 patents and with an SD of 0.80, if the hypothesized treatment effect on the UPE primary endpoint is observed then the associated 1-sided p-value will be very low, approximately $p < 0.001$; and with an SD of 0.63 the corresponding p-value would be lower still.

[Inker 2021] has established a strong relationship between treatment effects on UPE at 9 months versus treatment effects on eGFR total slope over 2 years in 12 randomized controlled trials involving 990 IgAN patients with a mean [mean ± SD] baseline urine protein of 1.8 [1.2 - 2.6] g/day. These data form the basis of multiple completed and ongoing randomized controlled trials in IgAN and also provide the foundation for the accelerated approval of both sparsentan and busedonide in IgAN patients with a baseline proteinuria of ≥ 1.5 g/g (being approximately equal to 2 g/day in a 70 kg patient). These data are therefore equally applicable to the OMS721-IGA-001 study population and trial design.

The reported trial level R^2 for association was 0.96 with intercept value of –0.85, 95% BCI (-3.01, 1.00) and slope value of –7.15, 95% BCI (-12.97, -2.71) (Figure 1). Accepting $R^2 = 0.96$ and estimating SD for the intercept and slope using the BCI under the assumption of Normality, a treatment effect on 24-hour UPE of at least 35% would therefore be expected to correspond to at least a 2.23 mL/min improvement in total eGFR slope over 2 years with an approximate 95% CI (1.76, 2.70) mL/min. The corresponding figures for 40% and 45% treatment effects on UPE at 9 months are 2.80, 95% CI (2.03, 3.57) mL/min and 3.42, 95% CI (2.25, 4.60) mL/min respectively.

Figure 1: Relationship Between Treatment Effects on Two-year eGFR Total Slope and on Proteinuria at 9 Months, Inker et al (2021)



1.3.2. 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.

A random coefficients model was applied using SAS PROC MIXED. The form of the model was:

$$yyyy_{iiiijjjj} = (\beta\beta\beta\beta_0 + bbbb_{0iiii}) + (\beta\beta\beta\beta_2 + bbbb_{2iiii})xxxx_{iiiijjjj} + eeee_{iiiijjjj}$$

where

- $yyyy_{iiiijjjj}$ is the eGFR value for patient $iiii$ at assessment time $jjjj$;

- $xxxx_{iiiiiiii}$ is the time of the $jjjj^{tttth}$ assessment for patient $iiii$;
- $\beta\beta\beta\beta_0$ and $\beta\beta\beta\beta_2$ are the overall fixed effects of intercept and time (or slope);
- $bbbb_{0iiii}$ and $bbbb_{2iiii}$ are the random intercept and slope effect associated with patient $iiii$;
- $eeee_{iiiiiiii}$ are the residual error for patient $iiii$ at time $jjjj$;

The random effects, $bbbb_{0iiii}$ and $bbbb_{2iiii}$ are assumed $iiii.iiii.dddd$ Normally distributed with variance components $\sigma\sigma\sigma\sigma_0^2$ and $\sigma\sigma\sigma\sigma_2^2$ and, independently, the random error $eeee_{iiiiiiii}$ is Normally distributed with variance $\sigma\sigma_{eeee}^2$.

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 $\sigma\sigma\sigma\sigma_2^2$ 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 $\sigma\sigma_{eeee}^2$ was estimated to be $= 6.5077^2$ mL/min/m^2.

The hypothesis for the rate of change in eGFR over 24 months in patients with a baseline UPE ≥ 2 g/day is,

H_0: $\beta\beta\beta\beta_d = \beta\beta\beta\beta_p$,

H_1: $\beta\beta\beta\beta_d \neq \beta\beta\beta\beta_p$,

where $\beta\beta\beta\beta_d$ and $\beta\beta\beta\beta$ represent the annualized slope for eGFR over 24 months for narsoplimab and placebo, respectively. As per [Zhao 2021] and [Carroll 2023] (submitted), the required sample size is given by,

$$NNNN = \frac{4(zzzz_{aaaaa} + zzzz_{ppppp})^2}{(\beta\beta\beta\beta_{DDDD} - \beta\beta\beta\beta_{PPPP})^2} \left(\frac{\sigma\sigma\sigma\sigma_{eeee}^2}{SSSSxxxxxxxx} + \sigma\sigma\sigma\sigma_{bbbb}^2 \right)$$

where α is the 1-sided Type I error, β Type II error, $zzzz_{uuuuu} = \Phi^{-1}(1 - uuuu)$ where $\Phi^{-1}(.)$ represents the inverse standard Normal distribution function, and $SSSSxxxxxxx$ is the sum of the squared differences of eGFR measurement times minus the mean time. With eGFR measured 3 monthly over 24 months, then $SSSSxxxxxxx = 378$.

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. Further, the smallest observed improvement in the UPE ≥ 2 g/day population that will yield p ≤ 0.025 1-sided with N = 280 is 2.3 mL/min/year, in line with [Inker 2021].

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 $\sigma\sigma\sigma\sigma_{bbbb}^2$ 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 $\sigma\sigma_{eeee}^2$ 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. And again, the smallest observed improvement in the overall population that will yield $p \leq 0.025$ 1-sided with N = 450 is 1.6 mL/min/year.

1.3.3. Blinded Sample Size Re-Estimation for UPE and eGFR Endpoints

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]:

$$\hat{\sigma}^2_{\text{adjusted}} = \hat{\sigma}^2_{\text{pooled}} - \frac{2}{n(n-1)}\Delta^2,$$

where $\hat{\sigma}^2_{\text{pooled}}$ 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.

1.3.4. 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 ≥ 2 g/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. See Section 2.9.7 for further details.

2. STATISTICAL METHODS

2.1. Study Endpoints

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

The key secondary endpoints of this study are:

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

Other secondary endpoints are:

- Change from baseline in log-transformed 24-hour UPE in g/day at Week 36 in the all-patients population (baseline 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 in the high-risk proteinuria group (baseline UPE ≥ 2 g/day)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 72 weeks in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 48 weeks in patients in the all-patients population (baseline 24-hour UPE > 1 g/day)
- Time-averaged change from baseline in the log-transformed 24-hour UPE between 36 weeks and 72 weeks in patients in the all-patients population (baseline 24-hour UPE > 1 g/day)
- Safety and tolerability of narsoplimab for the treatment of IgAN as assessed by adverse events (AEs), vital signs, clinical laboratory tests, and electrocardiograms (ECGs)

Tertiary Endpoints

- Change from baseline in log-transformed 24-hour uPCR over time in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day)
- Achievement of ≥ 50% reduction from baseline in 24-hour UPE at 36 weeks in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day)
- Achievement of ≥ 30% reduction from baseline in 24-hour UPE at 36 weeks in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day)
- Change from baseline in log-transformed 24-hour uPCR over time in patients in the all-patients population (baseline 24-hour UPE > 1 g/day)
- Achievement of ≥ 50% reduction from baseline in 24-hour UPE at 36 weeks in patients in the all-patients population (baseline 24-hour UPE > 1 g/day)
- Achievement of ≥ 30% reduction from baseline in 24-hour UPE at 36 weeks in patients in the all-patients population (baseline 24-hour UPE > 1 g/day)
- Time averaged change from baseline in the log-transformed 24-hour uPCR through 36 weeks in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day)
- Achievement of partial proteinuria remission defined as 24-hour UPE < 0.6 g at any time post baseline in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day)
- Achievement of complete proteinuria remission defined as 24-hour UPE < 0.3 g at any time post baseline in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day)
- Time averaged change from baseline in the log-transformed 24-hour uPCR through 36 weeks in patients in the all-patients population (baseline 24-hour UPE > 1 g/day)

- Achievement of partial proteinuria remission defined as 24-hour UPE < 0.6 g at any time post baseline in patients in the all-patients population (baseline 24-hour UPE > 1 g/day)
- Achievement of complete proteinuria remission defined as 24-hour UPE < 0.3 g at any time post baseline in patients in the all-patients population (baseline 24-hour UPE > 1 g/day)
- Use of rescue therapy for IgAN at any time post baseline in patients in the all-patients population (baseline 24-hour UPE > 1 g/day) and in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day)
- Change from baseline in eGFR at 36 weeks in patients in the all-patients population (baseline 24-hour UPE > 1 g/day) and in patients in the high-risk proteinuria group (baseline 24-hour UPE ≥ 2 g/day)
- Pharmacokinetics and pharmacodynamics of narsoplimab
- Occurrence of anti-drug antibodies (ADA) and, if present, neutralizing antibodies (Nab)

Exploratory endpoints 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 urine albumin/creatinine ratio (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/day)
- Achievement of 24-hour UPE of < 0.3 g/day 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 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
- Change from baseline in biomarkers of complement activity and disease pathology in kidneys, serum, plasma, or urine. Biomarkers may include, but not necessarily be limited to:
  - Mannan-binding lectin (MBL) (serum and urine)
  - Complement component 4a (C4a) (urine)
  - C4d (urine)
  - Kidney injury molecule 1 (urine)
  - Neutrophil gelatinase-associated lipocalin (urine)
  - Clusterin (urine)
  - Markers of tubular and glomerular damage
  - Soluble membrane attack complex (urine)
  - Collectin-11 (urine)

2.2. 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.

2.3. Estimand Framework for the Primary and Key Secondary Endpoints

Care is needed when selecting an estimand since the ICH E9 Estimand Addendum unfortunately promotes analyses that do not respect the randomization, such as ‘theoretical’ and ‘while on

treatment' estimands, and, thus, are likely to be heavily biased. The principal estimands chosen for the primary and key secondary efficacy endpoints outlined in Table 1 avoid such bias by respecting the randomization.

Table 1: Estimands For The Primary and Key Secondary Efficacy Endpoints

Endpoint	Treatment Policy Estimands
Primary	
Primary UPE Endpoint, Patients With Baseline UPE ≥ 2 g/day	• Treatment regimens to be evaluated = narsoplimab and placebo • The patient population to be evaluated = FAS of all randomized patients with a baseline UPE ≥ 2 g/day. • The primary UPE endpoint will be analyzed and formally tested for treatment comparison with first 180 patients in the high-risk proteinuria group through 36 weeks in the FAS population. • Patient-level outcome to be analyzed = log change in UPE from baseline to weeks 12, 24, 30 and 36 post randomization, analyzed via mixed model repeated measures analysis (MMRM). • Intercurrent events handling = all patients will be followed for UPE endpoint attainment regardless of early cessation of randomized treatment or the occurrence of intercurrent events such as the use additional systemic therapies. • The population-level estimate of treatment effect = the difference between narsoplimab and placebo in LSmean UPE log change from baseline to 9 months as extracted from the MMRM analysis.

Table 1: Estimands For The Primary and Key Secondary Efficacy Endpoints (Continued)

Endpoint	Treatment Policy Estimands
Key Secondary eGFR Endpoint, Patients With Baseline UPE ≥ 2 g/day	• Treatment regimens to be evaluated = As Primary UPE Endpoint. • The patient population to be evaluated = As Primary UPE Endpoint. • Patient-level outcome to be analyzed = eGFR values collected at 12, 24, 36, 48, 60,72, 84 and 96 weeks post randomization, analyzed via mixed model repeated measures random coefficients analysis. • Intercurrent events handling = Intercurrent events handling = As Primary UPE Endpoint. • The population-level estimate of treatment effect = the difference between narsoplimab and placebo in eGFR total slope over 96 weeks.
Key Secondary eGFR Endpoint, Patients With Baseline UPE > 1 g/day	• Treatment regimens to be evaluated = As Primary UPE Endpoint • The patient population to be evaluated = FAS of all randomized patients with a baseline UPE > 1 g/day. • Patient-level outcome to be analyzed = eGFR values collected at 12, 24, 36, 48, 60,72, 84, and 96 weeks post randomization, analyzed via mixed model repeated measures random coefficients analysis. • Intercurrent events handling = As Primary UPE Endpoint. • The population-level estimate of treatment effect = the difference between narsoplimab and placebo in eGFR total slope over 96 weeks.

2.4. Protocol Deviations/Violations

Protocol deviations and violations will be summarized outside of this statistical analysis plan.

2.5. Study Day

Study day is defined as:

- Event Date – First Dose Date + 1 if the event date is on or after the first dose date
- Event Date – First Dose Date if the event date is before the first dose date

Study Day 1 is defined as the first dose date.

2.6. Study Endpoint Baseline

When required for the statistical analysis of a variable, the baseline value will be the last recorded value prior to randomization. The exceptions are the baseline 24-hour UPE, 24-hour uPCR, and 24-hour uACR, which are defined as the average of the two respective pre-dose values collected during the last two weeks of the Run-In Period before randomization.

2.7. Analysis Visits

Two sets of analysis visits will be used. The first set (Table 2) is derived from the regular scheduled visits regardless of additional treatments (extended treatment, relapse retreatment, re-initiation of treatment open-label treatment, and open-label relapse retreatment; see the schedule of events in the protocol). Longitudinal data analyses will be based on the regular scheduled visits and time will be calculated from Day 1, unless otherwise specified.

The second set is derived for the additional treatment scheduled visits (Table 3).

Table 2: Analysis Visits for Regular Scheduled Visits

Visit	Target Day [Week]	Visit Window (Days)
4-week Run-In		
Screening	-63 [-9]	< -48
Run-In Visit 1	-35 [-5]	-48 to -21
Run-In Visit 2	-7 [-1]	-20 to -1
12-week Run-In		
Screening	-119 [-17]	< -104
Run-In Visit 1	-91 [-13]	-104 to -77
Run-In Visit 2	-63 [-9]	-76 to -49
Run-In Visit 3	-35 [-5]	-48 to -21
Run-In Visit 4	-7 [-1]	-20 to -1
Initial Treatment Visit 1	1 [1]	1 to 4
Initial Treatment Visit 12	78 [12]	5 to 120
Week 24	162 [24]	121 to 183
Week 30	204 [30]	184 to 225
Week 36	246 [36]	226 to 288 [33.1 to 41wk]

Table 2: Analysis Visits for Regular Scheduled Visits (Continued)

Visit	Target Day [Week]	Visit Window (Days)
Week 48	330 [48]	289 to 414 [41 to 60wk]
Week 72	498 [72]	415 to 582
Week 96	666 [96]	583 to 750
Week 120	834 [120]	751 to 918
Week 144	1002 [144]	919 to 1086

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.

Table 3: Analysis Visits and Time-points for Additional Treatment Scheduled Visits

Visit	Target Day* [Week]	Visit Window (Days)*
Extended treatment or retreatment		
Weekly Treatment Visits	(w-1)7 + 1 [w]	(w-1)7 - 2 to (w-1)7 + 4, w > 12

* Target day is relative to the first dose date in the extended treatment period.

2.8. 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

Multiple imputation-based sensitivity analyses relating to primary and key secondary efficacy endpoint missing data are described in Section 2.9.2.2.

2.9. Statistical Assessment of the Study Objectives

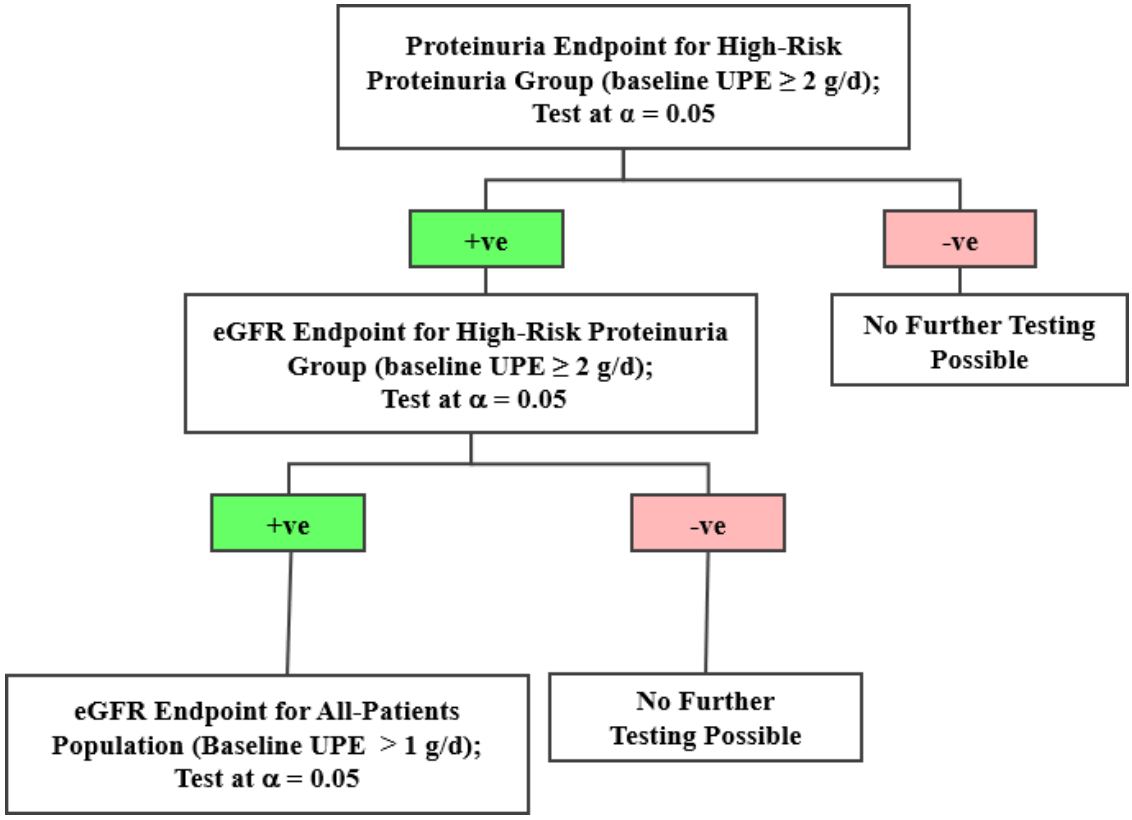
2.9.1. Multiplicity Comparisons and Multiplicity

The primary UPE endpoint will be analyzed and formally tested for treatment comparison with first 180 patients in the high-risk proteinuria group through 36 weeks in the FAS population. The primary efficacy endpoint (change in log-transformed 24-hour UPE from baseline to 36 weeks in the high-risk proteinuria group) and the 2 key secondary endpoints will be tested sequentially to preserve the overall type I error rate of 5% as depicted in Figure 2.

Key Secondary Efficacy Endpoints:

1. the rate of change in eGFR over 2 years in high-risk proteinuria group
2. the rate of change in eGFR over 2 years in the all-patients population

Figure 2: Overall Type I Error Control for the Primary and Key Secondary Endpoints



Abbreviations: UPE = urine protein excretion; +ve = P-value ≤ 0.05 in a 2-sided test; -ve = P-value > 0.05 in a 2-sided test; g = grams; d = day.

If the primary efficacy endpoint is statistically significant at 5% level in a 2-sided test, then the key secondary endpoint (1), the rate of change in eGFR over 2 years in the high-risk proteinuria group (baseline UPE ≥ 2 g/day), 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 (2), the rate of change in eGFR over 2 years in the all-patients population (baseline UPE > 1 g/day), 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.

2.9.2. Efficacy Analyses

Unless otherwise specified, time will be calculated from Day 1.

Table 2 will be used to determine the analysis values and the timepoints to be used in the analysis regardless of missed visits, extended treatment, or re-initiation of treatment.

The UPE primary efficacy endpoint in the high-risk proteinuria group is unaffected by the associated blinded SSRE and, hence, no special considerations apply to the analysis of UPE data pre and post the planned SSRE.

2.9.2.1. Analysis of the Primary UPE Efficacy Endpoint in the High-Risk Proteinuria Group (Baseline UPE ≥ 2 g/day)

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. SAS code will be of the form,

```
PROC MIXED DATA=X METHOD=REML;
  CLASS PATIENT RANDTRT VISIT STRATA;
  MODEL CHG_BL = BASE RANDTRT VISIT RANDTRT*VISIT STRATA
                 /DDFM=KR;
  REPEATED VISIT / PATIENT = PATIENT TYPE = UN;
  LSMEANS RANDTRT*VISIT/SLICE=VISIT PDIFF DIFF ALPHA=0.05 CL;
  ODS OUTPUT DIFFS=DIFF LSMEANS=LSMEANS;
RUN;
```

STRATA: Baseline eGFR level (≥ 30 to ≤ 45 mL/min/1.73 m^2 and > 45 mL/min/1.73 m^2)

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.

2.9.2.2. Primary UPE Efficacy Endpoint Sensitivity Analyses

Sensitivity 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. The approach will be implemented as follows:

- Step 1: Non-monotone missing data will be imputed first based on the MAR assumption and a multivariate joint Gaussian imputation model using Markov chain Monte Carlo (MCMC) method as per the MCMC statement in the SAS® PROC MI procedure. As a result, each imputed dataset will only have missing data at the end of patients' records, (a monotone missing data pattern). The MCMC method in the MI procedure will be used with multiple chains (option CHAIN=MULTIPLE), 100 burn-in iterations, and a non-informative prior. A separate imputation model will be used for each treatment arm. The imputation models will include the randomization stratification factors, baseline log UPE and change in log UPE at each time point. In case of non-convergence or non-estimability issues, a ridge prior and a single model will be considered with treatment arm added as explanatory variable to the model.
- Step 2: The remaining, monotone, missing data will be imputed using sequential regression multiple imputation model estimated based on data from the *placebo arm only*. Each sequential regression model (i.e., for imputation of values at a given time point) will include the stratification factors, baseline log UPE, and all previous values of UPE. Missing values at a given time point in placebo and narsoplimab treatment arms will be imputed from the same imputation model, conditional on patient values observed or imputed at previous time points.
- Step 3: The log change from baseline in UPE to each scheduled post-baseline visit will be calculated, based on observed and imputed data. Each of the imputed complete datasets from Step 2 will be analysed with the same MMRM model used for the primary analysis.
- Step 4: The results of the analysis of each imputed dataset, i.e., treatment effect estimates and their standard errors, will be combined via the SAS® PROC MIANALYZE procedure using Rubin's rules [Rubin 1987] to produce an overall treatment effect estimate and its associated 95% confidence interval and 2-sided p-value.

Example SAS code of the form to perform this first sensitivity analysis is contained in Appendix 1.

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.

The penalty to render a non-significant primary endpoint p-value will be determined via search as follows. Let the log scale treatment effect estimate from the primary UPE endpoint analysis be denoted as $\theta\theta\theta\theta\widehat{}$, then the set of penalty values, $\{\delta\delta\delta\delta\}$, to be evaluated will be $\widehat{}0.00 \cdot \widehat{} \theta\theta\widehat{}\widehat{}$, $0.05 \cdot \widehat{} \theta\theta\widehat{}\widehat{}$, ...,$1.00 \cdot \widehat{} \theta\theta\widehat{}\widehat{}$, $1.05 \cdot \widehat{} \theta\theta\widehat{}\widehat{}$, ..., $2 \cdot \widehat{}\theta\theta\theta\theta\widehat{}\widehat{}\widehat{}$. Hence, the starting penalty is zero and thus reflects the primary endpoint analysis assuming MAR; and the penalty $1.00 \cdot \widehat{} \theta\theta\widehat{}\widehat{}$ reflects a complete loss of the treatment effect in narsoplimab patients with missing data; and the penalty $2 \cdot \widehat{} \theta\theta\widehat{}\widehat{}$ reflects a complete reversal of the treatment effect in narsoplimab patients with missing data. For each penalty in the vector $\{\delta\delta\delta\delta\}$, missing data in both treatment arms will be imputed as

MAR under placebo and the penalty added to those patients with missing data in the narsoplimab arm. The resulting multiply imputed datasets will be analyzed as per the primary endpoint MMRM model as specified in Section 2.9.2.1 and the results combined using Rubin's rules as described above for Jump to Placebo.

The p-value, treatment effect estimate and 95% CI associated with each penalty will be displayed in a forest plot format to allow identification of the 'tipping point' penalty that renders the primary endpoint analysis p-value non significant.

Example SAS code of the form to perform this second sensitivity analysis is contained in Appendix 2.

It should be noted that there is no need for a two dimensional tipping point approach whereby penalties are applied to both placebo and narsoplimab as the approach described above, i.e. applying a penalty to the narsoplimab arm alone and zero penalty to the placebo arm, will yield identical results. This is the case since, in both approaches, missing data are multiply imputed under placebo in both arms. The only difference is that when a penalty $\{\delta\delta\delta\delta\}$ is applied only to narsoplimab patients with missing data and a penalty $\{0\}$ is applied to the placebo patients with missing data, the net penalty is $\{\delta\delta\delta\delta\}$; whereas if a penalty matrix $(\{\delta\delta\delta\delta\}, \{\delta\delta\delta\delta\}^{TTTT})$ is constructed whereby the penalty vector $\{\delta\delta\delta\delta\}$ is applied to narsoplimab patients with,

$\{\delta\delta\delta\delta\} = \{0.00 \cdot \delta\delta\delta\delta, 0.05 \cdot \delta\delta\delta\delta, \ldots, 1.00 \cdot \delta\delta\delta\delta, 1.05 \cdot \delta\delta\delta\delta, \ldots, 2 \cdot \delta\delta\delta\delta\}$

$\{\delta\delta\delta\delta\} = \{\delta\delta\delta\delta_0, \delta\delta\delta\delta_{0.05}, \ldots, \delta\delta\delta\delta_{1.00}, \delta\delta\delta\delta_{1.05}, \ldots, \delta\delta\delta\delta_{2.00}\}$

and, for each element, $\delta\delta\delta\delta_{iiii}$, $jjjj = 0, 0.05, \ldots, 2$, of $\{\delta\delta\delta\delta\}$, the same, transposed penalty vector, $\{\delta\delta\delta\delta\}^{TTTT}$, is applied to placebo patients with missing data, then the net penalty on the estimated treatment effect when applying element $\delta\delta\delta\delta_{iiii}$ to narsoplimab patients and $\delta\delta\delta\delta_{kkkk}$ to placebo patients with missing data will simply be $\delta\delta\delta\delta_{iiii} - \delta\delta\delta\delta_{kkkk}$ which is the same as application of a penalty $\delta\delta\delta\delta_{iiii-kkkk}$ to narsoplimab patients and a penalty of 0 to placebo patients with missing data.

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

2.9.2.3. Analysis of the Key Secondary Efficacy eGFR Endpoints

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 (as per Figure 2).

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:

$$yyyy_{iiiiiii} = (\beta\beta\beta\beta_0 + bbbb_{0iiii}) + \beta\beta\beta\beta_1 \cdot GGGG + (\beta\beta\beta\beta_2 + bbbb_{2iiii})xxxx_{iiiiiii} + \beta\beta\beta\beta_3 \cdot GGGG \cdot xxxx_{iiiiiii} + eeee_{iiiiiii}$$

where

- $yyyy_{iiiiiii}$ is the eGFR value for patient $iiii$ at assessment time $jjjj$;
- $xxxx_{iiiiiii}$ is the time of the $jjjj^{ttttth}$ assessment for patient $iiii$;
- $GGGG = 0, 1$ for placebo and narsoplimab
- $\beta\beta\beta\beta_0$ = intercept fixed placebo effect, $\beta\beta\beta\beta_0 + \beta\beta\beta\beta_1$ = intercept fixed narsoplimab effect and $\beta\beta\beta\beta_1$ = the fixed treatment effect on the intercept;
- $\beta\beta\beta\beta_2$ = slope fixed placebo effect, $\beta\beta\beta\beta_2 + \beta\beta\beta\beta_3$ = slope fixed narsoplimab effect and $\beta\beta\beta\beta_3$ = the fixed treatment effect on slope;
- $bbbb_{0iiii}$ and $bbbb_{2iiii}$ are the random intercept and slope effects associated with patient $iiii$;
- $eeee_{iiiiiii}$ are the residual error for patient $iiii$ at time $jjjj$, with $eeee_{iiiiiii}$;

For analysis of the rate of change in eGFR, time will be evaluated as actual assessment day relative to the randomization day. The random effects, $bbbb_{0jiii}$ and $bbbb_{2iiii}$ are assumed $iiii, iiii. dddd$ Normally distributed with variance components $\sigma\sigma\sigma\sigma^2$ and $\sigma\sigma\sigma\sigma^2$ and, independently, the random error $eeee_{iiiiiii}$ is Normally distributed with variance $\sigma\sigma_{ee}\sigma_e^2$.

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. Denoting time as **T**, the SAS code will be of the form;

```
PROC MIXED DATA=Y COVTEST CL;
  CLASS PATIENT RANDTRT STRAT1 STRAT2;
  MODEL Y = T RANDTRT RANDTRT*T STRAT1 STRAT2 STRAT1*STRAT2/ SOLUTION COVB;
  RANDOM INT T / TYPE=UN PATIENT=PATIENT SOLUTION G GCORR;

  ESTIMATE "INTERCEPT NAR"      INTERCEPT 1 RANDTRT  0  1                    / CL ALPHA=0.05;
  ESTIMATE "INTERCEPT PCB"      INTERCEPT 1 RANDTRT  1  0                    / CL ALPHA=0.05;
  ESTIMATE "INTERCEPT NAR V PCB"             RANDTRT  1 -1 T 0 RANDTRT*T 0 / CL ALPHA=0.05;

  ESTIMATE  "SLOPE  NAR"     T  1  RANDTRT*T  0  1  /  CL  ALPHA=0.05;
  ESTIMATE  "SLOPE  PCB"     T  1  RANDTRT*T  1  0  /  CL  ALPHA=0.05;
  ESTIMATE "SLOPE NAR v PCB"  T  0  RANDTRT*T  1 -1 / CL ALPHA=0.05;

  ODS OUTPUT "ESTIMATES"=EST;
  ODS OUTPUT SOLUTIONF=F;
  TITLE "RANDOM CO-EFFICIENTS ANALYSIS TOTAL SLOPE EGFR";
RUN;
TITLE;
```

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

- Jump to Placebo Multiple Imputation
- Tipping Point Multiple Imputation

- COVID-19

with these analyses executed in the same fashion as described for the primary UPE endpoint.

While prior FDA co-authored publications and supportive simulations demonstrate that the use of fixed weights as per Cui, Hung and Wang (1999) are necessary to avoid alpha inflation associated with the SSRE procedure, an exploratory analysis of eGFR will be performed using an unweighted test statistic for the rate of change in eGFR over 2 years in the high-risk proteinuria group as requested by FDA.

Given the limited eGFR data points during the first 12 weeks of the study, the presence of an early, acute effect on eGFR cannot be meaningfully assessed. Nevertheless, mean change eGFR data will be presented by treatment groups at all sampling timepoints during the 2-year follow-up study period.

2.9.2.3.1. Analysis of the Secondary UPE endpoint in the All-Patients Population at Week 36

The analysis of the secondary UPE endpoint change from baseline in log-transformed 24-hour UPE in g/day at Week 36 in the all-patients population (baseline 24-hour UPE > 1 g/day) will also be analyzed following the same methods listed above in Section 2.9.2.1 for the primary UPE endpoint change from baseline in log-transformed 24-hour UPE in g/day at Week 36 in the high-risk proteinuria group (baseline UPE ≥ 2 g/day).

2.9.2.3.2. Analysis of Other Secondary and Exploratory Efficacy Endpoints

These supportive analyses will be performed in both the high-risk proteinuria groups and the all-patients population.

Proteinuria durability will be evaluated by the time-adjusted area-under-the-curve (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 same 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. Both 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.

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, and randomization strata as fixed effects. Within-patient error will be modelled via an unstructured covariance matrix. The REML method will be used to estimate the model parameters. The difference in least squares (LS) means between the treatment groups and their respective 95% CIs will be estimated for each post-baseline scheduled visit. The LS mean will be estimated with 95% confidence interval (CI)for each treatment group. The ratio of the GMR between the treatment groups will also be estimated with 95% CI.

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 also be performed.

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

2.9.2.4. Other Efficacy Endpoints

All other efficacy endpoints will be analyzed for the FAS population.

Proteinuria durability will be evaluated by the time-adjusted AUC change from baseline in the log-transformed 24-hour UPE between 36 weeks and 48 weeks and between 36 weeks 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 same said time period. All UPE values collected over the said time period, including values collected at unscheduled visits, will be used to calculate the time average. 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. Both 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. Multiple imputations 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 model with treatment and randomization strata as factors using the Rubin's rules with 20 imputations.

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 regular scheduled visits), treatment by time interaction, randomization strata as fixed effects, 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-treated group only. The REML method will be used to estimate the model parameters. The difference in LS means between the treatment groups and their respective 95% Cis 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 log-transformed 24-hour uPCR through 36 weeks will be calculated as the AUC of the change from baseline in log-transformed 24-hour uPCR divided by the time from baseline to the last observation on or before Week 36. All 24-hour uPCR values collected from baseline to Week 36, including values collected at additional treatment visits and unscheduled visits, will be used to calculate the time adjusted AUC. Time

adjusted AUC of change in log-transformed 24-hour uPCR will be summarized descriptively. An analysis of covariance with treatment and randomization strata as factors and baseline uPCR as a covariate 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 Cochran–Mantel–Haenszel test stratified by the randomization stratum will be performed for the FAS population.

The following time-to-event endpoints will be analyzed by the KM method for each treatment group for the FAS population. If calculable, median time with 95% CI will be provided by treatment group. The HR, CI and p-value will be estimated via Cox regression analysis stratified for the randomization strata and with treatment as the sole class factor.

- Duration of treatment response will include patients in the FAS population who achieve ≥ 30% reduction from baseline in 24-hour UPE only. Patients who respond but do not relapse during the study will be censored at their last date of 24-hour UPE
- Duration of complete proteinuria remission will include patients in the FAS population who achieve 24-hour UPE < 0.3 g/day only. Patients who achieve complete proteinuria remission but whose 24-hour UPE does not increase to ≥ 0.3 g/day during study will be censored at the last date of 24-hour UPE
- Duration of partial proteinuria remission will include patients in the FAS population who achieve 24-hour UPE < 1 g/day only. Patients who achieve partial proteinuria remission but whose 24-hour UPE does not increase to > 1 g/day during study will be censored at the last date of 24-hour UPE

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

2.9.2.5. Exploratory Efficacy Analyses

Subgroup analyses for the primary efficacy endpoint and the two key secondary efficacy endpoints will be performed. The statistical method of the primary analysis for each of the endpoints will be used to analyze the following subgroups by including subgroup factor and treatment by subgroup interaction factors in the analysis model:

- Baseline 24-hour UPE level (< 2 g/day and ≥ 2 g/day)
- Baseline eGFR level (≥ 30 to ≤ 45 mL/min/1.73 m^2 and > 45 mL/min/1.73 m^2)
- Duration of IgAN diagnosis (≤ 2 years and > 2 years from randomization)
- Sex (Female and Male)
- Race (White and others)
- Age (< 65 and ≥ 65)

2.9.3. Pharmacokinetic, Pharmacodynamic and Immunogenicity Analysis

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.

2.9.4. Safety Analyses

All safety analyses will be descriptive in nature (Section 3.4).

2.9.5. Timing of Planned 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 blinded SSRE was planned and executed for the primary UPE endpoint. A CP-based SSRE for the key secondary endpoint of eGFR rate of decline in the high-risk proteinuria group is planned at the time of the formal analysis of the primary UPE endpoint in the same population with N = 180 patients. At this SSRE, no formal statistical testing will be performed on eGFR the data.

A formal interim analysis is planned for the primary UPE endpoint. The interim database will include the first 180 patients in the high-risk proteinuria group through 36 weeks in the FAS population. The primary and secondary UPE endpoints will be analyzed and formally tested for treatment comparisons. 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 analyses will be performed. Study sites and patients will remain blinded to the treatment assignment. The study will be unblinded at the study level only so that statistical analyses can be performed. At the time of the formal interim analysis of the primary UPE endpoint in the high-risk proteinuria group, if a treatment effect is proven statistically, the data may be used to support regulatory filings for approval.

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 UPE endpoint is statistically significant at the interim analysis. Other efficacy endpoints will also be descriptively summarized. Safety analyses will be performed.

2.9.6. Blinded Sample Size Re-Estimation for Primary Efficacy Endpoint

A blinded sample size re-estimation for the original primary efficacy endpoint was performed by the independent data monitoring committee (IDMC) when 168 patients (60% of 280) had completed the Week 36 visit. 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]:

$$V_{pooled}^2 = V_{observed}^2 - \frac{2}{4(m-1)}\Delta^2,$$

where V_{pooled}^2 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 IDMC statistician re-calculated the sample size using this adjusted variance.

2.9.7. Conditional Power Based Sample Size Re-Estimation for Rate of Change in eGFR

A conditional power (CP) based SSRE is planned for the annualized eGFR rate of change endpoint in the high-risk proteinuria group (baseline UPE ≥ 2 g/day) at the time of the planned UPE primary endpoint analysis in the same population. SSRE methodology to be employed is not the Mehta & Pocock 'Promising Zone' but rather the CHW fixed weights approach.

With the primary endpoint analysis to take place with N = the first 180 high-risk proteinuria patients, taking into account the minimum follow-up of 9 months and that recruitment of these 180 patients took 45 months, then, assuming non-linear accrual ($\eta\eta\eta\eta = 2$, [Carroll 2009]), recruitment of 280 high-risk proteinuria population would be expected in approximately 56 months. Fisher's Information with N=280 patients in a random coefficients analysis can be determined as follows:

Consider a randomized trial with two treatment groups, drug (D) and placebo (P), with $iiii = 1$ to $nnnn$ patients will be randomized to each treatment group for a total of $NNNN = 2nnnn$ patients. Each patient is scheduled to have a set of $jjjj = 1$ to $vvvv$ longitudinal values (e.g., eGFR assessments), $yyyy_{iiiiiiii}$, measured at times $xxxx_{iiiiiiii}$ over a follow-up period of $FFFF$ months. Denote slope estimate for placebo patient $iiii$ as $\beta\beta\beta\beta_{iiii}$ with variance $VVVV(\beta\beta\beta\beta\beta_{iiii}) = \frac{\sigma\sigma\sigma\sigma_{ee}^{2}}{SSSSxxxxxxxx_{iiii}}$, where $SSSSxxxxxxxx_{iiii}$ is the sum of the squared differences of measurement times minus the mean time. Thus, $SSSSxxxxxxxx_{iiii} = \sum_{iiii=1}^{vvvv}(xxxx_{iiiiiiii} - xxxxx_{iiii})^2$ and $xxxx_{iiii} = \frac{\sum_{iiii=1}^{vvvv} SSSS_{iiiiiii}}{vvvv}$.

Let $\beta_{iiii} \sim NNNN(\beta\beta\beta\beta_{bbbb}, \sigma\sigma\sigma\sigma^2)$, then $\beta\beta\beta\beta_{bbbb} = \frac{\sum_{iiii=1}^{nnnn}\beta_{iiii}}{nnnn}$ with variance $VVVV(\beta\beta\beta\beta_{bbbb}) = 1/\sum_{iiii=1}^{nnnn}\left(\frac{\sigma\sigma\sigma\sigma^2_{ee}}{SSSSxxxxxxxx_{iiii}} + \sigma\sigma\sigma\sigma^2_{bbbb}\right)$.

If all patients have equally spaced $yyyy_{iiiiiiii}$ values, then $FFFF = mmmmvvvv$ and,

$$SSSSxxxxxxxx_{iiii} = \sum_{iiii=1}^{vvvv}(xxxx_{iiiiiiii} - xxxxx_{iiii})^2 = (mmmm - mmmm)^2 + (2mmmm - mmmm)^2 + \cdots + (vvvvmmmm - mmmm)^2 = \frac{mmmm^2vvvv(vvvv^2 - 1)}{12}$$

Thus, $VVVV(\beta\beta\beta\beta_{bbbb})$ can be written as,

$$VVVV(\beta\beta\beta\beta_{bbbb}) = 1/\sum_{iiii=1}^{nnnn}\left(\frac{\sigma\sigma\sigma\sigma^2_{ee}}{SSSSxxxxxxxx_{iiii}} + \sigma\sigma\sigma\sigma^2_{bbbb}\right)^{-1} = \frac{2}{NNNN}\left(\sigma\sigma\sigma\sigma^2_{ee}\right)^{-1} + \sigma\sigma\sigma\sigma^2_{bbbb} = \frac{2}{NNNN}\left(\frac{\sigma\sigma\sigma\sigma^2_{ee}}{\frac{mmmm^2vvvv(vvvv^2 - 1)}{12}}\right) + \sigma\sigma\sigma\sigma^2_{bbbb}$$

Applying the same steps to drug treated patients, Fishers Information, $IIII_{FFFF}$, expected at the end of the trial with $NNNN$ patients followed for $FFFF$ months is given by

$$IIII_{FFFF} = \left[VVVV\left(\hat{\beta}_{DD} - \hat{\beta}_{PP}\right) \right]^{-1} = \left[2VVV\left(\hat{\beta}_{PP}\right) \right]^{-1} = \left[\frac{4}{SSSSxxxxx} + \sigma\sigma\sigma\sigma^{2} \right]^{-1} = \left[\frac{4}{\frac{mmmm^{2}vvvv(vvvv^{2}-1)}{12}} + \sigma\sigma\sigma\sigma^{2} \right]^{-1}$$

where $VVVV\left(\hat{\beta}_{DD}\right)$ and $VVVV\left(\hat{\beta}_{PP}\right)$ are the variances of the estimated slope values for the drug and placebo groups, respectively.

With $FFFF = 24$ and $mmmm = 3$ then $vvvv = 8$; further, with $\sigma\sigma\sigma\sigma_{bbbb}^{2} = \sigma\sigma\sigma\sigma_{2}^{2} = 6.4932^{2}$ mL/min/m^2 annually (= 0.7356^2 mL/min/m^2 monthly) and $\sigma\sigma\sigma\sigma_{eeee}^{2} = 6.5077^{2}$ mL/min/m^2 as per Section 1.3.2, then $IIII_{FFFF} = 107.175$.

Fisher's Information for the first N=180 patients, randomized over 45 months and followed for minimum follow-up of 9 months, is easily estimated in SAS to be $IIII_{IIII} = 52.591$ such that the information fraction for eGFR slope would be 52.591/107.175 = 49.1%; the associated SAS code for this computation is provided in Appendix 3.

At the time of the primary endpoint analysis with N = the first 180 high-risk proteinuria patients, the available eGFR data will be analyzed via random coefficients modelling (Section 2.9.2.3) to provide an estimate of the difference in annualized eGFR rate of decline between narsoplimab and placebo, $\hat{\beta}_{3iiii}$ along with its standard error, $SSSSSSSS\left(\hat{\beta}_{3iiii}\right)$, as well as between slope and residual error variance component estimates, $\sigma\sigma\sigma\sigma_{bbbbiiii}^{2}$ and $\sigma\sigma\sigma\sigma_{eeeeiiii}^{2}$. No p-value for the difference in annualized eGFR rate of decline will be generated. Denote the z-value for annualized eGFR rate of decline at the time of the primary endpoint analysis as,

$$zzzz_{iiii} = \frac{\hat{\beta}_{3iiii}}{SSSSSSSS\left(\hat{\beta}_{3iiii}\right)}$$

The CP of confirming a treatment effect on annualized eGFR rate of decline with the planned N = 280 randomized high-risk proteinuria patients followed for 24 months is calculated according to Mehta and Pocock (2011) as,

$$CCCCCCCC(zzzz_{iiii}) = 1 - \Phi\left[\frac{zzzz_{aaaa}\sqrt{IIII_{FFFF}} - zzzz_{iiii}\sqrt{IIII_{IIII}}}{\sqrt{IIII_{FFFF} - IIII_{IIII}}} - \frac{zzzz_{iiii}\sqrt{IIII_{FFFF} - IIII_{IIII}}}{\sqrt{IIII_{IIII}}} \right]$$

If the computed CP is < 85%, the sample size for the annualized eGFR rate of decline endpoint in the high-risk UPE group may be increased from the planned 280 patients up to a maximum of 360 patients to increase CP, with the recruitment period extended, if necessary. Note: should the sample size be increased in the high-risk proteinuria group up to a maximum of 360 patients, the all-patients population (i.e., all patients with baseline UPE > 1 g/day) will be approximately, N = 600 (assuming a ratio of high-risk proteinuria to non-high-risk proteinuria patient groups of 60:40).

To deliver a desired CP of 1-β, [Mehta 2011] have shown that the information post interim, ($IIII_{FFFF} - IIII_{IIII}$), should be increased to ($IIII^{*} - IIII_{IIII}$) where,

$$IIII^{*}_{FFFF} - IIII_{IIII} = \frac{IIII_{II}\ _{II}}{\{zzzz_{iiii}\}^{2}} \left(zzzz_{mmmm} \sqrt{IIII_{FF\,FF}} - zzzz_{iiii} \sqrt{\frac{IIII_{II}}{Z\,ZZ}} \right)^{2} \Big/ \left(IIII_{FFFF} - IIII_{II} \right)$$

The revised total sample size for the 2-year annualized eGFR rate of change endpoint in the high-risk proteinuria group will be $NNNN^{*} = nnnn_{iiii} + nnnn^{*}$, with $NNNN^{*} \epsilon\epsilon\epsilon\epsilon$ [280, 360] so that $nnnn^{*} \epsilon\epsilon\epsilon\epsilon$ [280 − $nnnn_{iiii}$, 360 − $nnnn_{iiii}$] (i.e., the total sample size, $NNNN^{*}$, for the eGFR rate of change endpoint in the high-risk proteinuria group will not be permitted to be less than 280 patients).

The required $NNNN^{*}$ to deliver the increase information content, $II_{FF}II_{FF}^{*}$, is computed via the relation

$$\{II_{FF}II_{FF}^{*}\}^{-1} = \frac{4}{NNNN^{*}} \left(\frac{\sigma\sigma\sigma\sigma}{SSSS_{sssssssss}} + \sigma\sigma\sigma\sigma\sigma_{iiii}^{2} \right)$$

where $SSSS_{sssssssss} = 378$ as per Section 1.3.2.

In order to avoid the potential for alpha inflation, data from pre and post the eGFR endpoint SSRE will be combined using the fixed weights approach described by [Cui 1999]. This approach guarantees alpha control regardless of mechanism for any increase in sample size. The approach fundamentally depends upon the long-established, basic properties of group sequential trial designs, being as follows:

- Assume two treatments, experimental (E) and control (C).
- The hypothesis to be tested for some parameter of interest, θ, is $H_0 : \theta_{TTTTTTTTTTTTTTT} = 0$ vs $H_1 : \theta_{TTTTTTTTTTTTTTT} \neq 0$.
- For the purposes of sizing, assume $\theta_{TTTTTTTTTTTTTTT} = \theta$ (>0) under the alternative.
- Let $\theta\theta\hat{\theta}$ be a sufficient statistic for θ with distribution $ffff(xxxx|\theta\theta\theta\theta) \sim NNNN(\theta\theta\theta\theta, VVVV^{-1})$.
- Hence zzzz = $\theta\theta\hat{\theta}\sqrt{VVVV}$ with distribution $ffff(zzzz|\theta\theta\theta\theta) \sim NNNN(\theta\theta\theta\theta\sqrt{VVVV}, 1)$.
- Trial size is governed by Type I and Type II errors, α and β, and the need to deliver the required Fishers Information content, $VVVV = (zzzz_{\alpha\alpha\alpha\alpha} + zzzz_{\beta\beta\beta\beta})^{2} / \theta\theta\theta\theta^{2}$.
- $KKKK$ analyses planned with the $iiii^{ttttth}$ having information content $VVVV_{iiii} = \frac{VVVV_{iiii}}{VVVV_{KKKK}}$
- Then,
  - $\theta\theta\theta\theta_{1}, \ldots, \theta\theta\theta\theta_{KKKK} \sim MMMMVVVVNNNN$ with $\theta\theta\theta\theta_{iii} \sim NNNN(\theta\theta\theta\theta, VVVV_{iii}^{-1})$ and $cccccccvvvv(\theta\theta_{pppp}, \theta\theta\theta\theta_{mmmm}) = VVVV_{mmmm}^{-1}$
  - $zzzz_{iiii} = \theta\theta\theta\theta_{iiii}\sqrt{VVVV_{iiii}}$ so that $zzzz_{1}, \ldots, zzzz_{KKKK} \sim MMMMVVVVNNNN$ with $zzzz_{iiii} \sim NNNN(\theta\theta\theta\theta\sqrt{VVVV_{iiii}}, 1)$ and $cccccccvvvv(zzzz_{pppp}, zzzz_{mmmm}) = \sqrt{VVVV_{pppp}/VVVV_{mmmm}}$
  - $SSSS_{iiii} = zzzz_{iiii}\sqrt{VVVV_{iiii}}$ so that $SSSS_{1}, \ldots, SSSS_{KKKK} \sim MMMMVVVVNNNN$ with $\theta\theta\theta\theta_{iiii} \sim NNNN(\theta\theta\theta\theta VVVV_{iiii}, VVVV_{iiii})$ and $cccccccvvvv(SSSS_{pppp}, SSSS_{mmmm}) = VVVV_{pppp}$
  - $\theta\theta_{1}, \ldots, \theta\theta\theta\theta_{KKKK}$, $zzzz_{1}, \ldots, zzzz_{KKKK}$ and $SSSS_{1}, \ldots, SSSS_{KKKK}$ ($SSSS_{iiii}$ being score statistics) have a joint canonical distribution
  - Thus independent increments apply to the score statistics i.e., $SSSS_{iiii} - SSSS_{iiii-1} \sim NNNN(\theta\theta\theta\theta(VVVV_{iiii} - VVVV_{iiii-1}), \theta\theta\theta\theta(VVVV_{iiii} - VVVV_{iiii-1}))$ independently of $SSSS_{1}, \ldots, SSSS_{iiii-1}$

These properties directly apply in the case of a random coefficients analysis with

$$VVVV = \frac{\sigma\sigma\sigma\sigma^{2}_{eeee}}{NNNN} + \sigma\sigma\sigma\sigma^{-1}_{2}$$

$$VVVV = \frac{4}{NNNN_{iiii}} \frac{SSSSxxxxxxx}{\sigma\sigma\sigma\sigma^{2}_{mmm}} + \sigma\sigma\sigma\sigma^{2-1}_{bbbb}$$

$$4 \quad SSSSxxxxxx$$

$$xx$$

Thus, the Cui, Hung and Wang fixed weights approach can be applied to sample size re-estimation based upon a random coefficients analysis. For the OMS721-IGA-001 trial, the weights to be applied are $\omega\omega\omega\omega_1 = \sqrt{180/280}$ and $\omega\omega\omega\omega_2 = \sqrt{100/280}$, respectively.

At the end of the study, when all patients $NNNN^{*} = nnnn_{iiii} + nnnn^{*}$ have completed a minimum follow-up of 96 weeks, the z-value for the eGFR endpoint in the $nnnn_{iiii}$ patients included in the interim SSRE calculation will be computed and denoted as $zzzz_{nnnnn}$; and, similarly, the z-value for the eGFR endpoint in the remaining $nnnn^{*} = NNNN^{*} - nnnn_{iiii}$ patients will be computed and denoted as $zzzz_{NNNN^{*}-nnnn_{iiii}}$. Then the combined z-value for the eGFR endpoint will be given as,

$$zzzz_{ccccpppppmmmmmbbbb} = \omega\omega\omega\omega_1 zzzz_{nnnn_{iiii}} + \omega\omega\omega\omega_2 zzzz_{NNNN^{*}-nnnn_{iiii}}$$

and the associated 1-sided p-value will be given as

$$pppp_{ccccpppppmmmmmbbbbb} = 1 - \Phi^{-1}(zzzz_{ccccpppppmmmmmbbbbb})$$

In terms of treatment effect estimation. denote the treatment effect estimate for the eGFR endpoint in the first $nnnn_{iiii}$ subjects as $\theta\theta\theta\theta_{nnnn}$ and in the $NNNN^{*} - nnnn_{iiii}$ subjects as $\theta\theta\theta\theta_{NNNN_{iiii}}$. Define $\omega\omega\omega\omega^{*}_{2} = \sqrt{NNNN/NNNN}$. As per [Lawrence 2003], the overall treatment effect point estimate for the eGFR endpoint, $\theta\theta\theta\theta$, and associated standard error, SE$\theta\theta\theta\theta$, are given by,

$$\theta\theta\theta\theta = \frac{\omega\omega\omega\omega^{2}_{1} \cdot \theta\theta\theta\theta_{nnnn_{iiii}} + \omega\omega\omega\omega_2 \cdot \sqrt{\omega\omega\omega\omega^{*2}_{2} - \omega\omega\omega\omega^{2}_{1}}\theta\theta_{NNNN^{*}-nnnn_{iiii}}}{\omega\omega\omega\omega^{2}_{1} + \omega\omega\omega\omega_2 \cdot \sqrt{\omega\omega\omega\omega^{*2}_{2} - \omega\omega\omega\omega^{2}_{1}}}$$

$$SSSSSSSS\theta\theta\theta\theta = \sqrt{\frac{4\sigma^{2}}{NNNN\left(\omega\omega\omega\omega^{2}_{1} + \omega\omega\omega\omega_2 \cdot \sqrt{\omega\omega\omega\omega^{*2}_{2} - \omega\omega\omega\omega^{2}_{1}}\right)}}$$

Further, denote the overall LS Mean for the eGFR endpoint in the treated arm as $LLLL_{DDDD}$, then,

$$LL_{DDDD} = \frac{\omega\omega\omega\omega^{2}_{1} \cdot LL_{DD\,DD,nn\,nn} + \omega\omega\omega\omega_2 \cdot \sqrt{\omega\omega\omega\omega^{*2}_{2} - \omega\omega\omega\omega^{2}_{1}}LL_{DDDD,NNNN^{*}-nnnn}}{\omega\omega\omega\omega^{2}_{1} + \omega\omega\omega\omega_2 \cdot \sqrt{\omega\omega\omega\omega^{*2}_{2} - \omega\omega\omega\omega^{2}_{1}}}$$

$$SSSSSSSS\hat{LL}_{DDDD} = \frac{2\sigma^2}{NNNN\left(\omega\omega\omega\omega^2 + \omega\omega\omega_2 \cdot \overline{\omega\omega\omega\omega^{*2}} - \alpha\alpha\alpha\omega^2\right)}$$

And, similarly for the placebo arm,

$$\hat{LL}_{PPPP} = \frac{\omega\omega\omega\omega^2 \cdot LL_{PP\,PP,\,nn\,nn} + \omega\omega\omega\omega_2 \cdot \overline{\omega\omega\omega\omega^{*2}} - \omega\omega\omega\omega^2 LL_{PPPP,NNNN^*-nnnn}}{\omega\omega\omega\omega^2 + \omega\omega\omega\omega_2 \cdot \overline{\omega\omega\omega\omega^{*2}} - \omega\omega\omega\omega^2}$$

$$SSSSSSSS\hat{LL}_{nnnn} = \frac{2\sigma^2}{NNNN\left(\omega\omega\omega\omega^2 + \omega\omega\omega\omega_2 \cdot \overline{\omega\omega\omega\omega^{*2}} - \omega\omega\omega\omega^2\right)}$$

and where,

$$\sigma^2 = \frac{2}{SSSSxxxxxxxx} + \sigma\sigma^2$$

based on the intended sample size, *NNNN*.

2.9.8. Other Statistical Considerations

In addition to the estimation of the bias-adjusted variance of the log-transformed 24-hour UPE change from baseline to Week 36 in the SSRE (Section 1.3.3), the bias-adjusted variance of the log-transformed 24-hour uPCR change from baseline to Week 36 will be estimated in a blinded fashion using the same formula in Section 1.3.3. If the log-transformed 24-hour uPCR bias-adjusted variance is substantially smaller than the log-transformed 24-hour UPE bias-adjusted variance, the primary endpoint may be changed to log-transformed 24-hour uPCR at Week 36 after consultation with the US Food and Drug Administration.

3. STATISTICAL SUMMARIES

3.1. General Conventions

All statistical analyses will be performed using SAS version 9.4 or later (SAS Institute Inc., Cary, NC). Study endpoints will be summarized with descriptive statistics, which include n, mean, standard deviation, median, and range (minimum, maximum) for continuous variables, and frequencies and percentages for categorical variables. All statistical tests will be performed at the two-sided significance using the applicable alpha level. Confidence intervals will be similarly constructed two-sided at the applicable confidence level.

3.2. Patient Disposition and Treatment

3.2.1. Patient Disposition

Data will be displayed in both the high-risk proteinuria group (baseline UPE ≥ 2 g/day) and the all-patients population (baseline UPE > 1 g/day).

An accounting of study patients by disposition will be tabulated by treatment group for the randomized population. 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 with 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 the 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% CI will be provided by treatment group.

3.2.2. Study Treatment Compliance and Extent of Exposure

3.2.2.1. Study 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 by treatment group in both the high-risk proteinuria group (baseline UPE ≥ 2 g/day) and the all-patients population (baseline UPE > 1 g/day).

3.2.2.2. Extent of Study Drug Exposure

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

- Cumulative study drug doses in milligrams taken by blinded treatment period (the Initial Treatment Period, the extended treatment period, the retreatment period, and the entire blinded treatment period) and treatment group
- Cumulative narsoplimab doses in milligrams during the open-label treatment period by treatment 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

3.2.3. Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be listed and summarized by treatment group in both the high-risk proteinuria group and the all-patients population.

3.2.4. Concomitant Medications

Concomitant medications will be coded with World Health Organization (WHO) Drug Dictionary (WHODrug) and will be summarized by WHODrug standardized medication name and treatment group. Prior (medications with end dates prior to the randomization date) and concomitant medications will be listed.

3.2.5. Medical and Surgical History

A listing of reported medical and surgical history will be provided by treatment group.

3.3. Analysis of Pharmacokinetic, Pharmacodynamic and Immunogenicity Endpoints

See Section 2.9.3.

3.4. Analysis of Safety Endpoints

Safety endpoints will be summarized separately for the blinded treatment period and the open-label treatment period.

3.4.1. Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as follows:

- During the blinded treatment period, an AE is treatment-emergent if it occurs or worsens in severity from pre-treatment after the first dose of study drug but before the first dose of narsoplimab in the open-label treatment period (blinded TEAE)
- During the open-label treatment period, an AE is treatment-emergent if it occurs or worsens in severity from the end of the blinded treatment period after the first dose of narsoplimab in the open-label treatment period (open-label TEAE)

All AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). An AE is considered treatment-related if the relationship to study drug is either probable or possible as assessed by the investigator.

Patient incidence by treatment group of the following AEs will be provided:

- Pre-treatment AEs (AEs that occurred prior to the start of study drug) by MedDRA system organ class (SOC), preferred term, and treatment group
- Blinded treatment period:

  - TEAEs by MedDRA SOC, preferred term, and treatment group
  - TEAEs by MedDRA preferred term and treatment group
  - TEAEs that are treatment-related by MedDRA SOC, preferred term, and treatment group
  - TEAEs by MedDRA preferred term, maximum severity, and treatment group
  - TEAEs leading to study discontinuation by MedDRA SOC, preferred term, and treatment group
  - TEAEs that are serious by MedDRA SOC, preferred term, and treatment group
  - TEAEs that are treatment-related and serious by MedDRA SOC, preferred term, and treatment group
  - TEAEs leading to death by MedDRA SOC, preferred term, and treatment group
- Open-label treatment period:
  - Open-label TEAEs by MedDRA SOC, preferred term, and treatment group
  - Open-label TEAEs by MedDRA preferred term and treatment group
  - Open-label TEAEs that are treatment-related by MedDRA SOC, preferred term, and treatment group
  - Open-label TEAEs by MedDRA preferred term, maximum severity, and treatment group
  - Open-label TEAEs leading to study discontinuation by MedDRA SOC, preferred term, and treatment group
  - Open-label TEAEs that are serious by MedDRA SOC, preferred term, and treatment group
  - Open-label TEAEs that are treatment-related and serious by MedDRA SOC, preferred term, and treatment group
  - Open-label TEAEs leading to death by MedDRA SOC, preferred term, and treatment group
- Blinded and open-label treatment periods combined for patients who receive narsoplimab only. TEAEs are determined relative to the first dose of narsoplimab
  - TEAEs by MedDRA SOC and preferred term
  - TEAEs by MedDRA preferred term
  - TEAEs that are treatment related by MedDRA SOC and preferred term
  - TEAEs by MedDRA preferred term and maximum severity
  - TEAEs leading to study discontinuation by MedDRA SOC and preferred term
  - TEAEs that are serious by MedDRA SOC and preferred term

- TEAEs that are treatment-related and serious by MedDRA SOC and preferred term
- TEAEs leading to death by MedDRA SOC and preferred term

3.4.2. Clinical Laboratory Tests

Summary statistics for the actual values and the change from baseline will be tabulated for laboratory results by treatment period (blinded and open-label), 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 period and treatment cohort. Shift tables comparing the baseline NCI CTCAE grade to the worst post-baseline grade will be provided by treatment period and treatment group.

3.4.3. Vital Signs

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

3.4.4. Electrocardiogram

The ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTc interval) at each time point as well as the change from baseline will be summarized with descriptive statistics by treatment period, treatment group, and scheduled visit. These parameters will be determined electronically by the ECG machine at the clinical site. QTc interval will be calculated using Fridericia's formula and will be categorized into the following groups: ≤ 450, > 450 – 480, > 480 – 500 and > 500 ms. Categorized QTc interval will be summarized with frequency and percentage by treatment period, treatment group, and scheduled visit. Shift tables comparing the baseline categorized QTc interval to the maximum post-baseline categorized QTc interval will be provided by treatment period and treatment group. In addition, increase of > 30 ms and > 60 ms from baseline in QTc interval will be summarized with frequency and percentage by treatment period, treatment group, and scheduled visit.

The overall ECG assessment will be reported as "Normal," or "Abnormal – not clinically significant" or "Abnormal – clinically significant" with respect to relevant abnormalities by the investigator. Shifts from the baseline ECG assessment to the worst post-baseline ECG assessment will be tabulated by treatment period and treatment group.

4. PROTOCOL AND SAP AMENDMENTS

Protocol Amendment 01 states that the p-value for the primary endpoint will be calculated by comparing to the effect size of -0.246. This effect size was estimated from the Inker's equation for the sample size calculation only. The SAP has clarified that the primary treatment comparison using the primary endpoint will be based on the two-sided p-value for the treatment difference in LS means at Week 36 (Section 2.9.2.1).

Protocol Amendment 02 was not released due to formatting errors identified after it was finalized. The formatting errors were corrected in Amendment A03.

Protocol Amendment 03 added criteria for re-initiation of study treatment and modifications to study procedures during the COVID-19 pandemic. Sensitivity analyses have been added to the SAP by excluding the data collected after the re-initiation of study treatment (Section 2.9.2).

Protocol Amendment 04 (soon to be released) adds new prohibited medications (SGL2Ti, Tarpeyo, Kerendia).

Protocol Amendment 05 will make the following major changes:

- The proteinuria responder analysis has been removed. Instead, UPE will be examined as a continuous variable (change in log-transformed 24-hour UPE from baseline to 36 weeks).
- The primary endpoint – change from baseline in log-transformed 24-hour UPE in g/day at 36 weeks – will only include the subset of patients with high-risk proteinuria (UPE ≥ 2 g/day) at baseline. All patients (UPE >1 g/day at baseline) will be examined for UPE change from baseline, but now as a secondary endpoint. Specifically, the amended protocol will assess change from baseline in the 24-hour UPE in patients with baseline UPE of ≥ 2 g/day, and the timing of analysis will remain unchanged at 36 weeks.
- In light of the new data published by Inker et al. [Inker 2021] regarding the relationship between treatment effects on annualized 2-year eGFR Rate of Change and treatment effects on mean change in proteinuria at 9 months, the duration of the study was changed from 3 years to 2 years post randomization
- Utilizing the IgAN database from the University of Leicester, UK, the sample size required to detect a difference of 3.48 and 2.45 mL/min in 2-year annualized eGFR Rate of Change between narsoplimab and placebo was determined to be 280 and 450 patients, respectively, for the high-risk proteinuria group (baseline UPE ≥ 2 g/day) and the all-patients population (UPE > 1 g/day), providing at least 85% power for a 2-sided test at 5% level of significance
- There were previously two sample size re-estimations (SSREs), one blinded SSRE for the UPE endpoint for all patients and the other for annualized eGFR rate of change endpoint. The former remained unchanged and was performed resulting in no change in the planned sample size of N = 280 for all patients. The latter has been removed in the proposed protocol amendment 05 and SAP, and has been replaced with a CP-based SSRE at the time of the primary UPE endpoint analysis in the high-risk proteinuria group (baseline UPE ≥ 2 g/day)

In reflection of these changes, the SAP was updated as follows:

- Data from [Inker 2021] regarding the relationship between treatment effects on 2-year annualized eGFR Rate of Decline and treatment effects on mean change in proteinuria at 9 months were added to the SAP
- Data from the University of Leicester IgAN database were used to estimate the annualized 2-year eGFR Rate of Decline for the placebo group with baseline proteinuria ≥ 2g/day. The sample size required to detect a difference of 3.48 mL/min in 2-year annualized eGFR Rate of Decline between narsoplimab and placebo in the

high-risk proteinuria group (baseline UPE ≥ 2g/day) patient population with at least 85% power for a 2-sided test at 5% level of significance, was determined to be 280 patients and this was added to the SAP

- Data from the University of Leicester IgAN database were used to estimate the annualized 2-year eGFR Rate of Decline for the all-patients placebo group with proteinuria > 1 g/d. The sample size required to detect a difference of 2.45 mL/min in 2-year annualized eGFR Rate of Decline between narsoplimab and placebo in the all-patients population with 85% power at the 2-sided alpha level of 5% was determined to be 450 patients and this was added to the SAP
- Testing of hypotheses for primary UPE endpoint and key secondary eGFR endpoints was revised to be hierarchical in nature to control overall Type-1 error at 5%

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APPENDIX 1. JUMP TO PLACEBO MULTIPLE IMPUTATION

A control-based pattern-mixture model approach as per [Ratitch 2011] whereby missing observations in both the narsoplimab and placebo groups are imputed using only data observed in the placebo group; this model reflects a 'jump to placebo (reference)' analysis.

Several steps are required to execute this sensitivity analysis.

In the first step, intermittently missing data (e.g., where a patient has week 12 and week 36 data recorded but has week 24 data missing) are imputed as non-monotone missing to generate a monotone missing pattern. The form of the associated SAS code is given below where the dataset **DATAIN** has already been sorted by randomized treatment (**RANDTRT**) and the randomization stratification factors **STRAT1** and **STRAT2**:

```
/*FIRST STEP IMPUTE NON-MONOTONE(INTERMITTENTLY)MISSING DATA*/
PROC MI DATA=DATAIN SEED=<VALUE> NIMPUTE=20 OUT=MI_OUT1;
  VAR BASE W12 W24 W30 W36 ;
  MCMC CHAIN=MULTIPLE PRIOR=JEFFREYS IMPUTE=MONOTONE;
  BY STRAT1 STRAT2 RANDTRT;
RUN;
```

where **BASE** = baseline log UPE, and **W12, W24, W30** and **W36** = week 12, 24, 30 and 36 change from baseline log UPU values.

The resulting dataset **MI_OUT1** is then sorted by **_IMPUTATION_** , **STRAT1, STRAT2** and **RANDTRT**. In the second step, **PROC MI** is called again utilizing the regression method under **MNAR** to complete imputation of the monotone missing datasets resulting from the first step. The SAS code will be of the following form:

```
 /*SECONDLY IMPUTE MONOTONE MISSING DATA AS MNAR JUMP TO PLACEBO*/
PROC MI DATA=MI_OUT1 SEED = <SEED> NIMPUTE = 1 OUT=MI_OUT2;
  BY_IMPUTATION_ STRAT1 STRAT2;
  CLASS RANDTRT;
  MONOTONE REG (W36 = BASE W12 W24 W30/ DETAILS);
  MNAR MODEL (W12 W24 W30 W36 / MODELOBS =(RANDTRT = 'PLACEBO'));
  VAR W12 W24 W30 W36 BASE;
 RUN;
```

The dataset **MI_OUT2** contains the 20 complete imputed data sets. This dataset will be transformed in a third step such that, for each patient, each post-baseline time-point is represented by a separate record.

```
/*THIRD STEP TRANSFORM IMPUTED DATASETS*/
DATA MI_OUT3; SET MI_OUT2;
 VISIT=12; CHG_BL=W12-BASE; OUTPUT;
 VISIT=24; CHG_BL=W24-BASE; OUTPUT;
 VISIT=30; CHG_BL=W30-BASE; OUTPUT;
 VISIT=36; CHG_BL=W36-BASE; OUTPUT;
RUN;
```

The 20 complete datasets in **MI_OUT3** will then be analyzed in a fourth step by MMRM via **PROC MIXED** as specified for the primary endpoint. The SAS code will be of the following form:

```
/*FOURTH STEP MMRM ANALYSIS OF IMPUTED DATASETS*/
PROC MIXED DATA=MI_OUT3 METHOD=REML;
  BY _IMPUTATION_;
  CLASS PATIENT RANDTRT VISIT STRAT1 STRAT2;
  MODEL CHG_BL = BASE RANDTRT VISIT RANDTRT*VISIT STRAT1 STRAT2
                 STRAT1*STRAT2 /DDFM=KR;
  REPEATED VISIT / PATIENT = PATIENT TYPE = UN;
  LSMEANS RANDTRT*VISIT/SLICE=VISIT PDIFF DIFF ALPHA=0.05 CL;
  ODS OUTPUT DIFFS=DIFF LSMEANS=LSMEANS;
RUN;
```

To obtain overall LSmean and treatment effect estimates, the **DIFF** and **LSMEANS** datasets are merged in a fifth step prior to combination across imputations using Rubin's rule in a sixth step via **PROC MIANALYZE**. The SAS code will be of the following form:

```
/*FIFTH STEP MERGE DIFF AND LSMEANS DATASETS*/
DATA DIFF2;
  SET DIFF (IN=A) LSMEANS;
  IF A THEN COMPARISON=RANDTRT||' VS '||LEFT(_RANDTRT);
  ELSE COMPARISON=RANDTRT;
RUN;
PROC SORT DATA=DIFF2;
  BY COMPARISON _IMPUTATION_;
RUN;


/*SIXTH STEP COMBINE MI ESTIMATES VIA MERGE DIFF AND LSMEANS
  DATASETS*/
PROC MIANALYZE DATA=DIFF2;
  BY COMPARISON;
  MODELEFFECTS ESTIMATE;
  STDERR STDERR;
ODS OUTPUT PARAMETERESTIMATES=MIESTS;
RUN;
```

The output dataset **MIESTS** contains the final, imputed results. The resulting multiply imputed means and difference in means between narsoplimab and placebo will be presented, along with the associated SEs, CIs and 2-sided p-values.

The same approach will be used for the analysis of the two key secondary endpoints, with **BASE** = baseline eGFR and log UPE change from baseline values at **W12, W24, W30** and **W36** replaced by absolute eGFR values at weeks **W12, W24, W36, W48, W60, W72, W84** and **W96**.

APPENDIX 2. TIPPING POINT MULTIPLE IMPUTATION

A tipping point analysis whereby missing data are imputed in the narsoplimab arm with an increasing degree of penalization and thus find the 'tipping point', i.e., that degree of penalization that renders a positive p-value for the primary endpoint non-significant.

All imputation steps are as described in Appendix 1 apart from the second step where monotone missing data are imputed for patients randomized to narsoplimab are adjusted using the **ADJUST** and **SHIFT** options:

```
 /*SECONDLY APPYING TIPPING POINT IMPUTATION*/
PROC MI DATA=MI_OUT1 SEED = <SEED> NIMPUTE = 1 OUT=MI_OUT2<DELTA>;
  BY_IMPUTATION_ STRAT1 STRAT2;
  CLASS RANDTRT;
  MONOTONE REG (W36 = BASE W12 W24 / DETAILS);
  MNAR ADJUST(W12 / SHIFT = <DELTA> ADJUSTOBS=(RANDTRT =
  'NARSOPLIMAB'));
  MNAR ADJUST(W24 / SHIFT = <DELTA> ADJUSTOBS=(RANDTRT =
  'NARSOPLIMAB'));
  MNAR ADJUST(W30 / SHIFT = <DELTA> ADJUSTOBS=(RANDTRT =
  'NARSOPLIMAB'));
  MNAR ADJUST(W36 / SHIFT = <DELTA> ADJUSTOBS=(RANDTRT =
  'NARSOPLIMAB'));
  VAR W12 W24 W36 BASE RANDTRT;
RUN;
```

The value of the penalty **<DELTA>** is progressively increased and the code re-run for each increase. This generates a series of **MI_OUT2<DELTA>** datasets. To each of these datasets, steps 3 to 6 as described in Appendix 1 will be applied, thus giving rise to a multiply imputed treatment effect estimate for each value of **<DELTA>** for narsoplimab vs placebo, along with its SE and CI. These treatment effect estimates and CIs will be plotted in a stacked forest plot format vs **<DELTA>**. The first value of **<DELTA>** whereby the CI includes zero will be identified as the tipping point.

APPENDIX 3. COMPUTING FISHERS INFORMATION FOR EGFR AT THE TIME OF THE UPE PRIMARY ENDPOINT ANALYSIS

```
options linesize=160 pagesize = 60 dquote nodate nonumber;

libname mdata 'C:\mydata';

/*
filename myfile 'C:\mydata\mydata.log';
proc printto log=myfile;
run;
*/

proc printto log=log;
run;

/*
With the primary endpoint analysis to take place with N =   180 high risk proteinuria patients,
taking into account the minimum follow-up of 9 months and that recruitment of these   180
patients took 45 months, relative to the planned final analysis of eGFR in the high-risk
proteinuria group with N = 280 patients,
*/

%macro datx(nsim,n,acc,k,fup,xfup,vis,ve,vb,d);

*********************************************************;
** nsim = number of simulations                        **;
** k    = non uniform accrual parameter k=1 = uniform  **;
**        k>1 = non uniform                            **;
** acc  = length of accural months                     **;
** fup  = length follow-up months                      **:
** xfup = max length of follow-up after last subj      **;
**        randomised                                   **;
** vis  = interval between visits in months            **:
** ve   = residual squared error after regression      **:
** vb   = between patient variance component for slope **:
*********************************************************;

data y;
nsim=&nsim;
k=&k;
acc=&acc;
fup=&fup;
xfup=&xfup;
vis=&vis;
ve=&ve;
vb=&vb;
if mod(&n,2) = 0 then n=&n;
if mod(&n,2) ne 0 then n=&n+1;
 do sim=1 to nsim by 1;
 do i=1 to n;
  reci=acc*(rand('UNIFORM',0,1)**(1/k));
  fupi=(acc-reci)+fup;
  if fupi > xfup then fupi=xfup;
  v=int(fupi/vis);
  vv=vis*v;
   do tm=vis to vv by vis;
   output;
  end;
  end;
end;
run;

/*
proc print data =y;
title 'y';
run;
```

```
title;
*/

data y;
 set y;
 g=1;
 if i<=n/2 then g=0;
run;

proc sort data = y;
by sim g i;
run;

proc univariate data = y noprint;
by sim g i;
var tm v;
output out = out2 mean= x v std=sdx n=nvist;
run;

data out2;
 set out2;
 sxxi = (nvist-1)*sdx**2;
 ve=&ve;
 vb=&vb;
 q=(ve/sxxi + vb);
 qinv=(ve/sxxi + vb)**-1;
run;

/*
proc print data = out2;
title 'out2';
run;
title;
*/

proc univariate data = out2 noprint;
by sim g;
var qinv;
output out = out3 sum =sum_qinv ;
run;

/*
proc print data = out3;
title 'out3';
run;
title;
*/

data out3;
 set out3;
 vslope =1/sum_qinv;
 sslope =sqrt(vslope);
run;

proc sort data = out3;
by g;
run;

proc univariate data = out3 noprint;
BY G;
var vslope sslope;
output out = out4 mean=vslope sslope std=sd_vslope sd_sslope n=nsims ;
run;

/*
proc print data = out4;
title 'out4';
run;
title;
*/
```

```
data d&d;
 set out4;
 dat="d&d ";
 nsim=&nsim;
k=&k;
acc=&acc;
fup=&fup;
xfup=&xfup;
vis=&vis;
ve=&ve;
vb=&vb;
n=&n;
run;

%mend;

*%macro dat(nsim,n,acc,k,fup,xfup,vis,ve,vb,d);

%datx(1000,180,45,    2,9 ,24,3,42.3499,0.5411,1);
%datx(1000,280,56.125,2,24,24,3,42.3499,0.5411,2);

data max;
 set d2;
 maxvslope=vslope;
keep g nsims maxvslope;
run;

/*
proc print data = max;
title 'max xx';
run;
title;
*/

data all;
 set d1 d2;
run;

proc sort data = all;
by g nsims acc     fup   xfup   vis      ve        vb      n ;
run;

proc sort data = max;
by g nsims ;
run;

/*
proc print data = all;
title 'all check';
run;
title;
*/

data all;
 merge all max;
 by g nsims;

vslope2arm = vslope*2;
vmax = maxvslope*2;

Fishi = 1/vslope2arm;
FishF =1/vmax;

inf= Fishi/FishF;

if k=1 then kc='Uniform ['||left(trim(put(round(k,0.1),3.1)))||']    ';
if k>1 then kc='Non-Uniform ['||left(trim(put(round(k,0.1),3.1)))||']';

run;

/*
```

```
proc print data = all;
title 'all max merged check';
run;
title;
*/

proc print data = all split='*' noobs;
where g=0;
var dat nsim kc acc fup xfup vis vb ve n Fishi FishF inf;
label dat='Run'
      nsim='#*Sims'
      kc='Accural*Type'
      acc='Accrual*Time*(months)'
      fup='Min FollowUp*(months)'
      xfup='Max FollowUp*(months)'
      vb = 'vb*monthly*(mL/min/m2)^2'
      ve = 've*(mL/min/m2)^2'
      n = 'Total*N'
      vis='Visit*Freq*(months)'
      fishi='Interim*Fishers Inf'
      fishf='Final*Fishers Inf'
      inf='Inf*Fraction';
run;

proc datasets lib=work
 nolist kill;
quit;
run;

proc printto log=log;
run;
```