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Clinical Development

LNP023/Iptacopan

CLNP023A2301

A multi-center, randomized, double-blind, placebo-controlled, parallel group, phase III study to evaluate the efficacy and safety of LNP023 in primary IgA nephropathy patients

# Statistical Analysis Plan (SAP)

| | |
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## Document History – Changes compared to previous final version of SAP

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| 12-Jan-2021 | Prior to DB lock | Creation of final version | N/A - First version | NA |
| 03-May-2022 | Prior to DB lock | Clinical Study Protocol (CSP) amendment v02 | Composite renal endpoint definition updated and renamed to "Composite Kindey Failure Endpoint". Wording "renal" and "RRT" updated to "kidney" and "KRT" as per CSP v02 throughout. | Sections 1.1, 1.2, 2.3.2, 2.4.1, 2.5, 2.6, 3.1.2, Tables 5-1, 5-2. |
| | | | α-spending revised so that 0.5% (one-sided) α is allocated at the interim analysis, and 2% (one-sided) α for testing remaining hypotheses. | Sections 2.5.2, 2.6, and 3 |
| | | | "To demonstrate the superiority of LNP023 vs placebo on slowing eGFR decrease measured by the change from baseline in eGFR" added as Secondary objective within the IA testing strategy. | Tables 1-1, 5-1, 5-2 Sections 1.1, 1.2.2, 2.6, 2.13, 3.1.2 |
| | | | Reduction of urine protein excretion by measuring UPCR sampled from a 24h urine collection at month 24 added as exploratory endpoint at final analysis | Table 1-2, Section 2.12 |
| | | | Additional intercurrent event specified for initiation of new IgAN background medication. Updates made accordingly throughout. | Section 1.2, 2.4, 2.5, 2.6, Tables 5-1 and 5-2 |
| | | | Sensitivity analyses (e.g. considering the intake of new background medication for IgAN, tipping point analyses) added | Section 2.5.5 |
| | | | Threshold for Age subgroup adjusted to reflect IgAN population being younger. | Section 2.2.1 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | Countries newly included in study added. | |
| | | | Dedicated table for Kidney biopsy information added. Geographic region subgroup summary by Sex added in Demographics table. Thresholds for Age group edited | Section 2.3.2 |
| | | | Summaries of considerable ACE/ARBs dose changes added. Aligned prior/ concomitant medications/non-drug therapies definitions with other LNP023 studies. Removed “overall” as per protocol text. Listings of booster vaccinations and ACE/ARB at baseline added, listing of prior/concomitant medications/non-drug therapies removed | Section 2.4 |
| | | | Tables of clinically notable laboratory abnormalities and liver event and laboratory trigger definitions updated as per CSP v02, appendix 16 | Tables 2-4, 2-5, Section 5.2.4 |
| | | | Displays of risk differences for most common AEs/TEAESIs and Kaplan-Meier estimate of cumulative incidence function added. Pre/post-treatment SAE and serious TEAESIs tables removed as captured in the pre/post treatment AE and TEAESI tables. TESAE tables by SOC, and PT and by severity replaced by TESAE by PT only. Per CSP v02, AE by SMQ table removed. Change from baseline replaced with absolute values in box-plots, shift tables removed. Minor clarifications throughout | Section 2.8 |
| | | | Percent Recovery added in Table 2.7, plot of individual trough concentrations | Section 2.9 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | by population removed as these also captured in listings | |
| | | | Objective related to patient interviews added, responder analysis for EORTC removed, other typographical corrections in PROs in line with CSP v02. | Tables 1-1 and 1-2, Section 2.10 |
| | | | Clarifying information from newly published literature added | Section 3.1.2 |
| | | | Guidance on handling data records containing confirmed cases of biological sample analysis after WoC added | Section 5.3 |
| 30-June-2023 | Prior to DB lock | Clinical Study Protocol (CSP) amendment v03 | Removed eGFR change from baseline at the IA from testing strategy and updated SRI population and total study size, in line with CSP v03 | Sections 1.1, 2.6, 2.13 and 3 |
| | | | Added clarification from CSP v03 regarding medication definitions | Section 1.1 |
| | | | Updated table of Objectives at the IA and associated sections in line with CSP v03 | Table 1-1, Sections 2.9, 2.10 |
| | | | Last contact and study day definitions updated for completeness. | Section 2.1.1 |
| | | | Clarification to the FAS participants applicable to the IA (IA-FAS) and associated analyses added in line with FDA feedback in all relevant sections. | Section 2.2, 2.3, 2.4-2.6, 2.10-2.12 |
| | | | Supplementary analyses for primary estimand & secondary estimands 1 & 3 at the IA on the FAS added | Section 2.5.6, 2.6.6 |
| | | | Ethnicity subgroup added in line with FDA feedback | Table 2-2 |
| | | | Updates/clarifications to demographic and baseline characteristics variables to be summarized made. | Section 2.3.2 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | Graphical outputs added, Screened but not randomized category replaced by in Run-in category | Section 2.3.1, 2.5.5. |
| | | | Background ACE/ARB updated to background IgAN medications. Added standalone protocol required vaccination history table and summary table in Asian Main study population participants. Prior medications' tables split to tables of medications taken before study enrollment and medications taken during the run-in. | Section 2.4.3 |
| | | | Clarification added on I/C event handling & editorial updates made, clarified I/C handling for subgroup analyses | Section 2.5.3, 2.5.6.3 |
| | | | Primary efficacy endpoints listings and diagnostic plots added, detail on non-administrative reasons added, plot for sensitivity 0.3 and sensitivity analyses 0.5-0.7 for final analysis added | Section 2.5, 5.2 |
| | | | Steps in case of logistic model non-convergence issues added. Kaplan-Meier curves replaced by cumulative incidence curves, consideration of analysis cut-off for composite added | Section 5.2.4, 2.6.1, 2.6.2.1. |
| | | | TESAEs listing and summary by SOC and PT included. Detail on the risk difference related derivations added, editorial wording change of incidence to occurrence, updated 95% CI derivation for exposure adjusted occurrence rate and related references, updated threshold for most frequent TEAEs for SRI | Sections 2.8, 2.8.1.1, 6 |
| | | | Listings consolidated i.e. abnormalities presented within main listing (rather than separate listing) for laboratory, ECG and Vital signs parameters | Sections 2.8.3, 2.8.4 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | Descriptive statistics for PGIS and exploratory analysis with PGIS as anchor added, clarifications on exploratory EQ-VAS & EORTC QLQ-C30 made | Section 2.10 |
| | | | Details on exploratory biomarkers added | Section 2.11, Table 2.8 |
| | | | GLMM replaced with logistic model for supportive FACIT responder analysis. | Section 4 |
| | | | Added detail on the handling of mis-stratifications, concomitant non-drug therapy date imputation added, imputed values for eGFR and FACIT-Fatigue total score, detail on missing data handling post treatment or study discontinuation added in Tables 5-1 & 5-2. | Sections 5, 6 |
| | | | Editorial updates to abbreviations list | List of abbreviations |
| | | | Cover page updated to Confidential as per latest Novartis template guidance | Cover page |
| 10-Sep-2023 | Prior to DBL | Minor updates | Central vs local lab clarification, liver abnormalities outputs aligned with FDA feedback across the LNP023 program, 2 listings added, dipstick listing & ranges not available removed, typos corrected. | Section 2.8.3, 2.8.4 |
| | | | Typographical error corrected | Section 2.2.1 |
| | | | Vaccinations listing scope broadened | Section 2.4.3 |
| | | | Clarified handling of multiple I/C | Section 2.5.3 |
| | | | Clarified SRI summaries on FAS at IA | Section 2.4.3, 2.5-6,2.10-12 |
| | | | Typo in matrix and unit corrected | Table 2-8 |
| | | | Removed overall utilization summary | Section 2.12 |
| | | | Region subgroup overlap with Geographic region stratification noted | Section 2.5.6.3 |
| | | | Steps in case of non-convergence for ethnicity subgroup analyses added | Section 5.2.2 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
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| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
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## List of abbreviations

| | |
|---|---|
| ACEi | Angiotensin Converting Enzyme inhibitor |
| AE | Adverse Event |
| Ae | Amount excreted |
| AESI | Adverse Event of Special Interest |
| ARB | Angiotensin Receptor Blocker |
| ATC | Anatomical Therapeutic Classification |
| AxMP | Auxiliary Medicinal Product |
| b.i.d. | Twice A Day |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CKD | Chronic Kidney Disease |
| CLr | Renal plasma clearance |
| CR | Copy-Reference |
| CS | Corticosteroids |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTT | Clinical Trial Team |
| CV | Coefficient of Variation |
| DILI | Drug Induced Liver Injury |
| DMS | Document Management System |
| DMC | Data Monitoring Committee |
| DBP | Diastolic Blood Pressure |
| eCDF | empirical Cumulative Distribution Function |
| ECG | Electrocardiogram |
| ePDF | empirical Probability Density Function |
| eCRF | Electronic Case Report Form |
| CRS | Case Retrieval Strategy |
| eGFR | Estimated Glomerular Filtration Rate |
| EOS | End of Study |
| EQ-5D-5L | EuroQol-5 Dimensions-5 Level |
| EQ VAS | EQ Visual Analogue Scale |
| ER | Emergency Room |
| FAS | Full Analysis Set |
| FMV | First-Morning-Void |
| FWER | FamilyWise Error Rate |
| GLMM | Generalized Linear Mixed Model |
| HDL | High-Density Lipoprotein |
| IA | Interim Analyses |
| I/C | Intercurrent event |
| ICF | Informed Consent Form |
| IgAN | IgA Nephropathy |
| IRT | Interactive Response Technology |
| IS | Immunosuppressant therapy |

| | |
|---|---|
| J2R | Jump-to-Reference |
| KRT | Kidney Replacement Therapy |
| LDL | Low-Density Lipoprotein |
| LLOQ | Lower Limit Of Qualification |
| MAR | Missing-At-Random |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| MMRM | Mixed Model of Repeated Measures |
| MVN | MultiVariate Normal |
| PK | Pharmacokinetics |
| PRO | Patient-reported Outcomes |
| PT | Preferred Term |
| RAP | Reporting & Analysis Process |
| RAS | Randomized Set |
| REP | Rollover Extension Program |
| SAE | Serious Adverse Events |
| SAF | Safety Set |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SBP | Systolic Blood Pressure |
| SCR | Screening Set |
| SD | Standard Deviation |
| SGLT2i | Sodium/glucose cotransporter-2 inhibitors |
| SOC | System Organ Class |
| SRI | Severe Renal Impairment |
| TA-P | Time-Averaged Proteinuria |
| TEAE | Treatment Emergent Adverse Event |
| TESAE | Treatment Emergent Serious Adverse Event |
| TFLs | Tables, Figures, Listings |
| UA-24h | Total urinary albumin/day (sampled from 24hr urine collection) |
| UACR 24h | Urine Albumin-To-Creatinine Ratio (sampled from 24hr urine collection) |
| ULOQ | Upper Limit Of Qualification |
| UP-24h | Total urinary protein/day (sampled from 24hr urine collection) |
| UPCR 24h | Urine Protein-To-Creatinine Ratio (sampled from 24hr urine collection) |
| UPCR FMV | Urine Protein-To-Creatinine Ratio (sampled from first-morning-void) |
| WHO | World Health Organization |

# 1 Introduction

This Statistical Analysis Plan (SAP) describes the detailed methodology and implementation of the planned statistical analyses outlined in Section 12 "Data analysis and statistical methods'' of the Clinical Study Protocol (CSP) v04 for CLNP023A2301. The analyses in this SAP will be used to support:

a. an interim Clinical Study Report (CSR) that may be produced for the purpose of an early submission for conditional/accelerated approval at the time of the Interim Analysis (IA) as outlined in the CSP.
b. the completion of the final CSR for CLNP023A2301.

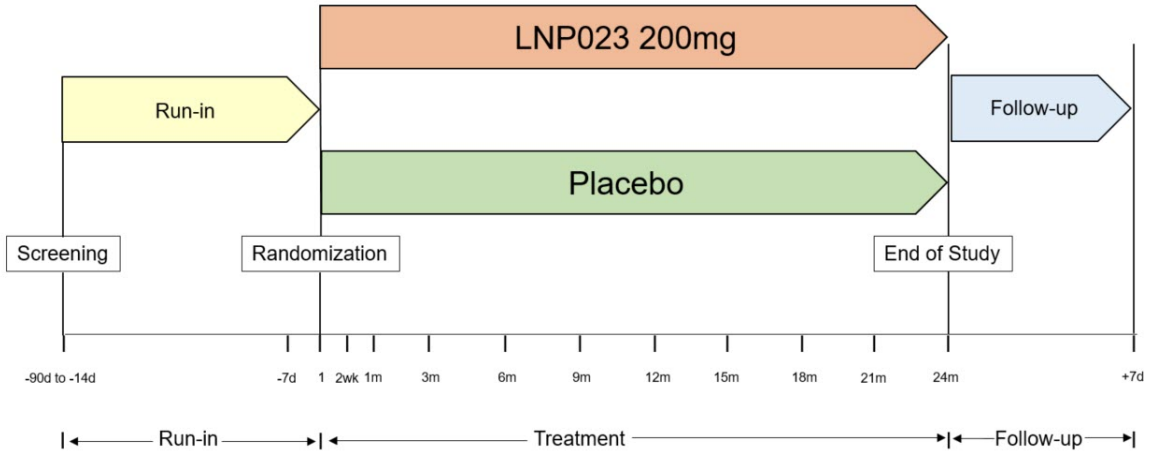
## 1.1 Study design

This is a multi-center, randomized, double-blinded, placebo-controlled study, which comprises a screening visit, followed by a run in period of 14 to approximately 90 days and a randomized double-blind 24 month treatment period for patients eligible for participation. The total study duration for each participant will be a minimum of approximately 24.5 months.

Approximately 470 biopsy-confirmed IgAN participants with UPCR ≥1g/g (113 mg/mmol) despite optimal supportive treatment, measured by central laboratory based on a first morning void (FMV) or a single 24 hour urine sample at screening as well as the mean (geometric) of two 24 hour urine collections at Baseline, will be enrolled:

- Main Study Population: approximately 430 participants with eGFR ≥ 30 mL/min/1.73m$^2$ at screening and Baseline.
- Severe Renal Impairment (SRI) population: approximately 40 participants with eGFR 20 - < 30 mL/min/1.73m$^2$ at screening and Baseline.

**Figure 1-1 Study Design**




**Screening Visit and Run-in Period**

After participants sign the informed consent form (ICF) prior to or at the screening visit, participant eligibility for study enrollment will be determined, followed by the assessments

applicable as per the CSP Assessment Schedule. If eligibility criteria are not met, the study candidate should be considered as having failed screening. Re-screening is permitted as per the process described in the CSP.

**Baseline and Randomization**

Approximately 7 days prior to the planned randomization visit, participants will visit the site for baseline evaluations. Participants who fulfill the CSP eligibility criteria following all baseline evaluations will continue to Randomization.

After meeting all eligibility criteria at baseline, participants will be randomized in a 1:1 ratio to receive either LNP023 200 mg b.i.d or matching placebo.

Participant randomization for the Main Study population will be stratified as follows:

- Geographic region (Asia vs. Non-Asia)
- Baseline UPCR (< 2 g/g [226 mg/mmol] vs. ≥ 2g/g [226 mg/mmol]) as measured by the mean (geometric) of two 24hr urine collections)
- Baseline eGFR (30-<45 mL/min/1.73m$^2$ vs. eGFR ≥45 mL/min/1.73m$^2$)

Participant randomization for the SRI population (i.e. with baseline eGFR 20 - <30mL/min/1.73m$^2$) will be stratified according to Geographic region (Asia vs. Non-Asia) only.

**Randomized Treatment Period**

The double-blind treatment period will start on the first day of dosing (Day 1). Participants are required to attend visits and complete the corresponding assessments as described in the CSP Assessment Schedule. Dose adjustments of study treatment are not allowed during the randomized treatment period.

**End of study and Follow-up**

The End of Study (EOS) visit will mark the end of the double blind treatment period. Eligible participants may be enrolled in the CLNP023A2002B rollover extension program (REP) in which they will receive open-label LNP023. Participants who do not enroll in the REP or do not complete Day 1 of the REP within 7 days of the EOS, should be contacted 7 days after the EOS visit for adverse event (AE) and serious adverse event (SAE) monitoring and any AEs reported should be recorded in the CLNP023A2301 study eCRF. The safety follow-up can be performed via a telephone call or at an on-site visit. For participants who do enroll in the REP within 7 days of the EOS, the REP Day 1 (first study drug administration) visit will serve as the safety follow up visit for the core CLNP023A2301 study, and any AE/SAEs experienced after the EOS and up to the first dose on the REP Day 1 should be recorded in the CLNP023A2301 study eCRF. If a participant enrolls in the REP directly and the REP Day 1 (first study drug administration) is the same day as the EOS visit of CLNP023A2301, then any AEs or SAEs experienced thereafter are only captured in the REP eCRF.

A pre-specified IA will be performed when approximately 250 participants of the Main Study population have completed the 9 months visit, however all data collected up to this point will be included in the IA. The primary objective of this IA is to demonstrate the superiority of LNP023 compared to placebo on proteinuria reduction as measured by UPCR sampled from a

24 hour urine collection at 9 months. In addition, the change from baseline in eGFR at 9 months, the annualized total eGFR slope estimated over 12 months, and the change from baseline in the FACIT-Fatigue scale at 9 months will also be evaluated and safety evaluations conducted. Of note, PK and (descriptive only) efficacy analysis of the SRI population will be included in the IA if a sufficient number of participants in this population is available. Results from this IA may serve as basis for accelerated/conditional approval.

Following the IA, the study will continue in a double-blind fashion until all participants have completed the study to the 24 month visit (EOS), and at which point the potential benefits of LNP023 on slowing IgAN progression will be evaluated to support full approval of LNP023 in treating patients with IgAN. The primary objective at the Final analysis is to demonstrate the superiority of LNP023 vs. placebo in slowing IgAN progression as measured by the annualized total eGFR slope over 24 months.

## 1.2 Study objectives, endpoints and estimands

The following objectives will be evaluated at the **INTERIM ANALYSIS.**

**Table 1-1 Objectives and related endpoints at Interim Analysis**

| **Objective(s)** | **Endpoint(s)** |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for primary objective(s)** |
| • To demonstrate superiority of LNP023 vs. placebo in the reduction of proteinuria at 9 months by measuring UPCR sampled from a 24h urine collection. | • Log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months |
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To evaluate the effect of LNP023 vs. placebo on slowing eGFR decrease measured by the change from baseline in eGFR | • Change from baseline in eGFR at 9 months |
| • To assess the effect of LNP023 vs. placebo on the proportion of study participants reaching proteinuria below 1g/g of UPCR (sampled from 24h urine collection) at 9 months. | • Proportion of participants reaching UPCR (sampled from 24h urine collection)<1g/g at 9 months, without receiving CS/IS or other newly approved drugs or initiating new background therapy for treatment of IgAN or initiating Kidney Replacement Therapy (KRT). |
| • To evaluate the effect of LNP023 vs. placebo on slowing IgAN progression measured by the annualized total slope of eGFR decline over 1 year. | • Annualized total eGFR slope estimated over 12 months |
| • To assess the effect of LNP023 vs. placebo on the change from baseline to 9 months in fatigue scale measured by the FACIT-Fatigue questionnaire. | • Change from baseline to 9 months in the fatigue scale measured by the FACIT-Fatigue questionnaire. |
| • To evaluate the safety and tolerability of LNP023 compared to placebo. | • Safety endpoints (including adverse events/serious adverse events, safety |

| Objective(s) | Endpoint(s) |
|---|---|
| | laboratory parameters, vital signs ) collected from baseline to 9 months. |
| **Exploratory objective(s)** | **Endpoint(s) for exploratory objective(s)** |
| • To evaluate the effect of LNP023 vs. placebo in slowing IgAN progression in participants whose baseline proteinuria is ≥ 2g/g of UPCR sampled from a 24h urine collection. | • Log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months.<br>• Annualized total eGFR slope estimated over 12 months. |
| • To evaluate the effect of LNP023 vs. placebo on the change from baseline in health-related quality of life measured by EQ-5D-5L, PGIS and EORTC QLQ-C30 questionnaires. | • Change from baseline in the EQ-5D-5L at 9 months<br>• Change from baseline in the EORTC QLQ-C30 at 9 months<br>• Change from baseline in the PGIS severity level at 9 months |
| • To evaluate the effect of LNP023 vs placebo on the reduction of urine protein and albumin excretion by measuring UP/UA/UACR sampled from a 24h urine collection and UPCR from first morning void (FMV). | • Log-transformed ratio to baseline in total urinary protein/day, total urinary albumin/day, UACR (sampled from 24h urine collection) and UPCR (sampled from first morning void, FMV) at 9 months |
| • To explore the utility of blood and/or urine biomarkers related to treatment with LNP023. | • Selected blood and/or urine biomarkers (including but not limited to C3 and C4) related to IgAN disease progression and LNP023 treatment at 9 months. |
| • To evaluate the effect of LNP023 vs. placebo on reducing healthcare resource utilization. | • Healthcare resource utilization endpoints (including number of ER visits and IgAN-related hospitalizations) collected from baseline to 9 months. |
| • To assess the effect of LNP023 vs. placebo on the use of corticosteroid or immunosuppressant therapy (CS/IS) and/or newly approved drugs for IgAN treatment due to disease progression over 9 months. | • Proportion of participants requiring the use of corticosteroid or immunosuppressant therapy (CS/IS) and/or newly approved drugs for IgAN treatment due to disease progression assessed from baseline to 9 months<br>. |
| • Evaluate Pharmacokinetics of LNP023 in participants with SRI and potentially other participant subgroups. | • Plasma: Non-compartmental parameters related to total parent drug, including but not limited to Tmax, Cmax and AUC. |

The following Objectives will be evaluated at the **STUDY COMPLETION.**

**Table 1-2 Objectives and related endpoints at the Final analysis**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for primary objective(s)** |
| • To demonstrate superiority of LNP023 vs. placebo in slowing IgAN progression measured by the annualized total slope of eGFR decline over 24 months. | • Annualized total eGFR slope estimated over 24 months. |

| Objective(s) | Endpoint(s) |
|---|---|
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To demonstrate the superiority of LNP023 vs. placebo on delaying the time to first occurrence of a composite kidney failure endpoint. | • Time from randomization to first occurrence of composite kidney failure endpoint event, defined as reaching either<br>• Sustained ≥30% decline in eGFR relative to baseline, or<br>• Sustained eGFR <15 mL/min/1.73m², or<br>• Maintenance dialysis, or<br>• Receipt of kidney transplant, or<br>• Death from kidney failure |
| • To demonstrate superiority of LNP023 vs. placebo in the reduction of proteinuria at 9 months by measuring UPCR sampled from a 24h urine collection. | • Log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months. |
| • To demonstrate the superiority of LNP023 vs. placebo on the proportion of study participants reaching proteinuria below 1g/g of UPCR (sampled from 24h urine collection) at 9 months. | • Proportion of participants reaching UPCR (sampled from 24h urine collection) <1g/g at 9 months without receiving CS/IS or other newly approved drugs or initiating new background therapy for treatment of IgAN or initiating KRT |
| • To demonstrate the superiority of LNP023 vs. placebo on the change from baseline to 9 months in the fatigue scale measured by FACIT-Fatigue questionnaire. | • Change from baseline to 9 months in the fatigue scale measured by the FACIT-Fatigue questionnaire. |
| • To evaluate the safety and tolerability of LNP023 compared to placebo. | • Safety endpoints (including adverse events/serious adverse events, safety laboratory parameters, vital signs) collected from baseline to the EOS |
| **Exploratory objective(s)** | **Endpoint(s) for exploratory objective(s)** |
| • To evaluate the effect of LNP023 vs. placebo on the proportion of participants reaching proteinuria below 1g/g of UPCR (sampled from 24h urine collection) at 24 months. | • Proportion of participants reaching UPCR (sampled from 24h urine collection) <1g/g at 24 months without receiving CS/IS or other newly approved drugs or initiating new background therapy for treatment of IgAN or initiating KRT. |
| • Evaluate Pharmacokinetics of LNP023. | • Plasma: Non-compartmental parameters related to total parent drug, including but not limited to Tmax, Cmax and AUC.<br>Urine: Non-compartmental parameters, including but not limited to the amount excreted (Ae) and renal plasma clearance (CLr). |
| • To assess the effect of LNP023 vs. placebo on the use of corticosteroid or immunosuppressant therapy (CS/IS) and/or | • Proportion of study participants requiring the use of corticosteroid or immunosuppressant therapy (CS/IS) |

| Objective(s) | Endpoint(s) |
|---|---|
| newly approved drugs for IgAN treatment due to disease progression over 24 months. | and/or newly approved drugs for IgAN treatment due to disease progression assessed from baseline to 24 months. |
| • To explore the utility of blood and/or urine biomarkers related to treatment effect with LNP023. | • Selected blood and/or urine biomarkers (including but not limited to C3 and C4) related to disease progression and LNP023 treatment at 9 and 24 months. |
| • To evaluate the effect of LNP023 vs placebo on the reduction of urine protein and albumin excretion by measuring UPCR/UP/UA/UACR sampled from a 24h urine collection and UPCR from first morning void (FMV). | • Log-transformed ratio to baseline in total urinary protein/day, total urinary albumin/day, UACR (sampled from 24h urine collection) and UPCR (sampled from first morning void, FMV) at 9 and 24 months, and UPCR (sampled from 24h urine collection) at 24 months. |
| • To evaluate the effect of LNP023 vs. placebo on the change from baseline in health-related quality of life measured by EQ-5D-5L, PGIS and EORTC QLQ-C30 questionnaires. | • Change from baseline to 9 and 24 months in the EQ-5D-5L.<br>Change from baseline to 9 and 24 months in the EORTC QLQ-C30.<br>Change from baseline to 9 and 24 months in the PGIS severity level. |
| • To evaluate the effect of LNP023 vs. placebo on the change from baseline at 24 months in the fatigue scale measured by FACIT-Fatigue questionnaire. | • Change from baseline to 24 months in the fatigue scale measured by the FACIT-Fatigue questionnaire. |
| • To evaluate the effect of LNP023 vs. placebo on the reduction of proteinuria over the treatment period as measured by time-averaged proteinuria reduction over 24 months. | • Time-averaged proteinuria [average of UPCR values (sampled from 24h urine collection)] from baseline to 24 months. |
| • To evaluate the effect of LNP023 vs. placebo on reducing healthcare resource utilization. | • Healthcare resource utilization endpoints (including number of ER visits and IgAN-related hospitalizations) collected from baseline to 24 months. |
| • To explore whether patients experienced meaningful change in fatigue, and further feedback on FACIT-Fatigue | • Participant responses to a semi-structured interview, conducted at 9 months, focusing on the patient experience with their symptoms, in particular fatigue |

### 1.2.1 Primary estimands

#### 1.2.1.1 Primary estimand at the Interim analysis

The primary clinical question of interest at the Interim Analysis is:

What is the treatment effect of LNP023 (200 mg b.i.d oral administration) vs. placebo on proteinuria reduction as measured by UPCR (sampled from 24h urine collection) in primary IgAN patients with eGFR $\geq$ 30 mL/min/1.73m$^2$ who are on background ACEi/ARB treatment, as though corticosteroids (CS), immunosuppressant therapy (IS), other newly approved drugs,

new background therapy for IgAN or kidney replacement therapy (KRT) were not available and regardless of unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason.

The justification for targeting this treatment effect is that we wish to estimate the relative effect of LNP023 vs placebo, on top of background ACEi/ARBs and any other background treatment for IgAN, in the absence of potentially confounding effects of CS/IS, any newly approved drugs or newly initiated background therapy for IgAN treatment that are not a part of the assigned treatment strategy. Further details can be found in Table 1-3 and Section 2.5. The primary estimand at the IA is described by the following attributes:

1. Population: Primary IgAN patients with eGFR $\geq 30$ mL/min/1.73m$^2$ who are on background ACEi/ARB treatment.
2. Endpoint: log-ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months
3. Treatment of interest: the randomized treatment (the investigational treatment LNP023 200 mg b.i.d or Placebo) regardless of unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason (treatment policy).

The summary measure used is: Ratio of geometric means between groups. The summary measure of the treatment effect will also be presented on the percentage scale.

Handling of remaining intercurrent events:

- Intake of CS/IS for IgAN treatment: as though these medications were not available (hypothetical strategy).
- Intake of other newly approved drugs for treatment of IgAN: as though these medications were not available (hypothetical strategy).
- Initiation of new background therapy for IgAN treatment (during the study): as though these medications were not available (hypothetical strategy).
- Treatment discontinuation for any reason (other than the intake of CS/IS and/or newly approved medications for treatment of IgAN): ignore (treatment policy strategy).
- Initiation of KRT (i.e. dialysis or transplant as defined in Section 2.6.1.1): as though KRT was not initiated and disease continued to progress (hypothetical strategy).

**Table 1-3 Justification of handling of intercurrent events**

| Intercurrent event | Handling Strategy | Justification |
|---|---|---|
| Intake of CS/IS for IgAN treatment | Hypothetical | LNP023 would ultimately be indicated as a chronic treatment for primary IgAN patients on top of background ACEi/ARBs treatment. CS/IS have the potential to confound the interpretation of the effect of this treatment strategy especially given the placebo controlled setting of the study where participants randomized to the placebo group may require such medications more often than participants randomized in the LNP023 group. Measurements after the intake of CS/IS for IgAN treatment will be excluded from analysis and imputed via a modeling approach accounting for |

| | | |
|---|---|---|
| | | the CS/IS intake as potentially indicative of a worsening of condition (see Section 2.5.3). |
| Intake of other newly approved drugs for treatment of IgAN | Hypothetical | Same justification as for the intercurrent (I/C) event of the intake of CS/IS for IgAN treatment . |
| Initiation of new background therapy for IgAN treatment | Hypothetical | LNP023 would ultimately be indicated as a chronic treatment for primary IgAN patients on top of background (ACEi/ARBs or other) treatment. Initiation of new background therapy during the study can confound the interpretation of the treatment strategy of interest especially given the placebo controlled setting of the study where placebo group participants may initiate new background therapy more often than participants randomized in the LNP023 group. As after initiation of new background therapy for IgAN participants remain on treatment, values after the I/C will be excluded and imputed based on the participants' previous trajectory and other similar participants in the same treatment group. |
| Treatment discontinuation due to any reason (other than the intake of CS/IS and/or newly approved medications for treatment of IgAN) | Treatment policy | After a treatment discontinuation it is assumed that patient cannot continue to derive benefit. Data collection will be maintained and available measurements post-treatment discontinuation used as if they had been obtained under the treatment assigned at randomization. In case measurements are missing, these will be handled as per Section 2.5.4. |
| Initiation of KRT | Hypothetical | Following initiation of KRT, primary efficacy endpoint values can no longer be reliably collected. Thus this event has the potential to confound the interpretation of the treatment effect of interest, especially given the placebo controlled setting of the study where participants in the placebo group may require KRT more often than participants randomized in the LNP023 group. Measurements after KRT will be handled as for the I/C event of the intake of CS/IS for IgAN treatment. |

#### 1.2.1.2 Primary estimand at the Final analysis

The primary clinical question of interest at the Final analysis is:

What is the treatment effect of LNP023 (200 mg b.i.d oral administration) vs. placebo in slowing IgAN progression as measured by the annualized total eGFR slope in primary IgAN patients with eGFR $\geq$ 30 mL/min/1.73m$^2$ who are on background ACEi/ARB treatment, as though CS/IS, or other newly approved drugs or new background therapy for IgAN or KRT were not available and regardless of unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason.

The justification for targeting this treatment effect is that we wish to estimate the relative effect of LNP023 vs placebo, on top of background ACEi/ARBs or any other background treatment for IgAN, in the absence of potentially confounding effects of CS/IS, any newly approved drugs or newly initiated background therapy for IgAN treatment that are not a part of the assigned treatment strategy. Further details can be found in Table 1-3 and Section 2.5.

The primary estimand at the Final analysis is described by the following attributes:

1. Population: Same as for the primary estimand at the IA.
2. Endpoint: Annualized total eGFR slope (mL/min/1.73m$^2$/year) estimated over 24 months.
3. Treatment of interest: Same as for the primary estimand at the IA.

The summary measure used is: Difference in means between groups.

The remaining intercurrent events for the primary estimand at the Final analysis as well as their handling strategies are the same as for the primary estimand at the IA (see Table 1-3).

### 1.2.2 Secondary estimands

#### 1.2.2.1 Secondary estimands at the Interim analysis

The following secondary estimands are considered at the IA:

1) Change from baseline in eGFR at month 9, where the Population and Treatment attributes as well as strategy applied to all I/Cs are the same as described in Section 1.2.1 for the primary estimand for the IA. This implies, for example, that eGFR data following the intake of CS/IS for IgAN treatment (handled with a hypothetical strategy) would be excluded from the analysis and imputed in a conservative manner in order to reflect participants' eGFR values would continue to worsen had the I/C not occurred.

2) Proportion of participants reaching UPCR 24h levels <1 g/g at 9 months, without receiving CS/IS or other newly approved drugs or initiating new background therapy for IgAN treatment or initiating KRT. The intake of CS/IS or other newly approved drugs or initiation of new background therapy for IgAN treatment and initiation of KRT are handled via the composite strategy (i.e. as part of the Endpoint attribute) so as to capture both the benefit of the drug in terms of proteinuria reduction as well as "poor" response to treatment. The Population and Treatment attributes are the same as for the primary estimands in Section 1.2.1.

The summary measure used is: Odds ratio between groups.

Handling of remaining intercurrent events:

- Treatment discontinuation for any reason (other than the intake of CS/IS or other newly approved drugs for treatment of IgAN): ignore (treatment policy strategy)

3) Annualized total eGFR slope (mL/min/1.73m$^2$/year) estimated over 12 months. The attributes and handling strategies for this estimand are the same as for the primary estimand at the Final analysis (see in Section 1.2.1).

4) Change from baseline to 9 months in the total score of the FACIT-Fatigue questionnaire, where the Population and Treatment attributes as well as strategy applied to all intercurrent events are the same as described in Section 1.2.1 for the primary estimand for the IA. This implies, for example, that FACIT-Fatigue data following the occurrence of the I/C event of intake of CS/IS for IgAN treatment (handled with a hypothetical strategy) would be excluded from the analysis and imputed in a conservative manner in order to reflect participants scores would continue to worsen had the intercurrent event not occurred.

#### 1.2.2.2 Secondary estimands at the Final Analysis

The following secondary estimands are considered at the Final Analysis:

1) The primary estimand at the IA, namely the log-ratio to baseline in UPCR 24h at 9 months, will be examined in case of non-significance at the IA as a secondary estimand at the Final Analysis (see Section 2.6). The attributes of this estimand as well as handling strategies for remaining intercurrent events remain the same as specified at the IA. All participant data collected to the EOS will be considered in the analysis.

2) Proportion of participants reaching UPCR 24h levels <1 g/g at 9 months, without receiving CS/IS or other newly approved drugs or initiating new background therapy for IgAN treatment or requiring KRT. The attributes of this estimand as well as handling strategies for remaining intercurrent events are the same as for the respective secondary estimand at the IA.

3) The estimand for the time to reaching the first occurrence of the composite kidney failure endpoint is defined by the following attributes:

1. Population: same as for the primary estimands (see Section 1.2.1)
2. Endpoint: Time from randomization to first occurrence of reaching either sustained ≥30% decline in eGFR relative to baseline, sustained eGFR <15 mL/min/1.73m$^2$, maintenance dialysis, receipt of kidney transplant, or death from kidney failure.
3. Treatment of interest: the randomized treatment (the investigational treatment LNP023 200 mg b.i.d or Placebo) regardless of unforeseen changes in permitted/concomitant medications, intake of CS/IS or other newly approved drugs or initiation of new background therapy for IgAN treatment, or treatment discontinuation for any reason (treatment policy).

The summary measure used is: Hazard ratio between groups.

Of the intercurrent events identified in Section 1.2.1, the intake of CS/IS, newly approved drugs or initiation of new background therapy for IgAN treatment will be handled using a treatment policy strategy, so that these medications form part of the Treatment attribute. The intercurrent event of treatment discontinuation for any reason will be handled as described in Section 1.2.1 for primary estimands. Note that initiation of KRT is captured by the dialysis and kidney transplantation components of the Endpoint attribute (see Section 2.6.1).

4) Change from baseline to 9 months in the total score of the FACIT-Fatigue questionnaire, where the Population and Treatment attributes as well as strategy applied to all intercurrent events are the same as described for the respective secondary estimand at the IA. All participant data collected to the EOS will be considered in the analysis.

For all primary and secondary estimands, CS/S and newly approved drugs for IgAN (including but not limited to delayed realease budesonide and endothelin inhibitors) are outlined in CSP Section 6.2.2. Background treatment with ACE/ARB may include other background medication for IgAN started prior to randomization, see CSP Section 5

### Estimand considerations in case of COVID-19 pandemic impact

The overarching principle for primary and secondary estimands is answering questions of interest regarding the treatment effect of LNP023 vs placebo that are valid in conditions when the COVID-19 pandemic is no longer present.

Data capture and clinical evaluation activities include possible adaptations to restrictions for participant access to investigational sites in case of a new infection wave. The planned analyses in Section 12 of the CSP may be supplemented by supportive as well as sensitivity analyses if required due to the presence of a considerable amount of deviations from the normal methods of participant follow up and data capture or other pandemic-related intercurrent events.

# 2 Statistical methods

## 2.1 Data analysis general information

All analyses described in this document will be performed by Novartis. Data will be analyzed according to Section 12 of the CLNP023A2301 CSP. The most recent version of the SAS® and R software available in the statistical programming environment will be used for the analysis. Periodic safety reviews for the monitoring of safety data by the external DMC will be performed by an external analysis team and related analysis will be described in a separate DMC SAP.

In general, categorical data will be presented as frequencies and percentages in descriptive statistics. For continuous data, mean, standard deviation, median, minimum and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

### 2.1.1 General definitions

The term "**study treatment**" and/or "**study drug**" refers to the study drug dispensed during the study, that is either LNP023 as 200 mg capsules or matching placebo capsules.

The term "**date of first administration of study drug/treatment**" refers to the date of first dosing of participants with study drug/treatment during the study.

The term "**date of last administration of study drug/treatment**" refers to the date of last actual administration of any study drug/treatment in the study.

The baseline visit can take place from Day -7 to Day -4. For analysis purposes, "**Baseline**" is defined as the last available assessment (scheduled or unscheduled) prior to or at the first administration of study treatment (Day 1), which differs depending on the parameter considered (generally randomization visit or baseline visit), unless otherwise specified (e.g. see below baseline definition for eGFR and parameters based on 24hr urine collections). That means that if the measurement is not recorded as per CSP or missing at the Randomization visit, then the value at the most recent assessment prior to the first administration of study treatment will be used as *baseline*.

The following parameters will generally have the *baseline* defined as the measurement recorded at the baseline visit: ECG, parameters based on first-morning-void urine sample (i.e. UPCR FMV), Patient-Reported-Outcomes (PROs). Note that for eGFR, the baseline visit value used for stratification will be used as *baseline,* and for parameters sampled from 24h urine collection

(i.e. UPCR 24h, UACR 24h, UA 24h, UP 24h) the mean (geometric) of the two scheduled parameter values, obtained from two distinct 24 hour urine collections, will be used in the analysis as the parameter measurement for the baseline visit and thus as the baseline for the analysis.

The following parameters will generally have the *baseline* defined as the measurement recorded at the randomization visit (i.e. prior to first study treatment administration): vital signs, urinalysis (other than parameters based on 24h collection or FMV urine sample as specified above), clinical chemistry, hematology, reproductive and thyroid hormone parameters, biomarkers.

The following assessments will have their *baseline* only recorded at the screening visit:

Body Height, Vaccination, Demography, Smoking/Alcohol History, Medical History/current medical conditions and Kidney biopsy.

**"Post-Baseline"** is defined for analysis purposes to be any value collected after the "baseline" as defined above for analysis purposes.

The term **"study day"** is defined relative to the analysis reference date, which is the date of first administration of study treatment.

The *study day* for a scheduled or unscheduled visit on or after the analysis reference date is defined as:

*Study day*= (Date of Visit) – (analysis reference date) +1.

The *study day* for a scheduled or unscheduled visit before the analysis reference date is defined as:

*Study day* = (Date of visit) – (analysis reference date).

Thus the analysis reference date (date of first administration of study treatment) will be study day 1 and the date directly prior the analysis reference date will be study day −1 (there is no study day 0). In cases participants did not receive any study treatment, the randomization date will be used instead of the date of first administration of study treatment as the analysis reference date. In this case, the randomization visit date is defined as study day 1 and the date directly prior to randomization is defined as study day -1.

For participants for whom first study drug administration occurred considerably after the Randomization day (i.e. > 2 weeks), the Day 1 and Baseline visit definition will remain the same as outlined above. Post baseline visits will not be re-mapped; for instance, if the Month 1 visit is the day of first study drug intake, then the Month 1 visit will be considered as Day 1 for analysis and the value measured at the next visit will still be considered as the Month 3 value and week 2 and Month 1 visits will be considered as missing. Hence in such cases the analysis reference date will be the date of the randomization visit.

The "**on-treatment period**" lasts from the date of first administration (inclusive) of study treatment to the date of the last actual administration of any study treatment in the core CLNP023A2301 study plus 7 days or until the date of first administration of study treatment in

the REP, whichever occurs first. This is the reference period for Treatment emergent Adverse Events.

The term **"unscheduled visit"** refers to visits that occurred not as part of the CSP assessment schedule. Data collected at unscheduled visits will, in general, not be used in 'by-visit tabulations' or graphs, but they will be included in analyses of safety parameters based on all post-baseline values such as summary statistics of clinically notable abnormalities of laboratory data. For efficacy evaluations, measurements from unscheduled visits will generally not be used, unless where otherwise specified. All data collected at both scheduled and unscheduled visits will be included in data listings.

**"Completion":** a participant will be considered to have completed the study:

- For participants that permanently discontinue treatment more than 7 days prior to the EOS visit: when they complete the EOS visit in the study.
- For participants who enroll in the REP directly (i.e. Day 1 of the REP is the same day as the EOS visit of the study): when they complete the EOS visit in the study.
- For all other participants: when they complete the safety follow-up visit in the study.
    - For participants who enroll in the REP within 7 days of the EOS visit in CLNP023A2301 study, the Day 1 (first study drug administration) visit of the REP will serve as the safety follow up visit for CLNP023A2301.

  The "**last contact**" date will be derived for participants randomized in the study and not known to have died at the analysis cut-off using the maximum complete date of the following:

    - All assessment dates (e.g. vital signs assessment, assessment date in third-party data such as central laboratory etc.)
    - Medication start and end dates (if not imputed), including study medication, concomitant medications, and therapies administered after study treatment discontinuation.
    - AE start and end dates (if not imputed).
    - Date of the last Disposition (including e.g. lost to follow-up) collected in the Disposition eCRF.
    - Date of last visit after randomization in the study.
    - Date of withdrawal of consent collected (in case of withdrawal from study) in the Withdrawal of Consent eCRF.

## 2.2 Analysis sets

The Screening set (SCR) will include all subjects screened during the study. If a subject has been screened multiple times then the subject should be included for his/her last screening. The purpose of the SCR set is to describe the number of screen or baseline failures. Screen or baseline failures are subjects included in the SCR set but not in the Randomized Analysis set.

The Randomized Analysis Set (RAS) consists of all randomized participants. This analysis set will not be used for any analyses, and is solely intended for providing complete information on how participants were randomized.

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to, taking into account the strata in which they were included during the randomization procedure. Mis-randomized participants, that is participants who were randomized incorrectly and did not receive any study drug will be excluded from this set. This will be the analysis set used for all efficacy analyses.

Note that the primary analysis at the IA will be conducted when approximately 250 participants in the Main Study population have completed the Month 9 visit. As such, all efficacy analyses (unless otherwise specified) will include the first 250 Main study population participants in the FAS who should have completed the Month 9 follow up prior to the analysis cut-off. This subset of the FAS will be referred to as **IA-FAS** for ease of reference in the document and in Tables, Figures and Listings (TFLs).

The Safety Set (SAF) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

**Table 2-1 Subject Classification**

| Analysis Set | Criteria that cause subjects to be excluded |
|---|---|
| SCR | Not having signed the Informed Consent |
| RAS | Not randomized/subject with no randomization number |
| FAS | Not in RAS;<br>Participant mis-randomized i.e. mistakenly randomized and no double-blind study drug given |
| SAF | No double-blind study drug taken |

### 2.2.1 Subgroup of interest

Subgroup analyses will be performed for the FAS (for the IA-FAS at the IA) or SAF depending on the parameters under consideration to explore the consistency of treatment effects and safety profile between the subgroups and the overall population. Subgroup analyses will be performed on the Main study population which forms the basis for the primary and secondary efficacy analyses.

Table 2-2 lists subgroup analysis planned for this study. The details about the variables for

which subgroup analyses will be performed are given in the corresponding analysis sections. Additional subgroups may be formed later for regional or country-wise analyses. Such additional exploratory subgroup analyses will not be captured in the CSR.

The following subgroup analyses are planned:

**Table 2-2 Specification of subgroups**

| Subgroup | Primary and selected Secondary Efficacy analysis | Selected Safety analysis |
|---|---|---|
| Region*<br>• North America<br>• Latin/Central America<br>• Asia/Pacific<br>• Europe and Other | x | |
| Geographic region**<br>• Asia<br>• Non-Asia | x | |
| Baseline UPCR***<br>• < 2 g/g [226 mg/mmol]<br>• ≥ 2 g/g [226 mg/mmol] | x | |
| CCI | | |
| Baseline eGFR<br>• 30-<45 mL/min/1.73m$^2$<br>• ≥45 mL/min/1.73m$^2$ | x | x |
| Age group<br>• <45 years<br>• ≥45 years | x | |
| Sex<br>• Male<br>• Female | x | |
| Race<br>• White<br>• Asian<br>• Other‡ | x | |
| Ethnicity‡<br>• Hispanic or Latino<br>• Non Hispanic or Latino | x | |

| | | |
|---|---|---|
| Baseline Hematuria<br>• ≥1+<br>• Negative/Trace | x | |
| Baseline SGLT2i use<br>• Yes<br>• No | x | |
| MEST-C score†:<br>• M score<br>  • M1<br>  • M0<br>• E score<br>  • E1<br>  • E0<br>• C score<br>  • C1 or C2<br>  • C0<br>• M1 or E1 or C1/C2<br>  • Yes<br>  • No<br>• M1 and E1 and C1/C2<br>  • Yes<br>  • No<br>• S score<br>  • S0<br>  • S1<br>• T score<br>  • T0<br>  • T1<br>  • T2 | x | |

**North America:* *United States of America, Canada*

***Latin/Central America****: Argentina, Brazil, Chile, Colombia, Mexico.*

***Asia/Pacific****: China, India, Japan, Malaysia, Singapore, Korea (the Republic of), Taiwan, Thailand, Vietnam.*

***Europe & Other:*** *Australia, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Slovakia, Slovenia, South Africa, Spain, Sweden, United Kingdom, Czech Republic, Hungary, Russian Federation, Turkey, Israel.*

****Asia:*** *China, India, Japan, Malaysia, Singapore, Korea (the Republic of), Taiwan, Thailand, Vietnam.*

***Non-Asia:*** *Argentina, Australia, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, Norway, Russian Federation, Slovakia, Slovenia, South Africa, Spain, Sweden, Turkey, United Kingdom, United States of America.*

*****baseline UPCR as measured by the mean (geometric) of two 24h urine collections*

ǂ*Other: Black or African American, Native Hawaiian/ Other Pacific Islander, American Indian/Alaska Native, or Unknown.*

ǂǂ *participants with ethnicity not reported or unknown will not be considered.*

†*Based on qualifying biopsy as per inclusion criteria.*

## 2.3 Patient disposition, demographics and other baseline characteristics

### 2.3.1 Patient disposition

The frequency and percentage of subjects screened, entered in the Run-in period, in the Run-in [applicable at the IA only] and randomized will be provided. In addition, the reasons for screen failure and baseline failure, derived from the Disposition and/or Inclusion/Exclusion criteria eCRF, will be provided. For subjects screened more than once, the data from the last screening visit will be used in the summaries. The SCR will be used for the above analyses.

The frequency and percentage of participants in the FAS, who completed the study, who permanently discontinued study drug, and who discontinued from the study will be summarized overall and by treatment group; the primary reason for study discontinuation will be similarly summarized.

The duration of double-blind follow-up, defined as the time from the randomization date to the first out of the participant's study completion date (or analysis cut-off date e.g. for the IA whichever occurs earlier), the participant's death date or the date of last contact (defined in Section 2.1.1), will be summarized via means of descriptive statistics by treatment group, overall and by population separately. This will be provided for the FAS set.

The time from randomization to permanent treatment discontinuation (excluding discontinuation due to death) will graphically be displayed by treatment group for the FAS using a Kaplan-Meier plot, overall and by population separately. Participants who did not permanently discontinue treatment will be censored at the Month 24 visit or analysis cut-off date (e.g. for the IA), whichever occurs earlier.

The number and percentage of participants will be summarized by protocol deviation category, overall and by treatment group, for the RAS. Participants with multiple protocol deviations in a category will only be counted once at each level of summarization. Criteria defining protocol deviations are provided in the Data Quality Plan.

The frequency and percentage of randomized participants included in the analysis sets defined in Section 2.2 will be presented overall and by treatment group for the RAS, with the exception of summary statistics of participants screened and screen failed (or baseline failed as appropriate) which will be on the SCR set.

The frequency and percentage of participants enrolled and randomized per region and country will be presented descriptively for the RAS.

Apart from summary statistics based on the SCR set, participant disposition will be presented overall and for the Main study and SRI populations separately.

At the IA, outputs provided on the FAS will also be produced on the IA-FAS.

### 2.3.2 Demographics and other baseline characteristics

The FAS will be used for the analyses in this section; at the IA, these analyses will also be done on the IA-FAS.

The following demographic and baseline characteristics variables, including disease characteristics and medical history at baseline, will be summarized descriptively for all participants and by treatment group, for the Main study and SRI populations separately; additional variables may be included if needed; selected demographic and baseline characteristics will be similarly listed together with the efficacy data.

Categorical data, including all subgroup variables listed in Table 2-2, will be presented as frequencies and percentages in descriptive statistics. For continuous data, n, mean, standard deviation, median, Q1 ($25^{th}$ percentile), Q3 ($75^{th}$ percentile), minimum and maximum will be presented.

- Age (years)
- Age groups (<45 vs ≥45 years, 18-<65, ≥65-<85 vs ≥85 years)
- Sex
- Race (White, Black/African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native)
- Geographic region (Asia vs. non Asia)
- Region of enrollment (as defined in Table 2-2)
- Ethnicity
- Weight [kg]
- Body mass index (BMI) [$kg/m^2$]
- Smoking and vaping history
- Alcohol history
- Pulse rate [bpm]

- Systolic Blood Pressure (SBP) [mmHg]
- Diastolic Blood Pressure (DBP) [mmHg]
- Baseline UPCR 24h [g/g]
- Baseline UPCR 24h category (<2 g/g [226 mg/mmol] vs. ≥2 g/g [226 mg/mmol])
- [redacted]
- Baseline UP-24h [g/d] category (<2; ≥2 to ≤3.5 vs >3.5 g/day)
- Baseline UPCR FMV [g/g]
- Baseline eGFR [mL/min/1.73m$^2$]
- Baseline eGFR category (30-<45 mL/min/1.73m$^2$ vs. ≥45 mL/min/1.73m$^2$)
- ACEi/ARB use at baseline
- SGLT2i use at baseline
- Prior treatments for IgA nephropathy
- Time from kidney biopsy to baseline (years)
- Relevant medical history and current medical conditions at baseline including but not limited to:
    - Hypertension (Yes/No)
    - Diabetes Type II (Yes/No)
    - Protocol required vaccination history

Geographic region information will be further summarized by sex. Additional ACEi/ARB use information, including whether the dose received is the maximally approved per local regulation or the maximally tolerated, will also be summarized. BMI will be calculated as weight (kg)/height$^2$ (m$^2$) from the collected height at Visit 1 (Screening Visit) and weight at baseline (as defined in Section 2.1.1). Baseline UPCR 24h refers to UPCR as measured by the mean (geometric) of two 24h urine collections at the Baseline Visit. Pulse rate, SBP and DBP measured in sitting position will be summarized.

Other relevant medical history and current medical conditions at baseline will be summarized separately by system organ class (SOC) and preferred term (PT), for all participants and by treatment group, for the Main study and SRI populations separately. Kidney biopsy information per the Oxford classification will be similarly summarized.

## 2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

### 2.4.1 Treatment of interest

The “treatment of interest” for the two treatment arms is the investigational treatment LNP023 200 mg b.i.d or Placebo respectively, regardless of unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason (treatment policy). In this case, the intake of CS/IS or other newly approved drugs or newly initiated background therapy for IgAN treatment does not form part of the treatment attribute.

Note that the above "treatment of interest" definition applies to all primary and secondary estimands, apart from the estimand for the composite kidney failure endpoint for which the "treatment of interest" is defined as follows:

the randomized treatment (the investigational treatment LNP023 200 mg b.i.d or Placebo) regardless of unforeseen changes in permitted/concomitant medications, intake of CS/IS or other newly approved drugs or initiation of new background therapy for IgAN treatment, or treatment discontinuation for any reason (treatment policy).

### 2.4.2 Study treatment

The Safety set will be used for the analyses below, unless otherwise specified. Descriptive statistics will be provided for the Main study and SRI populations separately.

The "**duration of double-blind treatment** will be computed as the time from the date of first study treatment administration to the minimum of the following:

- Date of the last actual administration of any study treatment in the core CLNP023A2301 study
- Date before first administration of study treatment in the REP
- Date of participant's death

Descriptive statistics of the double-blind treatment duration (in weeks) will be provided. Additionally, the frequency and percentage of participants will be provided by cumulative treatment duration:

- ≥4 weeks
- ≥12 weeks
- ≥6 months
- ≥9 months
- ≥12 months
- ≥18 months

The overall patient-years on-treatment will be summarized by treatment group. The overall patient-years on treatment will be computed based on the duration of treatment (in days) as follows:
Overall patient-years= $\sum_{i=1}^{n} double - blind\ treatment\ duration_i\ /365.25$,
where n is the total number of subjects in the SAF.

The **duration of exposure** to study treatment will be computed and summarized as the duration of double-blind treatment, but excluding temporary treatment interruptions. The minimal duration of interruption defined for exclusion from the duration of exposure is one full day without any dose taken.

The duration of exposure will be the basis for the dose intensity and relative dose intensity computation. The **dose intensity** (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the **relative dose intensity** (computed as the ratio of dose intensity and planned dose intensity so that for a participant receiving all doses as planned it is equal to one) will be summarized by means of descriptive statistics. The planned dose intensity for participants on LNP023 200 mg b.i.d will be 400 mg/day.

### 2.4.3 Prior, concomitant and post therapies

Analyses in this section will be based on the SAF, unless otherwise specified. Descriptive statistics will be provided for the Main study and SRI populations separately.

Prior medications and significant non-drug therapies are defined as any medications taken and stopped or significant non-drug therapies performed at least a day prior to the start of study treatment (Day 1).

Prior medications' tabulations will be further split into tabulations of medications taken before study enrollment, defined as any medications taken and stopped at least a day prior to the screening visit, and tabulations of medications taken during the run-in, defined as any medications taken at least once at or after the screening visit and stopped at least a day prior to the start of study treatment (i.e. Day 1).

Concomitant medications and significant non-drug therapies are defined as any medications taken at least once or significant non-drug therapies performed at or after the start of study treatment (i.e. with end date on or after Day 1, ongoing at EOS or with missing end date and start date prior to the end of study treatment).

Medications and significant non-drug therapies that started prior and were also continued after the start of study treatment (Day 1) will be considered Concomitant.

Prior or concomitant medications will be summarized in separate tabulations by treatment group based on the latest version of the coding dictionary (NovDTD based on WHODDE).Medications will be presented in alphabetic order, according to the Anatomical Therapeutic Chemical (ATC) classification system and by preferred term (PT), apart from medications taken before study enrollment that will be summarized by ATC only. Tables will show the number and percentage of participants receiving at least one drug of a particular PT and at least one drug in a particular ATC class. Prior or concomitant significant non-drug therapies will be similarly summarized according to the System Organ Class (SOC) and PT.

In addition, treatments received for IgAN prior to study enrollment (screening visit) and post-treatment medications will be likewise summarized. Post-treatment medications are defined as those which started after the last day of double-blind treatment duration (see Section 2.4.2).

A categorical summary of participants' protocol required vaccination history (as captured by the corresponding eCRF) by vaccine serogroup/polyvalent type will be provided by treatment group. A listing of protocol required vaccinations (with booster vaccinations received by participants any time during the study flagged) will also be provided.

Information on the ACEi/ARB use at baseline (as captured in the ACEi/ARB treatment eCRF), including reasons for ACEi/ARB intolerance or intolerance of maximally approved ACEi/ARB dose per local regulations, will be listed; at the IA, the listing will be based on the IA-FAS. Furthermore, certain classes of prior and concomitant medications, including but not limited to the following, will be summarized separately at the time of randomization and during the double-blind period:

- ACE/ARB or renin inhibitors
- Diuretics
- hydroxychloroquine
- Fish oil

- SGLT2 inhibitors

At the IA, the summaries of the above medications for the Main study population will be provided for the IA-FAS and FAS for the SRI. In addition, the above medications will be separately summarized during the double-blind period for participants of Asian ethnicity in the Main study population.

Descriptive statistics for background IgAN medications including the number and percentage of participants with a considerable dose change in their background IgAN medications (i.e. ≥50% change compared to baseline maintained for ≥14 days), including but not limited to ACEi/ARB and SGLT2i, during the double-blind treatment period will be provided. A participant with multiple qualifying dose changes will only be counted once in the tabulation. The time from baseline to first occurrence of a considerable dose change may also be graphically displayed by treatment group using a Kaplan-Meier plot, for the Main Study and SRI populations separately. Participants who did not experience a qualifying dose change will be censored at the Month 24 visit, date of last contact or analysis cut-off date (e.g. for the IA), whichever occurs earlier. At the IA, these outputs related to background IgAN medications will be provided for the IA-FAS.

The precise definition of the above medications will be provided in a separate document (including ATC and WHO drug code).

## 2.5 Analysis of the primary objectives/estimands

The primary analysis at the IA will be conducted when approximately 250 participants in the Main Study population have completed the Month 9 visit.

The final analysis will be conducted on all participant data at the time the trial ends. Study completion is defined as when the last participant finishes their End of Study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, the safety follow-up has been completed (as applicable) or, in the event of an early study termination decision, the date of that decision.

The aim of the primary estimand at the IA is answering the primary clinical question of interest in terms of proteinuria reduction (see Section 1.2.1) in order to support an accelerated/conditional approval submission.

The aim of the primary estimand at the final analysis is answering the primary clinical question of interest in terms of slowing IgAN progression (see Section 1.2.1) in order to support a full approval submission.

### 2.5.1 Primary endpoints

The **primary endpoint at the IA** is the log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months. The log-transformation used refers to the natural log (base on e).

The **primary endpoint at the final analysis** is the annualized total eGFR slope (mL/min/1.73m$^2$/year) estimated over 24 months.

Handling of intercurrent events is provided in Section 2.5.3. A tabular overview of the estimands related to the primary endpoints is given in the Appendix. The primary efficacy

analyses will consider the Main study population only (with the exception of descriptive statistics provided in the SRI population as well on the FAS) and will be based on the IA-FAS at the IA and the FAS at the final analysis (defined in Section 2.2).

Randomization strata will be based on the randomization stratification factors, as assigned in IRT, of geographic region (Asia vs. non-Asia), baseline UPCR (< 2 g/g [226 mg/mmol] vs. ≥ 2g/g [226 mg/mmol]) as measured by the mean (geometric) of two 24hr urine collections, and baseline eGFR (30-<45 mL/min/1.73m$^2$ vs. ≥45 mL/min/1.73m$^2$). For the SRI population, only the geographic region stratification factor is applicable.

Descriptive statistics for the primary endpoints (absolute value and ratio or change to baseline for UPCR 24h and eGFR respectively) will be provided by treatment group and timepoint, for the Main study and SRI populations separately.

### 2.5.2 Statistical hypothesis, model, and method of analysis

#### 2.5.2.1 Primary analysis at the IA

The following hypothesis will be tested at the one-sided 0.5% level to address the primary objective at the time of IA:

The comparison between LNP023 and placebo is defined as a one-sided hypothesis.

$H_0$: $\mu_{LNP023} - \mu_{Placebo} \geq 0$ versus $H_A$: $\mu_{LNP023} - \mu_{Placebo} < 0$

where $\mu_{LNP023}$ is the mean of the log-transformed ratio to baseline of UPCR 24h at the Month 9 visit in the LNP023 treatment arm and $\mu_{Placebo}$ is the corresponding mean in the placebo arm.

Statistical analysis will be carried out using a Mixed Model of Repeated Measures (MMRM) (following the imputation approach to handle intercurrent events described in Section 2.5.3) for the log ratio to baseline in UPCR 24h.

This model will have treatment, timepoint (as a categorical variable), randomization strata as fixed effects, treatment*timepoint and timepoint*log(baseline UPCR 24h) as interaction terms and baseline log (UPCR 24h) as a fixed covariate. The correlations between visits (aka. timepoints) within subjects will be modelled using an unstructured covariance matrix. In case of non-convergence issues, the Autoregressive (AR(1)) covariance structure will be employed in the first instance; further steps in case issues persist are described in the Appendix. The Kenward-Roger adjustment for degrees of freedom will be used.

The primary analysis will include all UPCR 24h values collected from baseline up to and including the Month 9 visit or up to the intake of CS/IS and/or other newly approved drugs for treatment of IgAN, whichever occurred earlier. Measurements following the intake of such medications will be imputed so as to reflect their intake is indicative of a poor response and UPCR 24h levels would deteriorate had these medications not been received (see Section 2.5.3 for detail). A hypothetical strategy will also be followed for values collected after the initiation of new background therapy for IgAN treatment and initiation of KRT (see Section 2.5.3 for detail).

The mean difference between LNP023 versus placebo (and its 95% confidence interval) will be calculated for the 9 month timepoint. This will be back-transformed so that the ratio of geometric means (LNP023 vs. placebo) is presented for the 9 month timepoint together with the two-sided 95% confidence interval and one-sided p-value for the hypothesis test. The study will be considered positive at the IA if the one-sided p-value for the hypothesis test performed is <0.005. The percent (%) reduction in UPCR of LNP023 vs placebo will also be presented for the 9 month timepoint.

The model estimated geometric mean of the ratio to baseline (and respective two-sided 95% CI) will be graphically presented over time by treatment group. The model estimated ratio of geometric means (LNP023 vs. placebo) will also be graphically presented (together with the respective two-sided 95% CI) over time.

At each visit where UPCR 24h is collected, the mean (geometric) of two UPCR 24h values obtained from two distinct 24 hour urine collections will be used in the analysis as the UPCR 24h measurement for that visit. In case only one value is available, that value will be instead used in the analysis. As defined in Section 2.1.1, the baseline for the analysis is the UPCR 24h measurement for the Baseline visit.

A listing of selected efficacy information will be produced; this may include (but is not limited to) the observed UPCR 24h measurements from baseline to Month 9 (included) and for the participants with an I/C, whether they took place post the first I/C or the first I/C handled with a hypothetical strategy. Diagnostic plots of participant profiles including UPCR values pre and post imputation as well as the reason for imputation may be also produced.

#### 2.5.2.2 Primary analysis at the Final analysis

The following hypothesis will be tested upon study completion:

The comparison between LNP023 and placebo is defined as a one-sided hypothesis.

$H_0$: $\beta_{LNP023} - \beta_{Placebo} \leq 0$ versus $H_A$: $\beta_{LNP023} - \beta_{Placebo} > 0$

where $\beta_{LNP023}$ is the mean annualized total slope of eGFR decline in the LNP023 treatment arm and $\beta_{Placebo}$ is the mean annualized total slope in the placebo arm. It is assumed that no acute hemodynamic effects on eGFR will be observed since participants will have been on a stable dose of background ACEi/ARB (or any other background) treatment during the study run-in phase.

The overall study Type I error will be controlled at one-sided 2.5%. The one-sided $\alpha$ to be used for the final analysis will be adjusted for multiplicity of testing according to the testing procedure described in Section 2.6.

Statistical analysis will be carried out using a longitudinal mixed effects model (following the imputation approach to handle intercurrent events described in Section 2.5.3) including the following fixed effects: treatment and randomization strata as factors and time (from randomization) as a continuous covariate. The treatment-by-time interaction (total slope) will also be fitted as a fixed effect. Subject-level intercept and slope (time) will also be included in the model as random effects with a common unstructured covariance matrix. This model allows the intercept and the slope (rate of change) to vary for each subject.

The above model can be mathematically described as follows:

$y_{ij} = (\alpha_{Placebo} + \beta_{Placebo}\, t_{ij})(1-z_j) + (\alpha_{LNP023} + \beta_{LNP023} t_{ij})z_j + \gamma_1 x_{1j} + \gamma_2 x_{2j} + \gamma_3 x_{3j} + u_{0j} + u_{1j}\, t_{ij} + e_{ij}$,

$= \alpha_{Placebo} + \beta_{Placebo}\, t_{ij} + [(\alpha_{LNP023} - \alpha_{Placebo}) + (\boldsymbol{\beta_{LNP023} - \beta_{Placebo}})t_{ij}]z_j + \gamma_1 x_{1j} + \gamma_2 x_{2j} + \gamma_3 x_{3j} + u_{0j} + u_{1j}\, t_{ij} + e_{ij}$,

where,

- $y_{ij}$ =eGFR for the j-th subject, j=1, 2,…, N at timepoint i, i=1,..,T,
- $t_{ij}$ the i-th timepoint for the j-th patient.
- $\beta_{LNP023}$ and $\beta_{Placebo}$ correspond to the annual eGFR rate of decline for the LNP023 and Placebo groups respectively.
- $\alpha_{Placebo}$ and $\alpha_{LNP023}$ are the fixed intercept (initial eGFR at baseline) for the LNP023 and Placebo group respectively.
- $z_j$ is the treatment group indicator variable $\in\{0,1\}$,
- $x_{1j}$ is the *geographic region stratum indicator,* $x_{2j}$ the *baseline UPCR category stratum indicator,* $x_{3j}$ the *baseline eGFR category stratum indicator,* with $\gamma_1$-$\gamma_3$ the corresponding coefficients.
- two subject-level random effects terms (intercept and slope) following a Bivariate zero-mean normal i.e. $\begin{pmatrix} u0j \\ u1j \end{pmatrix} \sim N(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2_{u0} & \\ \sigma_{u01} & \sigma^2_{u1} \end{pmatrix})$,
- $e_{ij}/u_{0j}, u_{1j}$ are conditionally independent residual error terms ~N(0, $\sigma_e^2$).

The model further assumes uncorrelated random effect terms for any pair of individuals j and j´. In case of non-convergence issues, the same model will be used but excluding the fixed effects terms for the stratification factors (see Appendix).

The primary analysis will include all eGFR values (measured at the central lab for scheduled and unscheduled visits) from baseline up to and including Month 24 or up to the occurrence of I/C handled with a hypothetical strategy (e.g. intake of CS/IS and/or other newly approved drugs for treatment of IgAN). The handling of measurements following such I/C events in the analysis is the same as for the primary estimand at the IA (see Section 2.5.3). As defined in Section 2.1.1, the baseline for the analysis is the eGFR value for the Baseline visit.

The treatment difference will be presented in terms of the difference between groups in the estimated mean annualized total slope ($\beta_{LNP023}$- $\beta_{Placebo}$) of eGFR decline (mL/min/1.73m$^2$ per year), together with the two-sided 95% confidence interval and 1-sided p-value.

A listing of selected efficacy information will be produced; this may include (but is not limited to) the observed eGFR measurements from baseline onwards and for the participants with an I/C, whether they took place post the first I/C or the first I/C handled with a hypothetical strategy. Diagnostic plots of participant profiles including eGFR values pre and post imputation as well as the reason for imputation may be also produced.

### 2.5.3 Handling of intercurrent events

The remaining intercurrent events (I/C) for the primary estimands at IA and Final analysis are the same and will be handled in the statistical analysis in line with the strategies described in Section 1.2.1 as follows:

- **Intake of corticosteroid or immunosuppressant therapy (CS/IS) for treatment of IgAN:** Values after the intake of CS/IS for treatment of IgAN will be excluded from the analysis (set to "missing"). The "jump-reference"("J2R") imputation approach ([Carpenter et al 2013][Kenward 2015]) will be used to impute values after the occurrence of this I/C event for participants in the LNP023 arm. Under this approach, values after the intake of such medications in the LNP023 group will be imputed assuming that a participant's mean profile follows that of placebo participants that remain in the study (i.e. the placebo group is used as the "reference" group) **(hypothetical strategy)**.
  - In more detail, values following this I/C are imputed for LNP023 participants assuming the joint distribution of their outcome data, before and after the I/C, is multivariate normal (MVN) with mean vector from the LNP023 group up to the occurrence of the I/C, and a mean vector following that observed for the reference group after the I/C. The covariance matrix matches that of LNP023 group for values prior to the I/C and that of the "reference group" for the conditional components of the values after the I/C, given the values before the I/C. Values for the placebo group will be handled under the Missing-At-Random (MAR) assumption.
  - For the analysis of UPCR 24h, the imputation will be implemented using reference based imputation approaches, for detail see [Carpenter et al 2013] and [Cro et al 2020], and for the analysis of eGFR slope, using a longitudinal mixed effects model in line with the corresponding primary analysis model. A large number of imputed datasets will be created, with their number chosen based on computational feasibility (but at least 200). Each imputed dataset will be analyzed using the analysis models described in Section 2.5.2 and the results will be combined using Rubin's rules. Further detail on the technical implementation is provided in Section 5.2.3 of the Appendix.
- **Intake of other newly approved drugs for treatment of IgAN:** values following the intake of such medications will be handled following the same principles outlined for the intake of CS/IS for IgAN treatment in order to reflect disease worsening **(hypothetical strategy)**.
- **Initiation of new background therapy for IgAN treatment**: values following the initiation of such therapies during the study will be handled under a MAR assumption for participants in the LNP023 group. As following the initiation of new background therapy for IgAN participants continue to receive the study treatment allocated, this approach aims to reflect that had the new background therapy not been available, participant values would be akin to those of other similar (e.g. in terms of previous measurement history) LNP023 group participants that remain in the study. Values for the placebo group will similarly be handled under the MAR assumption **(hypothetical strategy)**.
- **Treatment discontinuation for any reason (other than the intake of CS/IS or other newly approved drugs for treatment of IgAN):** UPCR 24h and eGFR measurements after discontinuation of study treatment will be collected and used in the analysis **(treatment policy strategy)**.
- **Initiation of kidney replacement therapy (KRT) i.e. dialysis or transplant as defined in** Section 2.6.1.1**:** the "J2R" imputation approach will be used to impute values

after initiation of KRT, in a similar fashion as for the I/C event of the intake of CS/IS for treatment of IgAN **(hypothetical strategy)**.

The 1st I/C handled with a hypothetical strategy will be taken as the basis for imputation. Note that in case two I/Cs handled with a hypothetical strategy occur on the same date, imputation will be done for the I/C handled under the most conservative assumption (i.e."J2R"). In cases where the 1st I/C is treatment discontinuation and this results to missing data prior to the occurrence of a I/C handled with hypothetical strategy, imputation will follow the steps in Section 2.5.4. To better understand the frequency/impact of intercurrent events, descriptive statistics for participants who had an intercurrent event impacting the primary estimands will be provided by treatment group over time, separately for each of the two primary estimands. Graphical displays (e.g. timelines or swimmer plot of I/C occurrence) may also be considered.

### 2.5.4 Handling of missing values not related to intercurrent event

In cases that participants who discontinue treatment for any non-administrative reason (see Section 5.2.2 for list of reasons) have missing data due to study withdrawal, data will be imputed so as to indicate a worsening in condition (i.e. "J2R" approach for participants in the LNP023 group and under MAR for the Placebo group). This imputation approach aims to be consistent with the inclusion of all data following treatment discontinuation in the analysis under a treatment policy approach.

The longitudinal models used for both primary estimands implicitly impute missing data under a MAR assumption (i.e. given the observed data [responses and covariates] missingness does not depend on the unobserved responses). Missing data linked to unavailability of 24h urine samples or intermittent missing eGFR measurements due to administrative reasons will be implicitly handled under the primary analysis models (i.e. MAR assumption) or imputed under MAR.

Missing primary endpoint values due to protocol deviations or other issues related to a pandemic are not anticipated as measures have been put in place in the CSP, where possible, to allow for the protocol assessments to be conducted (e.g. off-site visits). In case considerable missing data do occur for such reasons, values will be imputed under a model taking into account the participant's prior measurement history, important baseline covariates as well as participant status at the time of and the reasons for missingness. Missing data linked to unavailability of measurements due to administrative reasons (e.g. visit could not take place due to lockdown) will be implicitly handled under the primary analysis models (i.e. MAR assumption).

### 2.5.5 Sensitivity analyses

Sensitivity analyses to test assumptions made in the primary analyses in terms of considering alternative imputation approaches in the LNP023 arm following the intake of CS/IS and/or newly approved drugs for treatment of IgAN will be considered. These will include:

- Sensitivity analysis 0.1: imputation using the "*copy-reference*" approach ("CR") in the LNP023 arm in order to reflect the assumption that participant profiles will slowly regress back to the mean of the placebo arm following the occurrence of both these I/C events.

This is achieved by imputing post-I/C values assuming the joint distribution of an LNP023 participant's outcome data pre- and post-I/C is MVN with mean vector and covariance matrix corresponding to that of the reference arm, regardless of when the I/C occurred [Cro et al 2020].

- Sensitivity analysis 0.2: imputation under the MAR assumption following the I/C event of the intake of newly approved drugs in the LNP023 arm i.e. values post-I/C will be excluded/set as "missing" and handled with a MAR assumption. This reflects the assumption that the intake of a newly approved drug is not necessarily associated with worsening in condition, but rather commercial availability of an approved treatment for IgAN and had the new approved drug not been available, participant values would be akin to those of other similar (e.g. in terms of previous measurement history) LNP023 arm participants that remain in the study.

A tipping point analysis will be conducted as follows:

- Sensitivity analysis 0.3: For UPCR 24h, imputation under the MAR assumption will firstly be done following the intake of CS/IS for IgAN treatment and newly approved drugs for treatment of IgAN in the LNP023 and placebo arms respectively i.e. values at all timepoints post-I/C will be excluded/set as "missing" and imputed under MAR. Next, a value of $\delta$ will be added to all imputed log(UPCR 24h) values post I/C in the LNP023 arm prior to analyzing the multiply imputed data. This approach assumes that the marginal mean of imputed participant values is worse by some amount $\delta$ at each time point after intake of CS/IS or newly approved drugs for IgAN compared to the marginal mean of participants with observed data at the same time point. The "penalty" term $\delta$ will be implemented as additive on the imputed log(UPCR 24h) values. This will reflect a multiplicative "penalty" on the back-transformed UPCR scale, starting from 1 and increasing until 2 (i.e. 100% worsening) in increments of 0.1.

A tipping point analysis, varying the imputation assumption for the LNP023 arm from MAR to increasingly worsening assumptions, will be similarly implemented for the primary analysis of eGFR slope at the Final analysis. Results may also be graphically presented.

An additional sensitivity analysis will be done to test the primary analyses assumptions regarding the imputation approaches in the LNP023 arm following the I/C events of intake of CS/IS, newly approved drugs or initiation of new background for IgAN treatment:

- Sensitivity analysis 0.4: the "J2R" approach will be used to impute values following the aforementioned I/C events in cases where the I/C is judged by the investigator to have occurred due to disease progression (as recorded on the Concomitant Medications eCRF). In cases where the investigator did not consider disease progression to have occurred, a MAR assumption will be instead adopted. A MAR assumption is made in the Placebo arm regardless of investigator judgement; this assumption is conservative as it would be plausible to assume that placebo group participants with such I/Cs judged by investigators to have occurred due to disease progression may progress in a worse manner compared to other placebo participants. A tabular overview of the primary estimands and related sensitivity analyses is also given in the Appendix.

### Sensitivity analyses applicable to the primary analysis at the final analysis

Additional sensitivity analyses to those described above will be done only for the primary analysis at the Final analysis.

A sensitivity analysis will be done to assess any impact on the analysis of therapies which may be used as background for IgAN, have an impact on eGFR (e.g. acute decline due to SGLT2i initiation) but may increasingly be initiated in the study for other indications (e.g. SGLT2i initiated for Diabetes):

- Sensitivity analysis 0.5: the initiation of new background therapy will be considered as I/C and values following will be excluded/set as "missing" and handled under a MAR assumption for both the LNP023 and Placebo groups regardless of the reason the medication was given (as recorded on the Concomitant Medications eCRF).

A sensitivity analysis will be conducted to assess the choice of the imputation model:

- Sensitivity analysis 0.6: the imputation of values (either related to I/C handling or missingness) will be handled using an MMRM (in a similar fashion to Secondary estimand 1 at the IA, see Section 2.6.3) rather than the longitudinal mixed effects model used for the primary analysis.

A sensitivity analysis will be conducted varying the assumption for missing data imputation:

- Sensitivity analysis 0.7: all missing values will be handled under a MAR assumption for both the LNP023 and Placebo arms.

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[redacted]

### 2.5.6 Supplementary analyses

In addition to the detailed description below, a tabular overview of the supplementary estimands is given in the Appendix (Table 5-1 and Table 5-2).

#### 2.5.6.1 Supplementary estimands at the Interim analysis

**Supplementary estimand 1**

A supplementary clinical question of interest at the IA is: what is the treatment effect of LNP023 vs. placebo on proteinuria reduction as measured by UPCR (sampled from 24h urine collection) in primary IgAN patients with eGFR $\geq$ 30 mL/min/1.73m$^2$ who are on background ACEi/ARB treatment, regardless of intake of CS/IS or other newly approved drugs or initiation of new background therapy for treatment of IgAN, KRT, unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason.

This supplementary estimand's attributes will be the same as for the primary estimand at the IA apart from the treatment attribute which now broadly considers the randomized treatment with CS/IS or other newly approved drugs for treatment of IgAN taken and new background therapy for IgAN and KRT initiated as needed i.e. in this supplementary estimand, the intake of CS/IS or other newly approved drugs for treatment of IgAN, the initiation of new background therapy for IgAN treatment and KRT will be handled with the treatment policy strategy. Thus, data

collected after initiation of CS/IS, other newly approved drugs or new background therapy for IgAN treatment will be included in the analysis that will otherwise follow the same principles as outlined in Section 2.5.2.1. In cases that participants who took CS/IS or other newly approved drugs or new background therapy for IgAN treatment have missing data due to study withdrawal, missing data will be implicitly handled under the primary analysis models (i.e. MAR assumption) for this estimand in line with a treatment policy strategy. As data following KRT cannot reliably be collected, these will be considered as "missing" and handled under the primary analysis model (i.e. MAR assumption) to reflect participants' UPCR would continue to worsen.

#### Supplementary estimand 2

A further supplementary estimand to the primary estimand at the IA will be assessed; the same attributes, intercurrent events and corresponding handling strategies as for the primary IA estimand apply apart from the Endpoint attribute which is now the log-ratio to baseline in UPCR (from FMV) at 9 months. UPCR (obtained from a FMV sample) is an alternative measurement for quantifying proteinuria, which is more frequently assessed during the study and thus may offer increased precision in the analysis. Missing values not related to intercurrent event will be handled as per Section 2.5.4.

#### Supplementary analyses at the Interim analysis

The primary analysis at the IA as well as the Supplementary estimand 1 and 2 analyses will be repeated as supplementary analyses considering all data from all participants randomized and in the FAS at the time of the analysis cut-off.

### 2.5.6.2 Supplementary estimands at the Final analysis

#### Supplementary estimand 1

A supplementary clinical question of interest at the Final analysis is: what is the treatment effect of LNP023 vs. placebo in slowing IgAN progression as measured by the annualized total eGFR slope in primary IgAN patients with eGFR $\geq$ 30 mL/min/1.73m$^2$ who are on background ACEi/ARB treatment, regardless of intake of CS/IS or other newly approved drugs or initiation of new background therapy for treatment of IgAN, KRT, unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason.

This supplementary estimand's attributes will be the same as for the primary estimand at the final analysis apart from the treatment attribute which now broadly considers the randomized treatment with CS/IS or other newly approved drugs for treatment of IgAN taken and new background therapy for IgAN and KRT initiated as needed i.e. in this supplementary estimand, the intake of CS/IS or other newly approved drugs for treatment of IgAN, the initiation of new background therapy for IgAN treatment and KRT will be handled with the treatment policy strategy. Thus, data collected after initiation of CS/IS, other newly approved drugs or new background therapy for IgAN treatment will be included in the analysis that will otherwise follow the same principles as outlined in Section 2.5.2.2. In cases that participants who took CS/IS or other newly approved drugs or new background therapy for IgAN treatment have

missing data due to study withdrawal, missing data will be implicitly handled under the primary analysis models (i.e. MAR assumption) for this estimand in line with a treatment policy strategy. As data following KRT cannot reliably be collected, these will be considered as "missing" and handled under the primary analysis model (i.e. MAR assumption) to reflect participants would continue to deteriorate in the same fashion (e.g. linear decline in eGFR slope) as up to the initiation of KRT.

### Supplementary estimand 2

A further supplementary estimand to the primary estimand at the Final Analysis will be assessed; the same attributes, intercurrent events and corresponding handling strategies as for the primary estimand at the final analysis apply apart from the Endpoint attribute which is now the annualized long-term eGFR slope. This treatment effect is targeted in order to explore whether there are potential early short-term slope effects that differ to long-term slope effects.

Statistical analysis will be carried out using a longitudinal mixed effects model allowing now for two slope parameters, corresponding to short-term and long-term eGFR slope effects, in order to characterize longitudinal trends in the rate of eGFR decline. The model is formulated via the definition of a changepoint in time at which the long-term effect starts. The changepoint will be selected based on information from the PhII study of the program or by fitting the model considering changepoints at months 1 to 4 and selecting the changepoint corresponding to the best fitting model as determined by the Akaike's Information Criterion (AIC).

Should issues of model non-convergence arise, the model will be refit excluding the randomization strata fixed effect terms. If issues persist, a modified single-slope linear mixed-effects model excluding eGFR values prior to the changepoint will be instead fit.

### Supplementary estimand 3

A third supplementary estimand to the primary estimand at the Final Analysis will be assessed; the same attributes, intercurrent events and corresponding handling strategies as for the primary estimand at the final analysis apply apart from the Endpoint attribute which is now the change from baseline in eGFR at Month 24.

Statistical analysis will be carried out using an MMRM model for the change from baseline in eGFR. The model will include treatment, timepoint (as a categorical variable), randomization strata as fixed effects, treatment*timepoint and timepoint*baseline eGFR as interaction terms and baseline eGFR as a fixed covariate. The correlations between visits (aka timepoints) within subjects will be modelled using an unstructured covariance matrix. In case of non-convergence issues, the AR(1) covariance structure will be employed in the first instance; further steps in case issues persist are described in the Appendix. The Kenward-Roger adjustment for degrees of freedom will be used.

The mean difference between LNP023 versus placebo (and its 95% CI) will be calculated for all timepoints up to Month 24. The model estimated mean change from baseline (and respective two-sided 95% CI) will be graphically presented over time by treatment group.

### Supplementary estimand 4

Supplementary estimand 4 will have the same attributes as Supplementry estimand 3 at the final analysis apart from the Treatment attribute, which now broadly considers the randomized treatment with CS/IS or other newly approved drugs for treatment of IgAN taken and new background therapy for IgAN and KRT initiated as needed i.e. in this supplementary estimand, the intake of CS/IS or other newly approved drugs for treatment of IgAN, the initiation of new background therapy for IgAN treatment and KRT will be handled with the treatment policy strategy. Thus, data collected after initiation of CS/IS, other newly approved drugs or new background therapy for IgAN treatment will be included in the analysis that will otherwise follow the same principles as per Supplementary estimand 3. In cases that participants who took CS/IS or other newly approved drugs or new background therapy for IgAN treatment have missing data due to study withdrawal, missing data will be implicitly handled under the analysis model (i.e. MAR assumption) for this estimand in line with a treatment policy strategy. As data following KRT cannot reliably be collected, these will be considered as "missing" and handled under the analysis model (i.e. MAR assumption) to reflect participants would continue to deteriorate in the same fashion, as up to the initiation of KRT.

**Supplementary estimands in case of COVID-19 pandemic impact**

The potential impact of a wave of pandemic-related infections affecting measurements has been minimized by the implementation of measures in the CSP to allow for possible adaptations in data capture and clinical evaluation activities in case of restrictions to participant access to investigational sites due a new infection wave. Nevertheless, impact due to pandemic-related I/C events cannot be precluded at this stage. In case a considerable number of unforeseen pandemic-related I/C events occurs during the study, additional estimands of interest may become relevant. These may include, for instance, supplementary estimands answering the primary clinical questions of interest specified in Section 1.2.1 in the hypothetical scenario the pandemic disease did not exist or irrespective of effects related to the pandemic disease but in the absence of administrative/operational issues due to the pandemic. The definition of such additional estimands and pandemic-related I/C events, as well as associated analysis methodology will be defined in an amendment to the SAP should new infection waves of a pandemic with impact on the study occur.

### 2.5.6.3 Subgroup analysis

Subgroup analyses to assess the homogeneity of the treatment effect across subgroups of interest will be performed for the primary endpoints at the IA and Final analysis. The subgroups to be examined are listed in Table 2-2. Subgroup analysis results will graphically be presented as forest plots.

**Primary endpoint at the IA**

The estimated ratio of geometric means (LNP023 vs. placebo) and associated two-sided 95% CI will be provided for the 9 month timepoint for each individual subgroup using the MMRM for the log-transformed ratio to baseline in UPCR 24h described in Section 2.5.1 for the primary analysis. For the analysis of subgroups which are also stratification factors, the corresponding stratification factor term will be removed from the model; this includes the Region subgroup which largely overlaps with the Geographic region stratification factor.

**Primary endpoint at the Final analysis**

The difference between treatment groups in the estimated mean annualized total eGFR slope and two-sided 95% CI will be provided for each individual subgroup using the same longitudinal mixed effect model described in Section 2.5.2 for the primary analysis. For the analysis of subgroups which are also stratification factors, the corresponding stratification factor term will be removed from the model; this includes the Region subgroup which largely overlaps with the Geographic region stratification factor.

Intercurrent events as well as missing data not related to intercurrent events will be handled in the analysis as for the primary estimands at the IA and Final analysis respectively (Section 2.5.3 and Section 2.5.4).

Note that no adjustments for multiplicity are made for subgroup analyses hence findings should be interpreted with caution.

## 2.6 Analysis of secondary estimands

The sequentially rejective multiple test procedures ([Bretz et al 2009]) will be used for testing the hypotheses associated with the primary estimand at the Interim analysis ($H_1$), and the primary ($H_2$) and secondary estimands ($H_3$, $H_{41}$ and $H_{42}$) at the Final analysis in order to ensure strong control of the studywise type one error for multiplicity of testing at one-sided 2.5%. Hypothesis identifiers are provided in Table 2-3. The hypotheses associated with the secondary estimands at the Final analysis will be tested only if the null hypothesis associated with the primary estimand at the Final analysis is rejected.

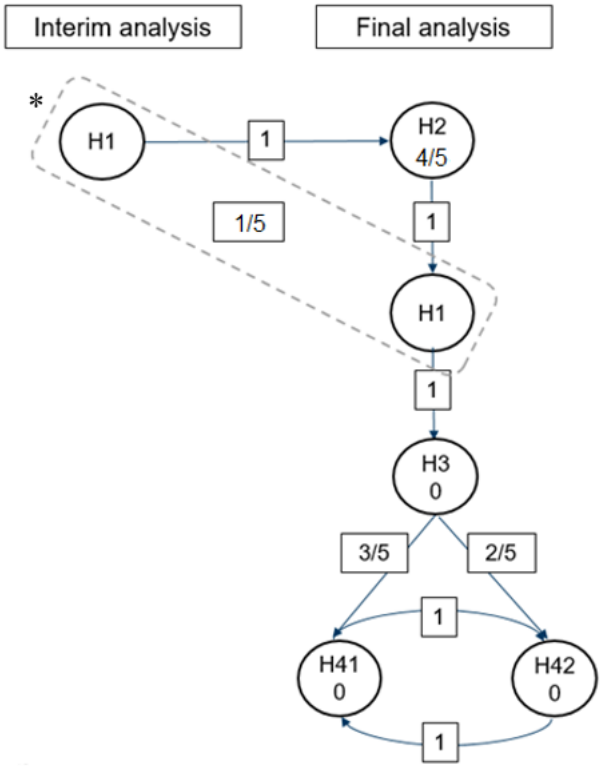
- The initial allocation of (local) significance levels is 1/5, 4/5, 0, 0, and 0 of the overall studywise alpha (of one-sided 2.5%) for the analysis of $H_1$, $H_2$, $H_3$, $H_{41}$ and $H_{42}$. Note that by design, $H_1$ will be tested first in order (i.e. first at the Interim analysis) and if not rejected, $H_1$ will be tested again in a group-sequential manner at the final analysis.
- The general algorithm for the testing procedure proceeds as follows: At the interim analysis, test $H_1$ at significance level of alpha/5 (i.e. 1-sided 0.5%).
  - If $H_1$ is rejected, propagate alpha/5 to $H_2$ and continue to test $H_2$, $H_3$, $H_{41}$ and $H_{42}$ at level alpha at the Final analysis (hierarchically for $H_2 \rightarrow H_3 \rightarrow (H_{41}, H_{42})$, with 3/5 and 2/5 of alpha to be propagated to $H_{41}$ and $H_{42}$ respectively in case of rejection of all previous hypotheses).
  - If $H_1$ cannot be rejected at the IA at level alpha/5, proceed to the Final analysis and test $H_2$ at level 4(alpha)/5 (i.e. 1-sided 2%). If $H_2$ is not rejected, the algorithm stops. If $H_2$ is rejected, test $H_1$ (now with all participant data) at local $alpha_F$=2.3% (adjusting for multiplicity in the group-sequential test of $H_1$ alone, given a correlation of $\sqrt{n_{IA}/n_{final}}$ in the group-sequential test at currently planned $n_{IA}$=250 and $n_{final}$=430. Should $n_{IA}$ and $n_{final}$ be different from planned at the time of final analysis, the value of $alpha_F$ will be accordingly revised). If $H_1$ is not rejected, the algorithm stops. If $H_1$ is instead rejected, test the remaining hypotheses $H_3$, $H_{41}$ and $H_{42}$ with full alpha according to the graph below. In the graph, nodes denote hypotheses and their initial allocation of (local) alpha. The numbers on edges denote the weights or proportions of alpha to be propagated to the alpha level specified in the

next nodes according to the directed edges once the current hypothesis node is rejected. It can be shown that this procedure controls the FWER rate at level alpha ([Bretz et al 2009]) .

**Table 2-3 Hypothesis Identifiers included in the testing procedure**

| Hypothesis | Endpoint |
|---|---|
| $H_1$ | % UPCR reduction from baseline to 9 months |
| $H_2$ | Annualized eGFR slope over 24 months |
| $H_3$ | Proportion of participants reaching UPCR<1g/g at 9 months |
| $H_{41}$ | Time-to-first event of the composite kidney failure endpoint |
| $H_{42}$ | Change from baseline to 9 months in FACIT-Fatigue |

**Figure 2-1 Graphical display of testing procedure**




*Note that $H_1$ is **only** tested at the final analysis (at $alpha_F$ adjusted to account for $H_1$ being tested and not rejected at the IA) in case of non-rejection at the IA and rejection of $H_2$.

Note that the hypotheses associated with the secondary estimands at the IA and the secondary safety objective (both at the IA and Final analysis) are not included in this testing procedure and will thus not be adjusted for multiplicity.

## 2.6.1 Secondary endpoints

### 2.6.1.1 Secondary endpoints at the Final Analysis

The log-ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months (log-transformation refers to the natural log [base on e]) will be tested as a secondary endpoint at the Final analysis, only in case of non-significance at the IA.

#### Secondary endpoints related to $H_3$, $H_{41}$, $H_{42}$

- Proportion of participants reaching UPCR 24h levels <1 g/g at 9 months, without receiving CS/IS or other newly approved drugs or initiating new background therapy for IgAN treatment or initiating KRT.
- Time from randomization to first occurrence of reaching either ([Levey et al 2020]):
    - a sustained ≥30% decline in eGFR relative to baseline over at least 4 weeks, or
    - sustained eGFR <15 mL/min/1.73m$^2$ over at least 4 weeks, or
    - maintenance dialysis, or
    - receipt of kidney transplantation, or
    - death from kidney failure

A **sustained** ≥30% decline in eGFR relative to baseline will be established if:

A ≥30% decline in eGFR relative to baseline is noted at any visit **and** is confirmed by an eGFR measurement obtained (at a scheduled or unscheduled visit) no sooner than 4 weeks after the initial result was noted (could be part of the next scheduled visit), unless maintenance dialysis is initiated within 4 weeks of the date the initial result was noted.

A **sustained** eGFR <15 mL/min/1.73m$^2$ will be established if:

An eGFR measurement <15mL/min/1.73m$^2$ is noted at any visit **and** it is confirmed by an eGFR measurement obtained (at a scheduled or unscheduled visit) no sooner than 4 weeks after the initial result was noted (could be part of the next scheduled visit), unless maintenance dialysis is initiated within 4 weeks of the date the initial result was noted.

For both endpoint components above, the date of the outcome is the onset of when the decline occurred first (not the date of confirmation). If the first decline occurs within 4 weeks of the EOS (or analysis cut-off at the IA), a confirmatory eGFR measurement is not required per protocol and it will be counted as an event.

**Maintenance** dialysis will be established at a visit based on the Dialysis eCRF if:

- the period between the date of initiation and termination is ≥4 weeks,
- dialysis is ongoing and the period between the date of initiation and the visit date is ≥ 4 weeks,
- the date of initiation is within 4 weeks of the EOS (or analysis cut-off at the IA), dialysis is ongoing at the EOS (or analysis cut-off at the IA) and the reason for initiation is progressive Chronic Kidney Disease (CKD),

- the period between the date of initiation and termination is <4 weeks, the reason for initiation is progressive CKD and the reason for termination is not "not medically required".

The date of the outcome event is the onset of maintenance dialysis.

Receipt of kidney transplantation will be captured in the Concomitant non-drug therapies/procedures eCRF.

Death from kidney failure will be established if a death occurs and the Primary cause of death captured in the Death eCRF is Kidney failure (as defined in the protocol).

- Change from baseline to 9 months in the total score of the FACIT-Fatigue questionnaire

#### 2.6.1.2 Secondary endpoints at the IA

- Change from baseline in eGFR at month 9.
- Proportion of participants reaching UPCR 24h levels <1 g/g at 9 months, without receiving CS/IS or other newly approved drugs or initiating new background therapy for IgAN treatment or initiating KRT.
- Annualized total eGFR slope (mL/min/1.73m$^2$/year) estimated over 12 months.
- Change from baseline to 9 months in the total score of the FACIT-Fatigue questionnaire.

Handling of intercurrent events is provided in Section 2.6.3. A tabular overview of the secondary estimands is also given in the Appendix. The secondary efficacy analyses will consider the Main study population only (with the exception of descriptive statistics provided in the SRI population as well on the FAS) and will be based on the IA-FAS and FAS set (defined in Section 2.2) at the IA and Final analysis respectively.

Descriptive statistics will be provided for secondary endpoints by treatment group, for the Main study and SRI populations separately; for secondary endpoints assessed at multiple visits, descriptive statistics will be further summarized by visit/timepoint.

### 2.6.2 Statistical hypothesis, model, and method of analysis

#### 2.6.2.1 Secondary analyses ($H_3$, $H_{41}$, $H_{42}$) at the Final analysis

The log-ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months (log-transformation refers to the natural log [base on e]) will be tested as a secondary endpoint at the Final analysis, only in case of non-significance at the IA. The modelling approach described in Section 2.5.2 will be used, considering all participant data collected to the EOS. Intercurrent events as well as missing data not related to intercurrent events will be handled in the analysis as for the primary estimand at the IA (Section 2.5.3 and Section 2.5.4).

#### Secondary estimand 2

**$H_3$:** The proportion of participants who have a response in terms of reaching UPCR (sampled from 24hr collection) <1g/g at 9 months, without receiving CS/IS or other newly approved drugs or initiating new background therapy for treatment of IgAN or initiating KRT, will be

analyzed using a logistic regression model (following the strategies for handling intercurrent events and missing data described in Section 2.6.3 and Section 2.6.4 respectively) with treatment and randomization strata as fixed effect factors, and baseline log (UPCR 24h) as a continuous covariate. The estimated odds ratio and the corresponding two-sided 95% confidence interval and 1-sided p-value will be provided. The difference in marginal proportions and associated two-sided 95% confidence interval will also be provided (see Appendix for detail).

The mean (geometric) of two UPCR 24h values obtained from two distinct 24 hour urine collections will be used as the UPCR 24h measurement for the Month 9 visit in order to derive the binary response endpoint (1 for a "response" and 0 otherwise). In case only one value is available, that value will be instead used. A participant will be considered to have achieved a "response" at month 9 if they have UPCR 24h <1g/g and did not previously receive CS/IS or other newly approved drugs for treatment of IgAN or initiate new background therapy for IgAN or initiate KRT.

### Secondary estimand 3

**$H_{41}$:** Time-to-first occurrence of a composite kidney failure endpoint of reaching either a sustained ≥30% decline in eGFR relative to baseline, or sustained eGFR <15 mL/min/1.73m$^2$, or maintenance dialysis, or receipt of kidney transplant, or death from kidney failure will be analyzed using a stratified Cox proportional hazards model with treatment as a fixed effect factor and stratified by geographic region as defined in Section 2.5.1. Ties will be adjusted for in the model using the exact method. The estimated hazard ratio and the corresponding two-sided 95% confidence interval and 1-sided p-value will be provided. Participants who have not had an event up to Month 24 will be censored in the analysis. Cumulative incidence curves will be presented by treatment group.

### Secondary estimand 4

**$H_{42}$:** The change from baseline to 9 months in the FACIT-Fatigue total score will be analyzed using a MMRM for the change from baseline to 9 months in the FACIT-Fatigue total score. This model will have treatment, timepoint (as a categorical variable), randomization strata as fixed effects, treatment*timepoint and timepoint*baseline FACIT-Fatigue total score as interaction terms and baseline FACIT-Fatigue total score as fixed covariate. The correlations between visits within subjects will be modelled using an unstructured covariance matrix. In case of non-convergence issues, the steps described in Appendix will be employed. Intercurrent events as well as missing data not related to intercurrent events will be handled in the analysis as for the primary estimand at the IA (Section 2.5.3 and Section 2.5.4), considering all participant data collected to the EOS.

The difference between the mean change from baseline to 9 months for LNP023 versus placebo will be presented, together with its two-sided 95% confidence interval and associated 1-sided p-value.

#### 2.6.2.2 Secondary analyses at the IA

**Secondary estimand 1**

The change from baseline in eGFR at month 9 will be analyzed using an MMRM as described in Section 2.5.2 for UPCR 24h, with the distinction that a log-transformation will not be applied and log(baseline UPCR 24h) will be replaced by baseline eGFR in all terms. eGFR values post study treatment initiation will be used (i.e. from Week 2 inclusive onwards) for the change from baseline calculations. I/C events as well as missing data not related to I/C events will be handled in the analysis as for the primary estimand at the IA (Section 2.5.3 and 2.5.4). As defined in Section 2.1.1, the baseline for the analysis is the eGFR value for the Baseline visit.

The mean difference between LNP023 versus placebo will be presented for the 9 month time point, together with its two-sided 95% CI. Graphical displays of mean changes from baseline over time by treatment group may be provided.

A descriptive summary table (similar to that for UPCR 24h, see Section 2.5.1) will be provided, for the Main Study and SRI populations separately.

**Secondary estimand 2**

The proportion of participants who have a response in terms of reaching UPCR (sampled from 24hr collection) <1g/g at 9 months, without receiving CS/IS or other newly approved drugs or initiating new background therapy for treatment of IgAN or initiating KRT will be analyzed at the IA following the approach described above for $H_3$.

**Secondary estimand 3**

The annualized total eGFR slope over 12 months will be evaluated using the same statistical analysis, intercurrent event and missing data handling approaches as the primary estimand at the Final analysis (see Section 2.5.2, Section 2.5.3 and Section 2.5.4). All eGFR values (measured at the central lab for scheduled and unscheduled visits) of participants who should have completed the Month 12 visit at the time of the IA will be included in the analysis.

**Secondary estimand 4**

The change from baseline to 9 months in the FACIT-Fatigue total score will be analyzed at the IA following the approach described above for $H_{42}$.

### 2.6.3 Handling of intercurrent events

For all secondary estimands the same I/C events as for the primary estimands apply, apart from cases where the I/C event itself forms part of the endpoint attribute (i.e. handled with the composite strategy). In general, the same strategies described in Section 2.5.3 for the primary estimands will be employed for handling intercurrent events applicable to the secondary estimands; the exception to this is the estimand for the composite kidney failure endpoint for which the intake of CS/IS and/or other newly approved drugs or initiation of new background therapy for IgAN will be handled via the treatment policy strategy.

### Secondary estimand 1 at the IA

The intercurrent events and associated handling strategies applicable are the same as described in Section 1.2.1.1 and Section 2.5.3 for the primary estimand at the IA.

### Secondary estimand 2 (at IA and Final analysis)

The intake of CS/IS or other newly approved drugs for IgAN treatment, the initiation of new background therapy for IgAN treatment and initiation of KRT are handled via the composite strategy (i.e. as part of the Endpoint attribute, see Section 1.2.2). Thus, in case CS/IS and/or other newly approved drugs for treatment of IgAN are taken or new background therapy for IgAN or KRT are initiated prior to or at Month 9, non-response (i.e. 0) will be imputed for the binary endpoint derivation. Treatment discontinuation for any reason (other than the intake of CS/IS or other newly approved drugs for treatment of IgAN) is handled with the same strategy as for primary estimands (see Section 2.5.3).

### Secondary estimand 3 at the IA

The intercurrent events and associated handling strategies applicable are the same as described in Section 1.2.1.2 and Section 2.5.3 for the primary estimand at the Final analysis.

### Secondary estimand 3 at the Final analysis

Of the intercurrent events identified in Section 1.2.1, the intake of CS/IS or newly approved drugs for IgAN treatment and the initiation of new background therapy for IgAN will be handled using a treatment policy strategy, so that these medications form part of the Treatment attribute. Data collected after the intake of such medications will be included in the analysis that will follow the principles outlined in Section 2.6.2.1. Treatment discontinuation for any reason (other than the intake of CS/IS or other newly approved drugs for treatment of IgAN) will be handled with the same strategy as for primary estimands (see Section 2.5.3). Note that initiation of KRT is captured within the Endpoint attribute (i.e. handled via the composite strategy).

### Secondary estimand 4 (at IA and Final analysis)

The intercurrent events and associated handling strategies applicable are the same as described in Section 1.2.1.1 for the primary estimand for the IA.

## 2.6.4 Handling of missing values not related to intercurrent event

### Secondary estimand 1 at the IA

The same missing data handling approaches as for the primary estimand at the Interim analysis will be employed (see Section 2.5.4).

### Secondary estimand 2 (at IA and Final analysis)

Missing data will be, in general, handled as described in Section 2.5.4 for the primary estimands so that they will be imputed on the continuous scale for UPCR 24h and used to derive this

binary endpoint. In case of missing data due to death from kidney failure, participants will be considered as they would have not reached UPCR 24h <1g/g, so that non-response (i.e. 0) will be imputed for the binary endpoint derivation.

The same missing data handling approach will be used at the IA and Final analysis.

### Secondary estimand 3 at the IA

The same missing data handling approaches as for the primary estimand at the Final analysis will be employed (see Section 2.5.4).

### Secondary estimand 3 at the Final Analysis

Participants who discontinue treatment for any reason (including AEs or lack of efficacy) will be followed until the EOS, and data will be collected and included in the analysis according to a treatment policy approach. In cases of study withdrawal or that following treatment discontinuation data collection cannot be maintained, censoring rules will apply for the composite endpoint and each of its individual components. Censoring will also take place in case of other competing events (e.g. death not from kidney failure) or administrative reasons (analysis timepoint) in line with a "while alive/while on planned study follow up" strategy. Thus, participants who have not had an event of the respective endpoint will be censored on the date of the last follow-up defined as:

For the non-mortality component endpoints, the earliest of the date of death, date of study consent withdrawal, date lost to follow-up, analysis timepoint.

For the death from kidney failure component endpoint, the earliest of the date of death not from kidney failure, date of study consent withdrawal, date lost to follow-up, analysis timepoint.

For the composite endpoint, censoring will occur at the earliest censoring date among its components.

The number of participants censored for the composite and each of its components individually, as well as reasons for censoring, will be summarized by treatment group using descriptive statistics.

A sensitivity analysis will be considered using multiple imputation under a J2R assumption for the LNP023 arm, as described in [Lu K. et al 2015], if a considerable amount (i.e. >10% overall) occurs of a) cases of study withdrawal b) cases that data collection post-treatment discontinuation cannot be maintained resulting in missing data due to non-administrative reasons. This method is based on a bayesian imputation model using control (placebo) time-to event data modeled with a piecewise exponential distribution in order to impute the time to event after non-administrative censoring point until a theoretical date of administrative censoring. For the placebo arm, a MAR assumption is made and the time to event will therefore be censored at the last assessment. To ensure model convergence, the number of pieces in the piecewise exponential will be such as to have at least one observed event in each interval. The imputation model will have the same covariates as the strata pre-specified in the primary analysis. Final HR estimate and 95% CI will be computed using proc mianalyze (applied to log(HR)) and using Rubin's rules.

As noted above, the jump-to-reference imputation is done until a theoretical date of administrative censoring; this date should be the analysis cut-off date for participants still alive at the analysis timepoint of the date of death if occurred earlier. Thus, the I/C of death is handled in line with a while-alive strategy.

#### Secondary estimand 4 (at IA and Final analysis)

The same missing data handling approaches as for the primary estimands will be employed (see Section 2.5.4).

### 2.6.5 Sensitivity analyses

#### Secondary estimand 1 at the IA

Two sensitivity analyses, in line with sensitivity analyses 0.1 and 0.2 described in Section 2.5.5 for the primary estimand at the IA, will be implemented.

#### Secondary estimand 3 at the Final Analysis

As the initiation of some new background therapies for IgAN may lead to an acute initial decline in eGFR that would resolve/fade away with time (i.e. not reflecting true harm), sensitivity analyses will be considered:

Sensitivity analysis 0.1: censoring will occur at the I/C event occurrence i.e. data collected following the I/C event occurrence will not be used in the analysis. Assuming participants in the placebo arm are more likely to have this I/C event, this approach is conservative as it considers the occurrence of the I/C event as uninformative (i.e. independent of a participant's condition).

As the proportion of participants with this I/C event is expected to be limited, the above sensitivity analysis will only be considered in the first instance. In case the proportion of participants with this I/C event is larger than expected (i.e. >10% overall), the following sensitivity analysis will also be done:

Sensitivity analysis 0.2: for the derivation of the composite endpoint (i.e. the eGFR-based components defined in the first 2 bulletpoints in Section 2.6.1.1), eGFR values following initiation of new background therapy for IgAN will be excluded from analysis, and instead imputed under the same assumptions specified for the primary estimand at the Final analysis (see Section 2.5.3). The analysis would then be done considering the composite endpoint as derived based on the imputed values. Final HR estimate and 95% CI will be computed using proc mianalyze (applied to log(HR)) and using Rubin's rules.

### 2.6.6 Supplementary analyses

In addition to the detailed description below, a tabular overview of the secondary estimands and related supplementary estimands is given in the Appendix Section 5.2.1.

### Secondary estimand 1 at the IA

A supplementary estimand of interest, in line with the supplementary estimand 1 for the primary estimand at the IA defined in Section 2.5.6, in which the intake of CS/IS or other newly approved drugs for treatment of IgAN, the initiation of new background therapy for IgAN and KRT are handled with the treatment policy strategy, will be examined.

### Secondary estimand 2 (at IA and Final analysis)

A supplementary estimand of interest will be examined where the Population attribute as well as summary measure are the same as specified in Sections 1.2.2 and 2.6.2 but the Treatment attribute is now defined broadly to consider the randomized treatment with CS/IS or other newly approved drugs for treatment of IgAN taken and new background therapy for IgAN treatment initiated as needed i.e. in this supplementary estimand, the intake of CS/IS or other newly approved drugs for treatment of IgAN and the initiation of new background therapy for IgAN are not part of the Endpoint attribute and will be handled with the treatment policy strategy. Thus, data collected after the intake of such medications will used for the derivation of the binary response endpoint used in the analysis, that will otherwise follow the same principles as outlined in Section 2.6.2. In cases that participants who took CS/IS or other newly approved drugs or initiated new background therapy for IgAN have missing data e.g. due to study withdrawal, data will be imputed on the continuous scale as described in Section 2.5.6, and used to derive the binary endpoint for this estimand.

This supplementary estimand will be examined both at the IA and Final analysis.

### Secondary estimand 3 at the IA

A supplementary estimand of interest, in line with the supplementary estimand 1 for the primary estimand at the Final analysis defined in Section 2.5.6 for which the intake of CS/IS or other newly approved drugs for treatment of IgAN, the initiation of new background therapy for IgAN and KRT are handled with the treatment policy strategy, will be examined.

### Secondary estimand 3 at the Final Analysis

The frequency and percentage of participants who have a composite kidney failure endpoint event will be provided by treatment group. Moreover, each of the components of the composite will be separately examined as an individual endpoint and the number and percentage of participants who have an individual component endpoint event will be summarized by treatment group. This summary will be provided for the IA-FAS at the IA and FAS at the final analysis (for SRI, the FAS applies for both analysis points); a listing of participants who have reached the composite kidney endpoint (including information on the individual component(s) reached) will similarly be produced.

Cumulative incidence curves will be presented individually for each component of the composite endpoint by treatment group (provided at least 5 component specific events occur per group).

The frequency and percentage of participants who have a composite kidney failure endpoint event will be provided by the type of 1$^{st}$ event and by treatment group.

Descriptive statistics for the supplementary analysis of this composite kidney failure estimand will also be provided for the Main Study and SRI populations separately.

### Secondary estimand 4 (at IA and Final analysis)

A supplementary estimand of interest will be examined for FACIT-Fatigue where the Population and Endpoint attributes as well as summary measure are the same as specified in Sections 1.2.2 and 2.6.2 but the Treatment attribute is now defined broadly to consider the randomized treatment with CS/IS or other newly approved drugs for treatment of IgAN taken and new background therapy for IgAN treatment and KRT initiated as needed i.e. in this supplementary estimand, these I/C events will be handled with the treatment policy strategy. Thus, data collected after the intake of such medications will be used in the analysis, that will otherwise follow the same principles as outlined in Section 2.6.2. In cases that following these I/C events participants have missing data due to study withdrawal, data will be imputed under a MAR assumption.

**Supportive responder analysis**

An additional supportive responder analysis of FACIT-Fatigue will be performed. A participant will be considered as a responder if they had at least a 5-point improvement in the FACIT-Fatigue total score from baseline at 9 months. Response data will be analyzed using a logistic model including treatment, randomization strata as fixed effects, and baseline FACIT-Fatigue total score as a fixed covariate, with logit as link function. The odds ratio between treatment arms at the 9 month timepoint will be estimated together with its two-sided 95% confidence interval.

I/C events as well as missing data not related to I/C events will be handled in the analysis as for the secondary estimand for FACIT-Fatigue defined in Section 2.6.2.1. For the responder-type analysis of FACIT-Fatigue, this implies data will be imputed on the continuous scale and used to derive the binary endpoint described above. As defined in Section 2.1.1, the FACIT-Fatigue value for the baseline visit will be used as baseline for the analysis.

The frequency and percentage of participants that achieve a response at 9 months will be summarized descriptively by treatment group, for the Main study and SRI populations separately.

Further sensitivity analyses to this supplementary estimand considering participants a responder if they had improvements of at least 3 points and above, as well as with a responder threshold equal to the proposed minimally important within-patient change derived as per Section 2.10.1 (if this differs from the 5 or 3-point improvement) will be considered.

### Supplementary analysis at the Interim analysis

The secondary estimand 1 and 3 analyses at the IA will be repeated considering all data from all participants randomized and in the FAS at the time of the analysis cut-off.

### 2.6.6.1 Subgroup analysis

Subgroup analysis for selected secondary endpoints at the IA and Final analysis described below will be performed for the subgroups listed in Table 2-2, apart from the Region and Sex subgroups that will only be presented for the primary endpoints. Subgroup analysis results will graphically be presented as forest plots.

#### Secondary estimand 1 at the IA

Subgroup analyses for the change from baseline in eGFR at Month 9 will be performed using the same approach as for the subgroup analyses described for the primary endpoint at the IA (see Section 2.5.6.3), for each individual subgroup. For the analysis of subgroups which are also stratification factors, the corresponding stratification term will be removed from the model. The mean difference between groups for the 9 month timepoint and associated 2-sided 95% confidence interval will be provided within each subgroup.

#### Secondary estimand 2 (at IA and Final analysis)

Subgroup analyses of the proportion of participants who have a response in terms of reaching UPCR (sampled from 24hr collection) <1g/g at 9 months, without receiving CS/IS or other newly approved drugs or initiating new background therapy for treatment of IgAN or initiating KRT, will be analyzed using the same logistic regression model described in Section 2.6.2.1 for each individual subgroup. For the analysis of subgroups which are also stratification factors, the corresponding stratification term will be removed from the model. The estimated odds ratio and associated two-sided 95% confidence interval will be provided within each subgroup.

#### Secondary estimand 3 at the IA

Subgroup analyses for the annualized total eGFR slope over 12 months will be performed using the same approach as for the subgroup analyses described for the primary endpoint the Final analysis (see Section 2.5.6.3), for each individual subgroup. Participants who have completed the Month 12 visit at the time of the IA will be included in the analysis. For the analysis of subgroups which are also stratification factors, the corresponding stratification term will be removed from the model. The difference between groups in the estimated mean annualized total slope of eGFR decline (mL/min/1.73m$^2$ per year) and associated 2-sided 95% confidence interval will be provided within each subgroup.

## 2.7 Analysis of secondary efficacy objectives without defined estimands

The analysis of all secondary efficacy objectives and associated estimands (see Table 1-1 and Table 1-2) are described in Section 2.6, apart for the safety objective which is described under Section 2.8 Safety Analyses.

## 2.8 Safety analyses

For all safety analyses, the safety set will be used, unless otherwise specified. All tables and listings will be presented by treatment group, for the Main study and SRI populations separately.

Additional listings generated for the SRI population only will be separately defined, unless otherwise specified. Graphical displays of parameters based on summary measures (e.g. box-plots) mentioned in this section will instead be provided as spaghetti plots for the SRI population due to the small size of this population.

Unless stated otherwise, safety summaries (tables, figures) include only data from the on-treatment period (defined in Section 2.1.1) with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In particular, summary tables for adverse events (AEs) will summarize only on-treatment events (treatment-emergent AEs), unless otherwise specified.

Summary statistics of the change from baseline to post-baseline visits will only be provided for participants with both baseline and post-baseline values.

At the time of the IA all safety data available will be included in the analysis. In case that less than 10 SRI participants are available at the IA, only individual-level descriptive statistics (e.g. listings, spaghetti plots) will be generated for the SRI population.

### 2.8.1 Adverse events (AEs)

All information obtained on adverse events (including SAEs and deaths) will be displayed by treatment group and participant; events occurring pre- or post- treatment will be marked in the listing. Adverse events will be coded using the most current MedDRA version (included in the TFLs as a footnote).

Adverse events occurring between informed consent and first administration of study treatment (pre-treatment) will be summarized by primary system organ class and preferred term for the SAF set. A similar summary table will be provided for AEs occurring post-treatment (i.e. after premature treatment discontinuation). For the AE/SAE reporting, post-treatment will be considered to be any events that started or increased in severity after the end of the on-treatment period.

Treatment emergent (serious) adverse events (TE(S)AEs) refer to events with a start date in the on-treatment period, or events present prior to but increased in severity in the on-treatment period based on preferred term.

The definition of the “on-treatment period” is provided in Section 2.1.1.

The number (and percentage) of participants with TEAEs will be summarized in the following ways:

- by treatment, primary system organ class (SOC) and preferred term (PT).
- by treatment, primary SOC, PT and maximum severity.

TESAEs summaries by SOC and PT will be provided. TEAEs and TESAEs will also be summarized by treatment and PT. Separate summaries by treatment and PT will be provided for study medication related AEs and SAEs, AEs and SAEs related to Auxiliary Medicinal Products (AxMP), and other significant TEAEs leading to discontinuation of treatment. TEAEs leading to discontinuation of treatment, AEs related to AxMP, and all SAEs will also be listed by treatment group. Note that based on EU CTR requirements, ACEi/ARB (background medication) are considered AxMP and the reporting of AEs related to AxMP will apply once

the study has been transitioned under EU CTR 536/2014 (23 July 2024), i.e., the information will only be reported for a subset of participants.

A participant with multiple adverse events within a primary SOC is only counted once towards the total of the primary SOC. For a participant with multiple AEs reported with the same PT, the AE with the greatest severity will be presented.

An overall summary of treatment-emergent adverse events (e.g. AEs/SAEs, AEs/SAEs suspected to be related to study drug, AEs leading to study treatment discontinuation) will be provided and will include the frequency and percentage of participants reporting particular events.

The most common adverse events (at least 5% of participants for each PT for the Main study population and at least 2 participants for each PT for the SRI population) will also be summarized by PT in descending frequency, starting from the most common event, together with associated risk differences (and 95% CI); the most common AE incidence as well as risk differences (with 95% CI) may also be graphically displayed by a forest plot. Risk differences will be estimated for iptacopan versus placebo with 95% CIs constructed by the method described in Agresti and Caffo [Agresti, Caffo 2000]. Details on the CI derivation are included in a separate project-level analysis plan.

The incidence of TEAEs/TESAEs will be summarized by PT for selected subgroups as defined in Table 2-2.

#### 2.8.1.1 Exposure adjusted occurrence rate and 95% confidence interval

Summary tables of exposure-adjusted TEAE and TESAE occurrence rates per 100 patient-years (and associated 95% CI) will additionally be provided by treatment group, SOC and PT. The number of episodes per 100 patient years will be presented.

The occurrence rate (number of episodes per 100 patient-years) will be calculated by treatment group as 100*(the total number of AE episodes from all participants in the population divided by the total number of patient-years). A participant may have multiple occurrences of the same event and all occurrences are counted.

Total patient-years will be computed as the (sum of the duration of on-treatment periods over patients, in days)/365.25. This approach will account for the length of follow-up time under the assumption that events occur with the same frequency at any point in time.

In addition, 95% CI will be presented for the occurrence rate (denoted as $\theta_i$ for the $i^{th}$ treatment group) and will be calculated by the asymptotically robust method discussed in [Scosyrev, 2016]. Details on the CI derivation are included in a separate project-level analysis plan.

#### 2.8.1.2 Adverse events reporting for safety disclosure requirements

To meet the data disclosure requirements on the public registries ClinicalTrials.gov and EudraCT, tables displaying deaths (all cause)/SAEs/Non-SAEs will be produced.

(1) Deaths and SAEs by SOC and PT,
(2) Non-serious AEs with incidence >5% by SOC and PT.

For the deaths and SAEs table (1) and the non-serious AEs table (2), the numbers and percentages are based on the SAF for the on-treatment period.

If for the same participant several consecutive (S)AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

#### 2.8.1.3 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) are defined in the latest version of the LNP023 Case Retrieval Strategy (CRS). This classification reflects the safety topics of interest identified in the current version of the LNP023 Development Safety Profiling Plan, and may be updated based on review of accumulating data. At the time of analyses, the latest version of the CRS will be used to identify the AESIs.

The frequency and percentage of participants with treatment emergent adverse events of special interest (TEAESI) will be summarized by treatment group, AESI definition/safety topic as specified in the CRS, and PT; risk differences (with associated 95% CI) will also be included in the TEAESI tabulation. Moreover, TEAESI will be summarized by treatment group, safety topic, PT and maximum severity.

Selected safety subgroup analysis (see Table 2-2) for TEAESIs will be presented by treatment group, AESI definition/safety topic as specified in the CRS, and PT.

A listing of participants experiencing AESIs will also be provided by treatment group. The CRS safety topic definitions used to identify AESIs will be provided as a listing.

The exposure adjusted occurence rate per 100 patient-years and associated 95% CI will be presented for each safety topic of interest AEs, and associated summary tables will be derived as described in Section 2.8.1.1; the occurence rate difference and its 95% CI (with the placebo group as reference) may also be included. A Kaplan-Meier estimate of the Cumulative Incidence Function censoring at the time of treatment discontinuation + 7 days (i.e. at the end of the on-treatment period) or analysis cutoff-date will also be presented by treatment group in order to capture the risk of presenting an AE while on-treatment.

### 2.8.2 Deaths

The frequency and percentage of deaths (on treatment and post treatment if appropriate) and the primary cause of death will be summarized and listed by treatment group.

### 2.8.3 Laboratory data

Laboratory evaluations' summaries will be presented for groups of laboratory data (hematology, clinical chemistry, urinalysis and reproductive and thyroid hormone panel) measured at the central lab (apart from urine dipstick summaries which will have also data measured at local

lab). Summary statistics (absolute values and change from baseline) will be provided for all laboratory data by treatment and visit/time. All laboratory data (central and local lab) will be listed by treatment group, participant, and visit/time except for urine dipstick data. Where normal ranges are available, abnormalities will be marked in the listing except for serum Creatinine and Bun which are expected to be abnormal due the disease itself. A similar listing of laboratory data will be provided for the SRI population.

The frequency and percentage of participants with clinically notable laboratory abnormalities (newly occuring or worsening) will also be provided by treatment group. Clinically notable laboratory results for selected parameters (as defined in CSP Appendix 16) are given in Table 2-4 below:

**Table 2-4 Clinically notable laboratory abnormalities for selected parameters**

| Parameter | Criteria* |
|---|---|
| **Hematology** | |
| Hematocrit | >50% increase, >20% decrease |
| Hemoglobin | >50% increase, >20% decrease |
| Platelet count | >75% increase, >50% decrease |
| RBC count | >50% increase, >20% decrease |
| WBC count | >50% increase, >50% decrease |
| Reticulocyte count | <0.3% or >2.8% |
| **Clinical chemistry** | |
| Alkaline phosphatase | >100% increase |
| ALT (SGPT) | >150% increase |
| AST (SGOT) | >150% increase |
| Calcium | >10% increase, >10% decrease |
| Chloride | >10% increase, >10% decrease |
| Potassium | >20% increase, >20% decrease |
| Total bilirubin | >100% increase, CCI [redacted] |
| Uric acid | >50% increase |

*for criteria defined via an increase or decrease, this refers to a percent change from baseline. ULN: Upper Limit of Normal.

Participants with any newly occurring or worsening on-treatment value meeting the clinically notable criteria will be counted under the applicable criteria. For a participant to meet the criterion of a newly occurring clinically notable value, the participant needs to have a baseline value which is not clinically notable for that parameter. For a participant to meet the criterion of a worsening clinically notable value, the participant needs to have a baseline value which is clinically notable as well as a worsened post-baseline value. For participants with a missing baseline value, any post-baseline notable value will be considered as newly occurring. All on-treatment values (from scheduled or unscheduled visits) will be considered.

When a criterion contains multiple laboratory parameters, the criterion will only be considered to be met when all conditions occur at the same timepoint (i.e., in the same sample). A case where all conditions are met at a post-baseline timepoint but not met at baseline will be considered as newly occurring. A case will be considered as worsening if all the criteria are met at baseline and at least one component is worsening from baseline, irrespective of whether the other(s) are better.

A summary of newly occuring liver enzyme abnormalities compared to baseline will be provided by treatment group. Liver enzyme abnormalities are defined based on the liver toxicities definitions on laboratory measurements in Table 2-5. These definitions do not account for the presence of TEAEs related to liver toxicities which are reported in the AE eCRF and will be summarized as part of the general TEAEs tables. The peak post-baseline values for each parameter will be evaluated according to the liver toxicity criteria. For criteria based on a combination of parameters, the peak value for each parameter may not necessarily be from the same assessment date.

**Table 2-5 Liver toxicities based on laboratory definitions**

| **Definition** |
|---|
| ALT >3x ULN |
| ALT >5x ULN |
| ALT >10x ULN |
| ALT >20x ULN |
| |
| AST >3x ULN |
| AST >5x ULN |
| AST >10x ULN |
| AST >20x ULN |
| |
| ALT or AST >3x ULN |
| ALT or AST >5x ULN |
| ALT or AST >8x ULN |
| ALT or AST >10x ULN |
| ALT or AST >20x ULN |
| |
| TBL >2x ULN |
| TBL >3x ULN |
| |
| ALP >2x ULN (>3x ULN in the presence of bone pathology*) |
| |

| |
|---|
| Combined elevations post-baseline |
| AST and ALT =< ULN at baseline |
| ALT or AST >3x ULN & TBL >2x ULN |
| ALT or AST >3x ULN & TBL >2x ULN & ALP <2x ULN |
| ALT or AST >3x ULN & TBL >2x ULN & ALP >=2x ULN |
| ALT or AST > ULN at baseline |
| ALT or AST >3x Bsl or 8x ULN & TBL (>2x Bsl and 2x ULN) |
| ALT or AST >3x Bsl or 8x ULN & TBL (>2x Bsl and 2x ULN) & ALP <2x ULN |
| ALT or AST >3x Bsl or 8x ULN & TBL (>2x Bsl and 2x ULN) & ALP >=2x ULN |
| |
| * the presence of bone pathology is confirmed by reported AEs or medical history of HLGT = “Bone disorders (excl congenital and fractures)” with a start date prior to the laboratory measurement and stop date posterior to the laboratory measurement |

AE: Adverse Event, AST=Aspartate aminotransferase; also known as SGOT, ALT=Alanine aminotransferase; also known as SGPT, ALP=Alkaline phosphotase, Bsl= baseline, TBL=Total bilirubin, ULN: upper limit of normal

In addition, the number of participants meeting the following potential drug induced liver injury (DILI) definitions will also be summarized. If a participant met the criteria for more than one category, the participant will only be counted once in the most severe category, with Hy’s law being the most severe category and cholestasis the least severe category.

- Hy’s Law defined as post-baseline TBL elevation to >=2x ULN along with concurrent ALP <2x ULN, occurring on or within 30 days after a post-baseline ALT or AST elevation to >=3x ULN.
- Temple’s corollary defined as ALT and/or AST >=3x ULN but there is no accompanying TBL elevation or jaundice (defined as with non-missing TBL reading <2XULN on the same date as ALT/AST).
- Cholestasis defined as Jaundice occurs (TBL >=2x ULN) with no or minimal hepatocellular injury (defined as non-missing ALT and AST < 3x ULN on the same date as TBL).

Box-plots of absolute values and percentage change from baseline over time will be provided by treatment group for each of the parameters listed in Table 2-6:

**Table 2-6 Selected hematological, thyroid and reproductive hormone level parameters**

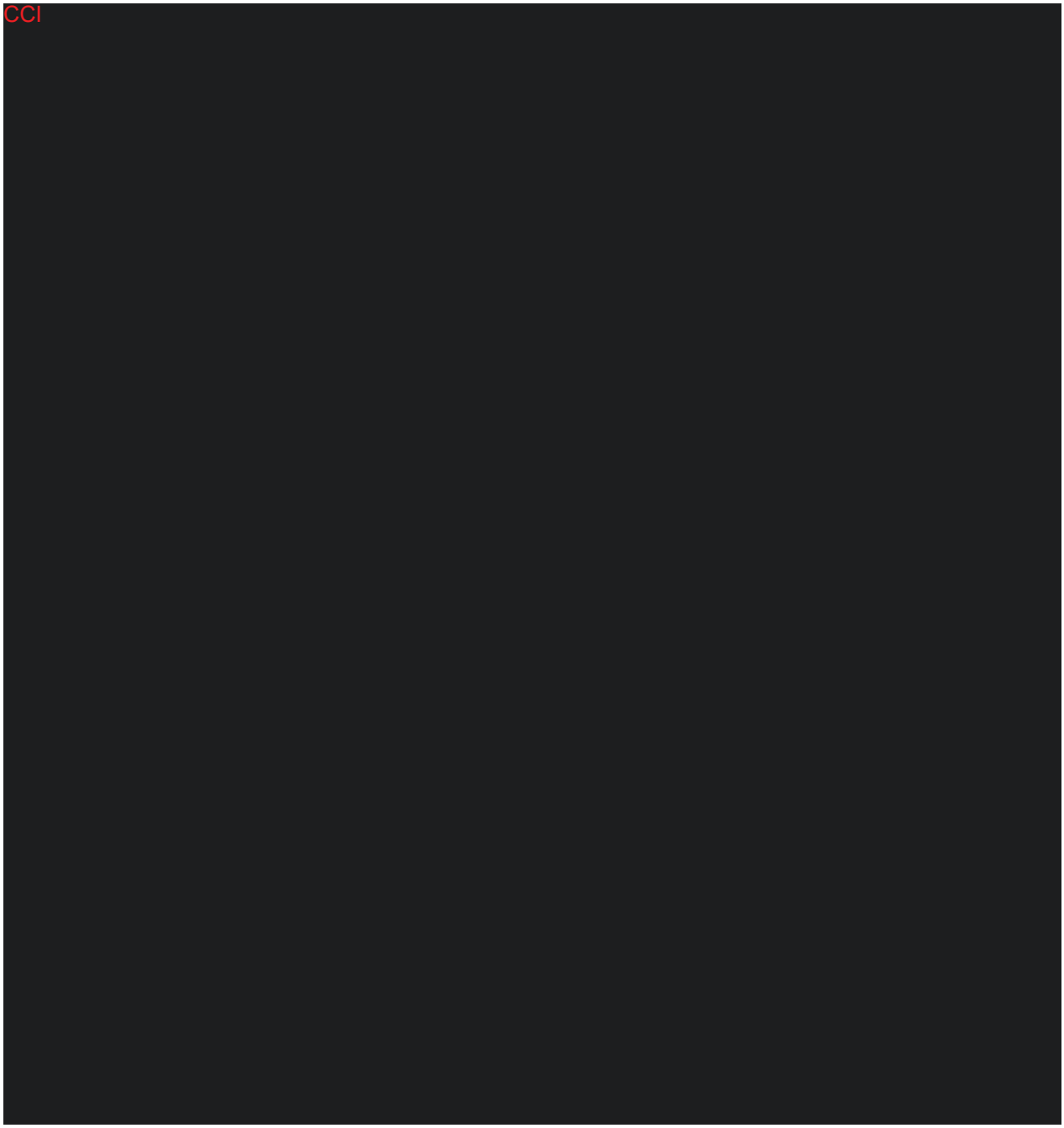
| Hematological | Thyroid hormone level | Reproductive hormone level | CCI |
|---|---|---|---|
| • RBC count<br>• Hemoglobin<br>• Reticulocyte count<br>• Platelet count<br>• Leukocyte count<br>• Lymphocyte count | • T3<br>• T4<br>• Reverse T3<br>• TSH | • Testosterone<br>• DHT<br>• LH<br>• FSH | [redacted] |

Note that displays of reproductive hormone level parameters will be further split by sex. Any remaining laboratory parameters may be similarly graphically presented. Where available, the ULN and LLN will be displayed.

Bar plots of occult blood categories (+4/+3/+2/+1/trace/negative) and bar plots showing the proportion of participants with hematuria (defined as an occult blood category of +1, +2, +3, or +4) based on urine dipstick will be provided over time by treatment group.

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### 2.8.4 Other safety data

#### 2.8.4.1 ECG and cardiac imaging data

The following ECG parameters will be obtained during the study and summarized descriptively: ECG mean heart rate, RR interval, PR interval, QRS duration, QT interval and corrected QT interval by the Fridericia criteria (QTcF). Summary statistics (absolute values and change from baseline) for all ECG parameters will be provided by treatment and time point. A listing of all

ECG data (with abnormalities flagged where ranges are available) will be provided for the Main study and SRI populations separately.

Box-plots of absolute values over time of the following ECG parameters will also be provided by treatment group: HR, QTcF interval.

Categorical summary statistics for ECG alert values will also be provided based on the number and proportion of participants meeting or exceeding the following predefined limits:

- QRS > 120 ms
- QRS increase from baseline > 25%
- QTcF > 500ms
- QTcF increase from baseline > 60 ms
- Resting heart rate sinus rhythm (HR) < 30 bpm
- HR decrease from baseline ≥ 25%
- HR > 130 bpm
- Ventricular tachychardia*
- New complete heart block (Grade III AV block)*
- Mobitz II AV block*

These participants will also be listed by treatment group.

*Noticeable ECG abnormalities such as ventricular tachychardia, new complete heart block (Grade III AV block) and Mobitz II AV block are reported as adverse events and will be described as part of AEs outputs.

### 2.8.4.2 Vital signs

Summary statistics (absolute values and change from baseline) will be provided for all vital signs data (weight, temperature, pulse rate, systolic blood pressure [SBP], diastolic blood pressure [DBP]) by treatment and visit/time. A listing of all vital signs data (with abnormalities flagged where ranges are available) will be provided for the Main study and SRI populations separately.

Box-plots of absolute values over time for pulse rate, SBP and DBP will also be provided by treatment group. Horizontal lines representing the upper limit of normal (ULN) and lower limit of normal (LLN) will be added as applicable.

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## 2.9 Pharmacokinetic endpoints

The PK analyses will include all participants in the SAF set with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement. Full PK profiles and calculation of respective PK parameters will only be generated for participants in the SRI population to investigate the impact of low eGFR on the exposure of LNP023. For all other participants only trough levels will be measured. At the time of the IA, only the PK of LNP023 in participants with SRI will be evaluated. PK analyses of other participant subgroups may potentially be evaluated, if a sufficient number of participants is available for analysis, and will be specified in a separate analysis plan.

Pharmacokinetic parameters will be determined using non-compartmental method(s) with Phoenix WinNonlin (Version 8.0 or higher) measured at the timepoints specified in CSP Section 8.5.1. Concentrations will be expressed in mass per volume units (ng/mL) and will refer to the free base.

The non-compartmental PK parameters to be determined (if feasible) are listed in Table 2-7 and additional PK parameters may be calculated if necessary, as outlined in the CSP.

**Table 2-7 Non-compartmental pharmacokinetic parameters**

| | |
|---|---|
| AUClast | The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1) |
| AUCtau | The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1) |
| Cmin | Lowest concentration in the concentration time profile. As the sample will be collected predose, Cmin is a surrogate for Ctrough. |
| Cmax | The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1) |
| Tmax | The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time) |
| CLr* | Renal clearance of LNP023 based on AUCtau and Ae (volume x time-1). |
| Ae* | Total amount of LNP023 excreted in urine over a 24h interval (mass). |
| Percent* Recovery | Percent of dose recovered in the urine (%) |

Parameters in Table 2-7 will be measured in plasma and urine for the SRI population only, apart from Cmin that will be assessed in all participants.

*only to be analyzed at the time of final analysis.

Pharmacokinetic parameters will be calculated for the SRI population only, apart from Cmin that will be assessed in all participants and will be summarized separately for the Main Study and SRI populations. Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV) (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below the LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. Unbound LNP023 PK concentrations and PK parameter data will be listed and summarized, if feasible.

LNP023 plasma concentration data will be summarized by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero; these will be distinguished from values missing. For full PK profiles in the SRI population, mean and individual plasma concentration-time profiles will be presented in both semi-log and linear scales. A spaghetti plot of the individual concentration-time profiles will also be considered for the SRI population. For trough levels, a plot of overlaying mean plasma concentration for the Main Study and SRI populations will be presented in both semi-log and linear scales per visit/sampling timepoint, if feasible.

Other planned analyses using pharmacokinetic data collected in this and other studies in participants with IgAN will be specified in a separate analysis plan, describing principles and methods which will include population PK modeling. These analyses will be described in a separate report.

## 2.10 Patient-reported outcomes

Analyses in this section will consider the Main study population only (with the exception of descriptive statistics provided in the SRI population as well for the FAS) and will be based on the IA-FAS at the IA and FAS at the final analysis (defined in Section 2.2).

A further exploratory analysis of FACIT-Fatigue will be conducted at the final analysis, following the same analysis principles as specified in Section 2.6.2.1 for the FACIT-Fatigue secondary estimand but considering the 24 month instead of the 9 month timepoint.

Three exploratory PRO questionnaires, PGIS, EORTC QLQ-C30 and EQ-5D-5L, will further be measured and analyzed at the IA and Final analysis to provide supportive quality-of-life information.

### 2.10.1 PGIS

Descriptive statistics of PGIS will be provided by visit and treatment group, for the Main population and SRI populations separately. Graphical displays (e.g barplot) will also be produced.

To further calibrate the performance of the FACIT-Fatigue in the context of treatment with LNP023 and determine within-patient, anchor-based minimally important change in FACIT-Fatigue total scores, analyses of changes in FACIT-Fatigue total scores will be examined by change in PGIS severity level by patient. The use of PGIS to calibrate baseline severity scale and subsequent changes will match unit changes in PGIS to changes in FACIT-Fatigue scores

to determine responder status. Once an anchor-based minimally important change in FACIT-Fatigue total score has been established, the supplementary responder analysis described in Section 2.6.6 will be repeated, considering a different responder definition as needed. The anchor-based analysis is described in detail in the following section:

### Determination of minimally important within-patient change

The determination of the magnitude corresponding to a minimally important within-patient change using anchor instruments will be done without use of treatment labels (i.e pooled across treatment groups). This will include:

- The median of FACIT-Fatigue change scores for the PGIS anchor instrument using categories derived from PGIS change scores in the direction of improvement, no change, or worsening at month 9 visit.

### Assessment using PGIS

PGIS focuses on current levels, and its use as anchor with respect to other multi-item instruments is through a change in score of severity. The PGIS change categories will be calculated from baseline to a scheduled visit, and indicate a worsening when there is an increase in symptoms severity, unchanged if the difference in severity symptoms is zero, and improvement if there is a decrease in symptoms severity.

The change in PGIS score will be classified as raw changes. The PGIS change categories considered (dependent on the distribution of changes) are:

- ≥ 2 grade worsening
- 1 grade worsening
- Stable: 0 grade change
- 1 grade improvement
- ≥2 grade improvement

Changes in the FACIT-Fatigue score should be consistent with changes in the PGIS, i.e., positively correlated. To determine the association between PGIS and FACIT-Fatigue score, polyserial correlations between PGIS change categories and FACIT-Fatigue change from baseline scores will be calculated for all visits up to (and including) Month 9 at which both the PGIS/FACIT-Fatigue were assessed ([Olsson et al. 1982]).

If the correlation coefficient is ≥0.3, this will be considered evidence of construct validity ([Revicki et al 2008]) and an anchor-based assessment to determine the minimally important within-patient change will be performed.

Descriptive statistics (see Section 2.1 for detail on continuous variables) of the change in FACIT-Fatigue score from baseline to Month 9 will be produced for each PGIS change category at the month 9 visit. In addition, the empirical cumulative distribution function (eCDF) and empirical probability density function (ePDF) of FACIT-Fatigue change scores will be displayed for each PGIS change category at the month 9 visit. Available sample size and

quantiles of the change scores will be identified from the eCDF. A value for the within-patient minimal meaningful change will be proposed based on these descriptive statistics and graphs. Note that for the anchor based analysis, only observed/available Main study population data will be considered.

### 2.10.2 Patient Interviews

At the time of the final analysis, participants' responses to the patient interview will be qualitatively analyzed and reported descriptively in a separate report. Results may be used in exploratory analysis of PRO measures and will be described, if applicable, in a separate program-level analysis plan.

### 2.10.3 EORTC QLQ-C30

The global health status scale, physical domain, and fatigue scale of the EORTC QLQ-C30 will be used to provide complementary information to FACIT-Fatigue on participant-reported symptoms and overall well-being.

Changes from baseline to 9 and 24 months in each of the individual domain/scales identified above will be analyzed following the same approach as for FACIT-Fatigue total score i.e. using an MMRM model as described in Section 2.6.2.1. Given the exploratory nature of this endpoint, data following the occurence of I/C events will be included in the analysis, in a treatment policy fashion; missing data are handled under MAR

The difference between the mean change from baseline to 9 months for LNP023 versus placebo will be presented, together with its two-sided 95% confidence interval.

Supportive responder analysis will similarly be provided at the final analysis for each of the global health status scale, physical domain, and fatigue scale of EORTC QLQ-C30. Response is defined as at least 10-point improvement in the relevant QLQ-C30 relevant domain/scale score. The analysis of the response data will be described in a separate program-level analysis plan.

Descriptive statistics of QLQ-C30 scales (absolute values and change from baseline) will also be provided by visit and treatment group, for the Main population and SRI populations separately.

### 2.10.4 EQ-5D-5L

EQ-5D-5L will be used to support Health Technology Assessment evaluations. Changes from baseline to 9 and 24 months in the EQ VAS will be analyzed following the same approach as for FACIT-Fatigue total score i.e. using an MMRM model as described in Section 2.6.2.1. Given the exploratory nature of this questionnaire, data following the occurence of I/C events will be included in the analysis, in a treatment policy fashion; missing data are handled under MAR.

The difference between the mean change from baseline to 9 months for LNP023 versus placebo will be presented, together with its two-95% confidence interval.

The EQ VAS score will be summarized (absolute values and change from baseline) by visit and treatment group, for the Main population and SRI population separately.

The number and percentage of participant responses for each of the five dimensions (each rated from 1 to 5 levels) in the descriptive system of the questionnaire will descriptively summarized by visit and treatment group, for the Main population and SRI population separately.

Note that for the analysis of the three additional exploratory PROs at the IA, the changes from baseline to 9 months will only be considered.

## 2.11 Biomarkers

The IA-FAS will be used at the IA and the FAS at the final analysis for all analyses in this section; for SRI, the FAS applies for both analysis points.

All biomarker parameter data (absolute values and percent change from baseline) will be summarized via descriptive statistics by treatment and timepoint, for the Main study and SRI populations separately. The biomarker parameters considered are listed in Table 2-8. Biomarkers measured in the urine will be considered both unadjusted and normalized by creatinine (as measured in the same urine sample).

The effect of LNP023 treatment on biomarkers will be explored graphically in the Main Study population using plots of the percent change from baseline in biomarker concentration, over visit/timepoint and by treatment group, based on the geometric mean i.e. calculated by back-transforming the mean of the log-transformed ratio to baseline biomarker values and presented as a percentage (e.g. a geometric mean ratio to baseline value of 1.2 will be presented as 20% in the plot, whereas a geometric mean ratio to baseline value of 0.8 will be presented as -20%).

CCI [redacted] Spaghetti plots of the biomarker parameters over time will be instead provided for the SRI population.

**Table 2-8 List of Biomarkers**

| Vendor | Biomarker** | Matrix | Unit | Description | Read out* |
|---|---|---|---|---|---|
| Central lab | Complement C3 | Serum | mg/L | Complement C3 | Complement C3 |
| Central lab | Complement C4 | Serum | mg/L | Complement C4 | Complement C4 |
| Central lab | Cystatin C | Serum | mg/L | Cystatin C | Cystatin C |
| Bioanalytical lab (SGS) | Wieslab | Serum | % | Alternative complement pathway activity | APFA |
| Bioanalytical lab (SGS) | Bb | Plasma | ng/mL | Circulating fragment Bb of Factor B | FBB |
| Bioanalytical lab (SGS) | sC5b-9 | Plasma | ng/mL | Soluble sC5b-9 | SC5b-9 |
| Bioanalytical lab (Eurofins) | sC5b-9 | Urine | pg/mL | Soluble sC5b-9, unadjusted concentration | SC5b-9 |
| Bioanalytical lab (Eurofins) | Creatinine | Urine | mmol/L | Creatinine | URINARY CREATININE |
| Bioanalytical lab (Eurofins) | sC5b-9/Creatinine | Urine | pg/nmoL | Soluble sC5B-9 normalized by creatinine | |

* Biomarker name exactly as it will appear in the dataset

** Biomarkers other than those in the Central lab were collected only for participants part of the biomarker sub-study (see protocol section 8.5.2.)

Any further exploratory biomarker analyses will be described in a separate data exploration plan.

**Handling of LLOQ and ULOQ**

Biomarker data are reported as concentration results, measured using a specific assay with a working range defined by the two following limits: Lower limit of quantification (LLOQ) and Upper limit of quantification (ULOQ). Values which fall below the LLOQ or above the ULOQ are reported as < LLOQ * dilution factor (dilution factor: if sample diluted and concentration measured still below LLOQ) and > ULOQ * dilution factor, respectively.

To ensure that biomarkers only have numerical values, censored values will be imputed as follows

- Values below the LLOQ are replaced by LLOQ*dilution factor/2.
- Values above the ULOQ are replaced by ULOQ*dilution factor.

Imputed values are used for summary statistics, inferential analyses and plots (with a special symbol). In the summary tables, the frequency (n, %) of values below the LLOQ and above the ULOQ respectively, will be included.

If the proportion of imputed data is more than 20% for any treatment group at any time point, a footnote is added to the summary statistics table stating that the proportion of values outside the limits of quantification is more than 20% for some treatment group at some time points, and that in such cases summary statistics may be biased.

## 2.12 Other Exploratory analyses

All exploratory endpoints listed below will be summarized descriptively for the Main Study and SRI populations separately. Note that any inferential statistics/modelling resulting in comparisons between treatment groups will only consider the Main Study population. Exploratory objectives related to PK, PRO and biomarker endpoints are described in the relevant sub-sections (Section 2.9, Section 2.10 and Section 2.11 respectively). The Trial feedback questionnaire information will be described and presented in a separate report.

The following exploratory endpoints will be analyzed based on the IA-FAS at the IA (with the exception of descriptive statistics provided in the SRI population on the FAS) and the FAS at the final analysis:

**At the Interim analysis**

- Log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months and annualized total eGFR slope estimated over 12 months in the subgroup of participants whose baseline proteinuria is ≥ 2g/g of UPCR (sampled from 24h urine collection)

The analysis of the log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months and annualized total eGFR slope estimated over 12 months for the subgroup of participants with baseline UPCR ≥2g/g is described earlier in the SAP as part of Sections 2.5.6.3 and 2.6.6.1 for Subgroup analyses at the IA.

- Log-transformed ratio to baseline in total urinary protein/day, total urinary albumin/day, UACR (sampled from 24h urine collection) and UPCR (sampled from first morning void, FMV) at 9 months.

  The MMRM described in Section 2.5.2 for UPCR 24h will be used to similarly analyze each of following endpoints individually:

  - log-transformed ratio to baseline in total urinary protein/day (24h-UP),
  - log-transformed ratio to baseline in total urinary albumin/day (24h-UA),
  - log-transformed ratio to baseline in UACR sampled from 24h urine collection (UACR 24h)
  - log-transformed ratio to baseline in UPCR sampled from first morning void (UPCR FMV) (also described under Section 2.5.6 Supplementary analyses)

  Intercurrent events as well as missing data not related to intercurrent events will be handled in the analysis as for the primary estimand at the IA (Section 2.5.3 and Section 2.5.4).

  The mean difference between LNP023 versus placebo (and its two-sided 95% CI) will be calculated for the 9 month time point. This will be back-transformed so that the ratio of geometric means (LNP023 vs. placebo) is presented for the 9 month time point together with the respective 95% CI. The model estimated geometric mean of the ratio to baseline (and respective 95% CI) by treatment group may be graphically presented over time by treatment group.

  A descriptive summary table (similar to that for UPCR 24h, see Section 2.5.1) will also be provided for these exploratory endpoints, for the Main Study and SRI populations separately; associated graphical displays may also be produced.

  At each visit where endpoints based on 24hr urine collections are collected, the mean (geometric) of two values, obtained from two distinct 24 hour urine collections as for UPCR 24h, will be used in the analysis as the measurement for that visit. In case only one value is available, that value will be instead used in the analysis.

  In order to correct for cases of under/over-collection of a 24hr urine sample, 24h-UP and 24h-UA values will be calculated using the following formula and used in the derivation of the mean value for the analysis:

$$Corrected\ 24h\ parameter = \frac{(measured\ parameter\ content\ \times 24\ )}{length\ of\ time\ (in\ hour) sample\ collected\ over}$$

- Proportion of participants requiring the use of CS/IS and/or newly approved drugs for IgAN treatment due to disease progression assessed from baseline to 9 months.

  Descriptive statistics (i.e. the frequency and percentage of participants) of the endpoint and each of its components individually (i.e. use of CS/IS vs. use of newly approved drugs) will be summarized by treatment group, for the Main study and SRI populations separately.

- Healthcare resource utilization endpoints (including number of ER visits and IgAN-related hospitalizations) collected from baseline to 9 months.

  Endpoints related to health resource utilization will be used to describe medical resources used by the study participants in relation to their IgAN. Healthcare resource utilization endpoints collected from baseline to 9 months will be summarized descriptively over time. The frequency and percentage of participants requiring the use of different healthcare facilities will be provided for the Main study and SRI populations separately, for the following categories: at least once, 0, 1, 2, 3, >=4 encounters/stays. The total number of participant encounters/stays in each facility type will also be summarized descriptively for the Main study and SRI populations separately. The number of days spent in each healthcare facility will be similarly summarized.

**At the Final analysis**

- Proportion of participants requiring the use of CS/IS and/or newly approved drugs for IgAN treatment due to disease progression assessed from baseline to 24 months.
  The same analysis principles as specified above for the corresponding exploratory endpoint at the IA will be employed, considering now the endpoint at the 24 months timepoint.

- Proportion of participants reaching UPCR (sampled from 24h urine collection) <1g/g at 24 months, without receiving CS/IS or other newly approved drugs for treatment of IgAN or initiating KRT.
  The above endpoint will be analyzed using the approach described in Section 2.6.2 for Secondary Estimand 2 at the Interim and Final analysis.

- Log-transformed ratio to baseline in total urinary protein/day, total urinary albumin/day, UACR (sampled from 24h urine collection), UPCR (sampled from first morning void, FMV), and UPCR (sampled from 24h urine collection) at 24 months.
  The same analysis principles as specified above for the corresponding exploratory endpoints at the IA will be employed, considering reductions from baseline to the 24 month timepoint.

- Time-averaged proteinuria [average of UPCR values (sampled from 24h urine collection)] from baseline to 24 months.

  Time-averaged proteinuria (TA-P), defined as the average of UPCR 24h values measured at pre-defined intervals (i.e. at Month 6, Month 9 and Month 24) from baseline to 24 months, will be calculated. A weighted mean, with weights assigned to “capture” the time elapsed since the last measurement, will be used for the calculation as follows:

- For each participant who has UPCR 24h value at Month 24, the TA-P over 24 months will be calculated as $\frac{6*x_1+3*x_2+15*x_3}{24}$ where $x_1$, $x_2$ and $x_3$ correspond to the log-transformed UPCR 24h for Month 6, Month 9 and Month 24 visit respectively, and will be back-transformed and reported on the original scale. In case of missing $x_1$ or $x_2$, weights will be updated to reflect the time since last measurement captured.
- Note that at visits where two distinct 24 hour urine collections are done, the mean (geometric) of two UPCR values obtained will be used for the above calculations, as described for the primary analysis (see Section 2.5.2).

The mean TA-P in each treatment group as well as the difference between groups will provided, together with the corresponding 95% CI, for the Main study and SRI populations separately.

- Healthcare resource utilization endpoints (including number of ER visits and IgAN-related hospitalizations) collected from baseline to 24 months.

The same analysis principles as specified above for the corresponding exploratory endpoints at the IA will be employed, considering now healthcare resource utilization data collected from baseline to 24 months.

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## 2.13 Interim analysis

An interim analysis is planned when approximately 250 participants in the Main Study population have completed the Month 9 visit. All participants randomized prior to the IA cut-off date will be included in the analysis. The primary purpose of this IA is to demonstrate superiority of LNP023 vs placebo on proteinuria reduction, based on percentage change from

baseline in UPCR 24h (i.e. log-transformed ratio to baseline in UPCR 24h), in order to support accelerated/conditional marketing authorization (see Section 1.1 of the SAP and Section 4.4 of CSP). Table 1-1 outlines the objectives and associated endpoints to be assessed at the IA.

To ensure strong control of the studywise type one error for multiplicity of testing to one sided 0.025, the sequentially rejective multiple test procedures ([Bretz et al 2009]), described in Section 2.6, will be used for testing the hypotheses associated with the primary endpoint at the IA ($H_1$), and the primary ($H_2$) and three secondary endpoints ($H_3$, $H_{41}$ and $H_{42}$) at the Final analysis.

The results of the IA will further inform decision making for the current study e.g. proceed with submission, continue or stop for safety or other reasons. As noted, it is expected that submission for accelerated/conditional approval may occur following this IA. Detailed information about the sponsor staff and other personnel who will have access to the unblinded data during the time of and following the initial submission and the measures taken to restrict access to participant level treatment codes will be provided in a separate Unblinding plan.

Periodic safety DMC reviews for the monitoring of safety data will be conducted by the external DMC during the course of the study. Investigators, participants and Sponsor staff will remain blinded during the safety DMC reviews. Separate dedicated RAP documentation (safety DMC SAP and TFLs) will be prepared and associated analysis will performed by an external analysis team, not involved in study conduct. Further detail on the periodic safety reviews is provided in the DMC charter. Such safety analyses do not inflate the type I error for the primary efficacy hypothesis testing and thus no adjustment for multiplicity is required.

# 3 Sample size calculation

EAST® version 6.4 [Cytel 2016] and R® software [R Core 2017] were used to conduct the sample size calculations described in this section.

## 3.1 Primary endpoints

**Interim analysis**

The log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) will be used to estimate the ratio of geometric means between the LNP023 and placebo groups. Assuming a true reduction in UPCR in the range of 25%-30% and a standard deviation of 0.7 (on the log-scale, estimated from [Fellström et al 2017]), a sample size of at least 250 participants provides at least 75-92% power that the primary analysis will be statistically significant at the one-sided 0.5% significance level.

**Final analysis**

The annualized total eGFR slope (mL/min/1.73m$^2$/year) estimated over 24 months will be used to estimate the difference in means between the LPN023 and placebo groups. Based on the relationship characterized by Inker el al ([Inker 2021], figure S6), a 25% - 30% true UPCR reduction is expected to translate into a clinically meaningful treatment effect of ~ 1.2-1.7 (mL/min/1.73m2 per year) difference in total eGFR slope over 2 years. Power for eGFR slope has been computed considering an assumed true difference of 1.1 in order to be conservative in the calculation. Uncorrelated test statistics for the hypothesis tests for proteinuria and eGFR

were assumed (i.e. the primary hypothesis test at the final analysis is assumed to be independent to the primary hypothesis test at the IA) in order to be conservative in the power calculation.

Assuming a true treatment difference in annualized total eGFR slope over 2 years of 1.1 and a standard deviation of 3.5 (informed from [Greene et al 2019]), a sample size of approximately 430 participants provides at least 89%-90% power that the primary analysis will be statistically significant at the one-sided significance level defined by the testing procedure described in Section 2.6.2.

## 3.2 Secondary endpoints

Nominal power at 1-sided 2.5% alpha for selected key secondary endpoints tested at the Final analysis is presented in the following section.

Calculations were conducted based on assumptions on the standard deviation and placebo event rates informed from published data ([Fellström et al 2017], [Lv et al 2017], [Macdonald et al 2012]) and assuming given treatment effects for LNP023 versus placebo. For the time-to-event endpoint, an accrual duration of 24 months, a fixed study duration of 48 months and follow-up of 24 months are further assumed.

For the comparison of LNP023 vs placebo on the proportion of participants achieving UPCR <1g/g, the current planned sample size provides 96% power, assuming response rates of 15% and 30% for placebo and LNP023 respectively.

Assuming an event rate of 16% in placebo over 2 years, and a hazard ratio of 58%-48%, the planned sample size provides 52-75% power for the comparison of LNP023 vs placebo on the composite kidney failure endpoint.

For the change from baseline to month 9 in the FACIT-Fatigue, the planned sample size provides 93-99% power assuming a true treatment difference of 4-5 points and a common standard deviation of 12.

# 4 Change to protocol specified analyses

The supportive responder analysis of FACIT-Fatigue will be conducted using a logistic model instead of a Generalized Linear Mixed Model (GLMM) due to numerical/out of memory issues with the GLIMMIX procedure in SAS. This is not expected to result in considerable differences in the Month 9 estimate as the correlation between visits (within patient) is likely to be limited.

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 AE date imputation

The imputation rules for AE dates will be included in a separate project-level analysis plan.

### 5.1.2 Concomitant medication date imputation

The imputation rules for Concomitant medications will be included in a separate project-level analysis plan. The same rules will be employed for concomitant non-drug therapies non relevant to efficacy analyses.

### 5.1.3 Laboratory data

For summary tables on laboratory parameters with values which are lower or greater than the respective limit of quantification (where these are available), the following imputation rule will be used:

- values less than Lower Limit of Quantification (LLoQ) will be imputed to 0.5×LLoQ
- values greater than Upper Limit of Quantification (ULoQ) will be imputed to 1.5×ULoQ.

The number and percentage of values below the LLoQ and above the ULoQ will be presented, if feasible, in the tables. For laboratory parameter figures, imputed values will be displayed.

## 5.2 Statistical models

### 5.2.1 Tabular view of estimands and associated estimation methods

**Table 5-1 Overview of estimands and estimation methods at the Interim Analysis**

| **Estimand** | **Endpoint** | **Handling Strategy for intercurrent events** | | | | | **Summary measure** | **Missing data handling** |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| **Primary estimand** | | | | | | | | |
| **Primary estimand‡** | log-ratio to baseline in $UPCR_{24h}$ at 9 months | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: MAR for LNP023, MAR for Placebo) | treatment policy | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | ratio of geometric means between groups | "J2R" for LNP023, MAR for Placebo |
| Sensitivity analysis 0.1 | | hypothetical (analysis assumptions: "**CR**" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: "**CR**" for LNP023, MAR for Placebo) | | | | | |
| Sensitivity analysis 0.2 | | | hypothetical (analysis assumptions: | | | | | |

| Estimand | Endpoint | Handling Strategy for intercurrent events | | | | | Summary measure | Missing data handling |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| | | | **MAR** for LNP023, MAR for Placebo) | | | | | |
| Sensitivity analysis 0.3 | | hypothetical (**tipping point analysis** for LNP023, MAR for Placebo) | hypothetical (**tipping point analysis** for LNP023, MAR for Placebo) | | | | | |
| Sensitivity analysis 0.4 | | hypothetical (analysis assumptions: LNP023: **"J2R" if I/C event due to disease progression**, MAR otherwise Placebo: MAR) | hypothetical (analysis assumptions: LNP023**: "J2R" if I/C event due to disease progression**, MAR otherwise Placebo: MAR) | hypothetical (analysis assumptions: "LNP023: **"J2R" if I/C event due to disease progression**, MAR otherwise Placebo: MAR) | | | | |

| **Estimand** | **Endpoint** | **Handling Strategy for intercurrent events** | | | | | **Summary measure** | **Missing data handling** |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| **Supplementary estimands‡** | | | | | | | | |
| Supplementary estimand 1 | log-ratio to baseline in $UPCR_{24h}$ at 9 months | **treatment policy** | **treatment policy** | **treatment policy** | treatment policy | **treatment policy (MAR model)** | ratio of geometric means between groups | "J2R" for LNP023, MAR for Placebo |
| Supplementary estimand 2 | log-ratio to baseline in **$UPCR_{FMV}$** at 9 months | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: "MAR" for LNP023, MAR for Placebo) | treatment policy | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | ratio of geometric means between groups | "J2R" for LNP023, MAR for Placebo |
| **Secondary estimands** | | | | | | | | |
| **Secondary estimand 1‡** | Change from baseline in eGFR at 9 months | hypothetical (analysis assumptions: "J2R" for LNP023, | hypothetical (analysis assumptions: "J2R" for LNP023, | hypothetical (analysis assumptions: MAR for LNP023, | treatment policy | hypothetical (analysis assumptions: "J2R" for LNP023, | Difference in means between groups | "J2R" for LNP023, MAR for Placebo |

| **Estimand** | **Endpoint** | **Handling Strategy for intercurrent events** | | | | | **Summary measure** | **Missing data handling** |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| | | MAR for Placebo) | MAR for Placebo) | MAR for Placebo) | | MAR for Placebo) | | |
| Sensitivity analysis 0.1 | | hypothetical (analysis assumptions: "**CR**" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: "**CR**" for LNP023, MAR for Placebo) | | | | | |
| Sensitivity analysis 0.2 | | | hypothetical (analysis assumptions: **MAR** for LNP023, MAR for Placebo) | | | | | |
| **Supplementary estimands** | | | | | | | | |
| Supplementary | | **treatment policy** | **treatment policy** | **treatment policy** | treatment policy | **treatment policy** | Difference in means | "J2R" for LNP023, MAR for Placebo |

| **Estimand** | **Endpoint** | **Handling Strategy for intercurrent events** | | | | | **Summary measure** | **Missing data handling** |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| estimand 1.1 | | | | | | **(MAR model)** | between groups | |
| **Secondary estimand 2** | proportion with $UPCR_{24h}$ <1g/g at 9 months **without receiving CS/IS, other newly approved drugs for IgAN, initiating new background therapy for IgAN** | composite ("without receiving CS/IS") | composite ("without receiving other newly approved drugs for IgAN") | composite ("without initiating new background therapy for IgAN treatment") | treatment policy | Composite ("without initiating KRT") | odds ratio | "J2R" for LNP023, MAR for Placebo. imputation done on continuous scale. For missing data due to death from kidney failure, non-response is imputed. |

| **Estimand** | **Endpoint** | **Handling Strategy for intercurrent events** | | | | | **Summary measure** | **Missing data handling** |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| | **treatment or KRT** | | | | | | | |
| Supplementary estimand 2.1 | proportion with $UPCR_{24h}$ <1g/g at 9 months **without initiating KRT** | **treatment policy** | **treatment policy** | **treatment policy** | treatment policy | composite ("without initiating KRT") | odds ratio | "J2R" for LNP023, MAR for Placebo. imputation done on continuous scale. For missing data due to death from kidney failure, non-response is imputed. |
| **Secondary estimand 3‡** | annualized total eGFR slope | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: MAR for LNP023, MAR for Placebo) | treatment policy | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | mean difference in slopes | "J2R" for LNP023, MAR for Placebo |
| Supplementary | annualized total eGFR slope | **treatment policy** | **treatment policy** | **treatment policy** | treatment policy | **treatment policy (MAR model)** | mean difference in slopes | |

| **Estimand** | **Endpoint** | **Handling Strategy for intercurrent events** | | | | | **Summary measure** | **Missing data handling** |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| estimand 3.1 | | | | | | | | |
| **Secondary estimand 4** | change from baseline to 9 months in the FACIT-Fatigue total score | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: MAR for LNP023, MAR for Placebo) | treatment policy | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | difference in means between groups | "J2R" for LNP023, MAR for Placebo |
| Supplementary estimand 4.1 | change from baseline to 9 months in the FACIT-Fatigue total score | **treatment policy** | **treatment policy** | **treatment policy** | treatment policy | **treatment policy** | difference in means between groups | "J2R" for LNP023, MAR for Placebo |
| Supplementary estimand 4.2 | **proportion achieving ≥5-point improvement** | hypothetical (analysis assumptions: | hypothetical (analysis assumptions: | hypothetical (analysis assumptions: MAR for LNP023, | treatment policy | hypothetical (analysis assumptions: | **odds ratio** | "J2R" for LNP023, MAR for Placebo, imputation done on continuous scale. |

| Estimand | Endpoint | Handling Strategy for intercurrent events | | | | | Summary measure | Missing data handling |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| | in the FACIT-Fatigue total score at 9 months | "J2R" for LNP023, MAR for Placebo, imputation done on continuous scale) | "J2R" for LNP023, MAR for Placebo, imputation done on continuous scale) | MAR for Placebo, imputation done on continuous scale) | | "J2R" for LNP023, MAR for Placebo, imputation done on continuous scale) | | |

"CR": copy-reference; "J2R": jump-to-reference; MAR: missing-at-random

Sensitivity analyses: cells left "blank" in the table for components that are unchanged vs the main analysis

Supplementary analyses: attributes and/or handling strategies that differ to the primary estimand are marked in "**bold**" text.

*In case of missing data due to non-administrative reasons post the I/C of Treatment discontinuation (D/C) for any reason or study D/C. For administrative reasons, MAR assumption considered for both arms.

‡these analyses will be repeated as supplementary on the FAS instead of the IA-FAS.

**Table 5-2 Overview of estimands and estimation methods at the Final analysis**

| **Estimand** | **Endpoint** | **Handling Strategy for intercurrent events** | | | | | **Summary measure** | **Missing data handling** |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| **Primary estimand** | | | | | | | | |
| **Primary estimand** | annualized total eGFR slope | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: MAR for LNP023, MAR for Placebo) | treatment policy | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | mean difference in slopes | "J2R" for LNP023, MAR for Placebo |
| Sensitivity analysis 0.1 | | hypothetical (analysis assumptions: "**CR**" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: "**CR**" for LNP023, MAR for Placebo) | | | | | |
| Sensitivity analysis 0.2 | | | hypothetical (analysis assumptions: | | | | | |

| Estimand | Endpoint | Handling Strategy for intercurrent events | | | | | Summary measure | Missing data handling |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| | | | **MAR** for LNP023, MAR for Placebo) | | | | | |
| Sensitivity analysis 0.3 | | hypothetical (**tipping point analysis** for LNP023, MAR for Placebo) | hypothetical (**tipping point analysis** for LNP023, MAR for Placebo) | | | | | |
| Sensitivity analysis 0.4 | | hypothetical (analysis assumptions: LNP023: "**J2R" if I/C event due to disease progression**, MAR otherwise Placebo: MAR) | hypothetical (analysis assumptions: LNP023: **"J2R" if I/C event due to disease progression**, MAR otherwise Placebo: MAR) | hypothetical (analysis assumptions: LNP023: **"J2R" if I/C event due to disease progression**, MAR otherwise Placebo: MAR) | | | | |

| Estimand | Endpoint | Handling Strategy for intercurrent events | | | | | Summary measure | Missing data handling |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| Sensitivity analysis 0.5 | | | | hypothetical (analysis assumptions: **new background therapy used for IgAN initiated for other indications** LNP023: MAR Placebo: MAR) | | | | |
| Sensitivity analysis 0.6 | | assumptions same as primary analysis, **imputation via MMRM** | assumptions same as primary analysis, **imputation via MMRM** | assumptions same as primary analysis, **imputation via MMRM** | assumptions same as primary analysis, **imputation via MMRM** | assumptions same as primary analysis, **imputation via MMRM** | | assumptions same as primary analysis, **imputation via MMRM** |

| Estimand | Endpoint | Handling Strategy for intercurrent events | | | | | Summary measure | Missing data handling |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| Sensitivity analysis 0.7 | | | | | | | | **MAR** for LNP023, MAR for Placebo |
| CCI [redacted] | | | | | | | | |
| **Supplementary estimands** | | | | | | | | |
| Supplementary estimand 1 | annualized total eGFR slope | **treatment policy** | **treatment policy** | **treatment policy** | treatment policy | **treatment policy (MAR model)** | mean difference in slopes | "J2R" for LNP023, MAR for Placebo |
| Supplementary estimand 2 | annualized **long term** eGFR slope | hypothetical (analysis assumptions: | hypothetical (analysis assumptions: | hypothetical (analysis assumptions: | treatment policy | hypothetical (analysis assumptions: | mean difference in slopes | "J2R" for LNP023, MAR for Placebo |

| Estimand | Endpoint | Handling Strategy for intercurrent events | | | | | Summary measure | Missing data handling |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| | | "J2R" for LNP023, MAR for Placebo) | "J2R" for LNP023, MAR for Placebo) | MAR for LNP023, MAR for Placebo) | | "J2R" for LNP023, MAR for Placebo) | | |
| Supplementary estimand 3 | **Change from baseline to 24 months in eGFR** | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | hypothetical (analysis assumptions: MAR for LNP023, MAR for Placebo) | treatment policy | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo) | **difference in means between groups** | "J2R" for LNP023, MAR for Placebo |
| Supplementary estimand 4 | **Change from baseline to 24 months in eGFR** | **treatment policy** | **treatment policy** | **treatment policy** | treatment policy | **treatment policy (MAR model)** | **difference in means between groups** | "J2R" for LNP023, MAR for Placebo |
| **Secondary estimands** | | | | | | | | |
| **Secondary estimand 2** | proportion with | composite ("without | composite ("without | composite ("without | treatment policy | Composite ("without | odds ratio | "J2R" for LNP023, |

| Estimand | Endpoint | Handling Strategy for intercurrent events | | | | | Summary measure | Missing data handling |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| | $UPCR_{24h}$ <1g/g at 9 months **without receiving CS/IS, other newly approved drugs for IgAN, initiating new background therapy for IgAN treatment or KRT** | receiving CS/IS") | receiving other newly approved drugs for IgAN") | initiating new background therapy for IgAN treatment") | | initiating KRT") | | MAR for Placebo. imputation done on continuous scale.<br>For missing data due to death from kidney failure, non-response is imputed. |
| Supplementary estimand 2.1 | proportion with $UPCR_{24h}$ | **treatment policy** | **treatment policy** | **treatment policy** | treatment policy | composite ("without | odds ratio | "J2R" for LNP023, |

| Estimand | Endpoint | Handling Strategy for intercurrent events | | | | | Summary measure | Missing data handling |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| | <1g/g at 9 months **without initiating KRT** | | | | | initiating KRT") | | MAR for Placebo. imputation done on continuous scale.<br>For missing data due to death from kidney failure, non-response is imputed. |
| **Secondary estimand 3** | Time-to-first occurrence of reaching either a sustained ≥30% decline in eGFR relative to baseline, or sustained eGFR <15 mL/min/1.73 | treatment policy | treatment policy | treatment policy | treatment policy | composite (part of dialysis and kidney transplantation components) | Hazard ratio | Censoring |

| Estimand | Endpoint | Handling Strategy for intercurrent events | | | | | Summary measure | Missing data handling |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| | $m^2$, or maintenance dialysis, or receipt of kidney transplant, or death from kidney failure | | | | | | | |
| Sensitivity analysis 0.1 | | | | **hypothetical (censoring)** | | | | |
| Sensitivity analysis 0.2 | | | | **hypothetical** (analysis **adjusting for non-informative censoring)** | | | | |
| **Secondary estimand 4** | change from baseline to 9 months in the FACIT- | hypothetical (analysis assumptions: | hypothetical (analysis assumptions: | hypothetical (analysis assumptions: | treatment policy | hypothetical (analysis assumptions: | difference in means between groups | "J2R" for LNP023, MAR for Placebo |

| Estimand | Endpoint | Handling Strategy for intercurrent events | | | | | Summary measure | Missing data handling |
|---|---|---|---|---|---|---|---|---|
| | | **Intake of CS/IS** | **Intake of other newly approved drugs for IgAN** | **Initiation of new background therapy for IgAN treatment** | **Treatment discontinuation for any reason** | **Initiation of KRT** | | **Due to non-administrative reasons post D/C*** |
| | Fatigue total score | "J2R" for LNP023, MAR for Placebo) | "J2R" for LNP023, MAR for Placebo) | MAR for LNP023, MAR for Placebo) | | "J2R" for LNP023, MAR for Placebo) | | |
| Supplementary estimand 4.1 | change from baseline to 9 months in the FACIT-Fatigue total score | **treatment policy** | **treatment policy** | **treatment policy** | treatment policy | **treatment policy** | difference in means between groups | "J2R" for LNP023, MAR for Placebo |
| Supplementary estimand 4.2 | **proportion achieving ≥5-point improvement** in the FACIT-Fatigue total score at 9 months | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo, imputation done on continuous scale) | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo, imputation done on continuous scale) | hypothetical (analysis assumptions: MAR for LNP023, MAR for Placebo, imputation done on continuous scale) | treatment policy | hypothetical (analysis assumptions: "J2R" for LNP023, MAR for Placebo, imputation done on continuous scale) | **odds ratio** | "J2R" for LNP023, MAR for Placebo, imputation done on continuous scale |

”CR”: copy-reference; ”J2R”: jump-to-reference; MAR: missing-at-random; MMRM: Mixed Model of Repeated Measures.

Sensitivity analyses: cells left “blank” in the table for components that are unchanged vs the main analysis

Supplementary analyses: attributes and/or handling strategies that differ to the primary estimand are marked in “**bold**” text.

*In case of missing data due to non-administrative reasons post the I/C of Treatment discontinuation (D/C) for any reason or study D/C. For administrative reasons, MAR assumption considered for both arms.

### 5.2.2 General considerations

#### General principles in case of non-convergence

In case non-convergence issues in analysis models are encountered, the following steps should be taken in a sequential order until convergence is achieved:

1. Use the autoregressive (AR(1)) covariance structure (applicable to MMRMs).
2. Remove stratification factors.
3. Remove *baseline_value*timepoint* interaction term (where such a term is included in the original model).
4. Use the compound symmetry (CS) covariance structure (applicable to MMRMs).

Note that at the time of the IA, the sparsity of observations at visits occurring later in the study follow-up (i.e. beyond Month 12) may lead to non-convergence issues in longitudinal analysis and/or imputation models. If this issue occurs, the first step that will be considered is to implement the models considering data up to (and including) Month 12. In case non-convergence issues persist, the steps outlined above will be followed.

For the Ethnicity subgroup analysis, the first step that will be considered is to remove the Geographical region stratification factor for which categories may be largely overlap (e.g. non-Asia with Hispanic or Latino). In case non-convergence issues persist, the steps outlined above will be followed.

#### Handling of mis-stratifications

For participants randomized in the wrong stratum, the stratum assigned per randomization should be used in analysis models adjusting for stratification factors and for subgroup analysis by stratification factor. This offers the advantage of maintaining randomization balance within each stratum. As mis-stratification cases are expected to be very few, limited to no impact on subgroup analysis interpretation due to mis-classification is expected [Ke et al. 2017].

#### Non-administrative reasons for missing data

Data will be considered to be missing **due to non-administrative reasons** if:

- the participant discontinued treatment or study for any of the below reasons (as recorded in the Disposition eCRF):
  - Adverse event
  - Physician decision

**OR**

- if prior to study discontinuation, the participant had prematurely discontinued treatment due to “Failure to meet continuation criteria”.

### 5.2.3 Analysis of primary objectives/estimands

In the description below, “missing” refers to values after the occurence of the I/C events of intake of CS/IS or other newly approved drugs for treatment of IgAN handled with a

hypothetical strategy, as described in Table 1-3, which will be excluded from the analysis and subsequently imputed to indicate a worsening in condition.

1. For the analysis of UPCR 24h, the imputation could be implemented for example using the "five macros" available from the DIA working group website https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-working-group (for detail see [Carpenter et al 2013] and [Cro et al 2020]). The first step in implementing this pattern mixture imputation approach is to fit a Bayesian normal repeated measures model, taking into consideration the longitudinal data structure, to estimate model parameters. The model will include the same covariates as the primary analysis model. Then the estimated parameters will be used to build possible predicted profiles for the "missing" values in a separate imputation model, one for each pattern of withdrawal (under a "jump-to-reference" (J2R) assumption [i.e. based on the "reference" placebo group] for the LNP023 group and a MAR assumption for the placebo group). "Missing" values for a participant are then imputed based on the profile of predicted means that matches their treatment, their time of withdrawal and other covariates. A large number of imputed datasets will be created, with their number chosen based on computational feasibility, but at least 200. Each dataset will then be analyzed using the MMRM model described in Section 2.5.2 and the results will be combined using Rubin's rules.
2. For the analysis of eGFR slope, fit the longitudinal mixed effects model described in Section 2.5.2.2, setting the treatment indicator for "missing" values (values after the I/C) in the LNP023 group to that for the placebo group. Then use the estimated conditional expected values for "missing" data given the observed data, and associated conditional standard errors predicted in order to build a MVN distribution. From this MVN distribution, draw responses for "missing" values in the LNP023 group. For the placebo group, values can be left as "missing" and handled implicitly under MAR by the analysis model. The imputation step will be repeated multiple times (at least 200) and a large number of imputed datasets created. Each dataset will be analyzed using the longitudinal mixed effects model described in Section 2.5.2.2 and the results will be combined using Rubin's rules.

In case eGFR is imputed to negative values which are implausible, such negative values will be replaced with a random draw from a Uniform distribution[1,14] to reflect that the value has dropped below the clinical convention threshold for kidney failure.

### 5.2.4 Analysis of secondary objectives/estimands

#### Secondary estimand 2

For the analysis of Secondary Estimand 2, the logistic regression model described in Section 2.6.2 will be used. The marginal standardization method will be used to calculate the mean response rate in each treatment group as well as their difference. This method uses the same fitted logistic model, but involves using the model to predict, for each participant in the study, the mean outcome assuming assignment to each of the two treatment groups in turn, assuming each participant's observed values for other covariates (e.g. baseline log (UPCR 24h)). Averaging these predictions for each treatment group provides the estimate of the mean response rate for each treatment group. Then the difference will be derived based on the

estimated mean response rates comparing LNP023 vs Placebo. The SAS macro Margins (see Reference Section) will be used to implement this method.

In cases of very low or very high response rates in either treatment group (i.e <0.05 or >0.95), bootstrapping will be used instead of the marginal standardization method.

For cases where the model does not reach appropriate convergence, the marginal risk difference will not be presented and instead the steps described in Section 5.2.2 will be followed until convergence is achieved. In case non-convergence issues persist due to sparsity or no response in one of the treatment arms, the logistic regression model described in Section 2.6.2.1 will be instead implemented based on Firth's penalized maximum likelihood method ([Heinze & Schemper, 2002]) ([Firth, 1993]). Any further convergence issues and supporting outputs will be documented in the appendix of the CSR.

### Secondary estimand 4

In case FACIT-Fatigue is imputed to values less than 0 or above 52 which are implausible, such values will be replaced with 0 and 52 respectively.

## 5.3 Rule of exclusion criteria of analysis sets

The analysis sets definitions are given in Section 2.2, and criteria for subject classification to analysis sets are outlined in Table 2-1. Data records containing confirmed cases of biological sample analysis after Withdrawal of Consent, when not allowed per ICF or local regulations, will be flagged and excluded from all analyses including listings.

## 5.4 Laboratory data definitions

MedDRA codes listed in Table 5-3 are based on MedDRA version 23.1 The list will be updated for each MedDRA version change and will be included in the CRS. The latest CRS version will be used as reference for analyses.

| **Table 5-3 Definition of symptoms and AEs for liver toxicities Term in CRS** | **MedDRA term(s)** |
|---|---|
| **Bone pathology** | HLGT = Bone disorders (excl. congenital and fractures) |
| **Symptoms of liver disorder** | |
| Severe Fatigue (1) | PT = Fatigue |
| Abdominal pain (right upper quadrant) | PT = Abdominal pain upper |
| Nausea | PT = Nausea |
| Vomiting | PT = Vomiting |
| General malaise | PT = Malaise |
| Rash with eosinophilia | PT = Drug reaction with eosinophilia and systemic symptoms |
| **Gilbert syndrome** | PT = Gilbert's syndrome |
| **Jaundice** | PT = Jaundice<br>PT = Jaundice cholestatic |

| | |
|---|---|
| **Liver toxicities** | |
| Hepatic failure | HLT = Hepatic failure and associated disorders |
| Hepatic fibrosis and cirrhosis | HLT = Hepatic fibrosis and cirrhosis<br>PT = Hepatic cirrhosis |
| Non-infectious hepatitis | PT = Hepatitis<br>PT = Hepatitis acute<br>PT = Hepatitis toxic<br>PT = Hepatitis fulminant<br>PT = Hepatitis chronic active<br>PT = Hepatitis chronic persistent |
| Liver neoplasm | HLGT = Hepatobiliary neoplasms |

HLT: High Level Term
HLGT: High Level Group Term
(1) presence of Fatigue term with severity ≥ “Severe”

CCI

[redacted]

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