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LNP023 (Iptacopan)

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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

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List of abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
AESI	Adverse Event of Special Interest
AKIN	Acute Kidney Injury Network
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti-HBc	Hepatitis B core antibody
Anti-HCV	Hepatitis C antibody
AP	Alternative Pathway
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AxMP	Auxiliary Medicinal Product
b.i.d.	Twice A Day
BUN	Blood Urea Nitrogen
C3G	Complement-3-Glomerulopathy
CFR	Code Of Federal Regulation
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
COA	Clinical Outcome Assessment
COVID-19	Coronavirus Disease 2019
CP	Classical Pathway
CRA	Clinical Research Associate
CRF	Case Report/Record Form (Paper or Electronic)
CRO	Contract Research Organization
CS	Corticosteroids
CTP	Clinical Trial Protocol
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EORTC QLQ-C30	European Organization For The Research And Treatment Of Cancer Quality Of Life Questionnaire
EOS	End Of Study
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
EQ VAS	EuroQol Visual Analogue Scale
EQ-5D-5L	EuroQol - 5 Dimensions- 5 Level
eSource	Electronic Source
ESRD	End-Stage Renal Disease

EU CTR	European Union Clinical Trial Regulations
FACIT	Functional Assessment Of Chronic Illness Therapy
FB	Factor B
FMV	First Morning Void
FSGS	Focal-Segmental Glomerulosclerosis
GCP	Good Clinical Practice
GCS	Global Clinical Supply
Gd-IgA	Galactose-Deficient IgA
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GLMM	Generalized Linear Mixed Model
GN	Glomerulonephritis
h	Hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV-RNA	Hepatitis C virus ribonucleic acid
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality Of Life
HRU	Healthcare Resource Utilization
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council For Harmonization Of Technical Requirements For Registration Of Pharmaceuticals For Human Use
IEC	Independent Ethics Committee
IgAN	Immunoglobulin A Nephropathy
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IS	Immunosuppressant Therapy
IUD	Intrauterine Device
IUS	Intrauterine System
KDIGO	Kidney Disease Improving Global Outcomes
KRT	Kidney Replacement Therapy
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LLOQ	Lower Limit Of Quantification
LMW	Low Molecular Weight
LOAEL	Lowest Observed Adverse Effect Level
LP	Lectin Pathway
MAD	Multiple Ascending Dose

MAR	Missing At Random
MDRD	Modification Of Diet In Renal Disease
MedDRA	Medical Dictionary For Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
MMF	Mycophenolate Mofetil
MMRM	Mixed Model Of Repeated Measures
MN	Membranous Nephropathy
MPS	Mycophenolate Sodium
NKF	National Kidney Foundation
NYHA	New York Heart Association
OATP	Organic Anion-Transporting Polypeptide
ORN	Off-Site Research Nurse
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Hemoglobinuria
PRO	Patient Reported Outcomes
PT	Prothrombin Time
QMS	Quality Management System
QTcF	QT Interval Corrected By Fridericia's Formula
RAAS	Renin-Angiotensin-Aldosterone System
RAS	Renin-Angiotensin System
RBC	Red Blood Cell(s)
REP	Rollover Extension Program
RPGN	Rapidly Progressive Glomerulonephritis
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sCR	Serum Creatinine
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
SRI	Severe Renal Impairment
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total Bilirubin
TFQ	Trial Feedback Questionnaire
UA	Urine Albumin
UACR	Urine Albumin-To-Creatinine Ratio
UK	United Kingdom
ULN	Upper Limit of Normal
UP	Urine Protein
UPCR	Urine Protein-To-Creatinine Ratio
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal Of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Auxiliary Medicinal Product (AxMP)	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess endpoints in the clinical trial). Concomitant therapy is not considered as AxMP.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial/study	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational Product/Investigational Medicinal Product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or

	when used for an unapproved indication, or when used to gain further information about an approved use.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional	A qualified healthcare professional, such as those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection.
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm assignment
Remote	Describes any trial activities performed at a location that is not the investigative site.
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant’s intervention or other treatment)
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.

Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 5 (18-Oct-2024)

This is the fifth amendment to the protocol, which has now completed enrollment with a total of 518 randomized patients. The purpose of the protocol amendment is to implement changes based on Investigator's Brochure (IB) version 11, release date 27-Jun-2024.

Major Changes to the protocol:

The following updates were made to in line with IB version 11.

- Added text into Section 6.2.1.1 to consider caution if co-administration of iptacopan with sensitive CYP3A4 or CYP2C8 substrates is required based on feedback from Health Authorities.
- Added text to Section 6.2.3 that co-administration of iptacopan with strong CYP2C8 inhibitors (e.g., gemfibrozil) and strong CYP2C8 inducers (e.g., rifampin) is prohibited based on feedback from Health Authorities. Table 6-2 was updated accordingly.
- Removed restrictions regarding concomitant use of live vaccines from Table 6-2.

Other changes to the protocol:

- Added a reference to the IB – Section 7 in Section 4.5.
- Removed "bilateral tubal ligation" as a form of sterilization in Section 5.2 (Exclusion criteria) and inserted it as a form of contraception in a separate bullet as follows: "Bilateral tubal occlusion, bilateral tubal ligation (at least 6 weeks before taking investigational drug)." Replaced bilateral tubal ligation with bilateral salpingectomy as a method of female sterilization in Section 5.2 (Exclusion criteria) and in the list of procedures exempting women from pregnancy testing in Section 8.4.3.
- Additional minor changes were made for clarification purposes, and to correct typographical errors and inconsistencies in the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, if applicable.

Amendment 4 (15-Feb-2024)

This is the fourth protocol amendment to the protocol. The purpose of the protocol amendment is to implement the changes based on Investigator's Brochure (IB) version 10 release date 07-July-2023 and changes related to European Union Clinical Trial Regulations (EU CTR) 536/2014.

Major Changes to the protocol:

CCI [redacted]

- Updated text in Section 4.5 and Section 6.6.2 to clarify response to infections caused by encapsulated bacteria from permanent study treatment discontinuation to temporary treatment interruption. This is in line with growing experience and evidence from completed and ongoing iptacopan studies in different indications, as well as feedback from investigators, with a further recommendation of bacterial cultures collection in all patients with suspicion of bacterial infections, and a consideration for prophylactic antibiotics and early booster vaccinations in patients with recurrent infections and/or in patients taking concomitant immunosuppressants.

Minor changes to the protocol:

- Section 4.3 and Section 6.1.2 language was updated to clarify that background therapies ACEi and ARB are considered auxiliary medicinal products (AxMP) per the new EU CTR. Collecting, assessing, and reporting of AEs related to AxMP was updated in Section 10.1.1 and Section 10.1.3.
- Section 10.1.3 and Table 16-1 was updated to indicate that all potential cases of Hy's law must be reported as SAEs.
- The protocol was updated in line with current CTP template (version 8.0). Clarifications regarding preparation and dispensation was added to Section 6.7. Clarifications regarding adverse event reporting via an Electronic Data Collection Tool was added to Section 10.1. Clarification of the requirement to report abnormal pregnancy outcomes as serious adverse events was added to Section 10.1.4. Details regarding data quality assurance was added in Section 13.4.
- Additional minor changes were made for clarification purposes, and to correct typographical errors and inconsistencies in the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, if applicable.

Amendment 3 (17-Mar-2023)

Amendment rationale

This is the third protocol amendment to the protocol. The purpose of the current protocol amendment is to implement the following:

Major Changes to the protocol

- Removal of the cap of approximately 150 biomarker sub study participants in order to allow for generation of additional biomarker information. Section 8.5.2.1 is updated accordingly.
- The number of SRI population participants is increased from approximately 20 to up to approximately 40 to allow for a comprehensive characterization of PK in this population. As a result, the study will enroll 470 participants instead of 450. Section 1.2, Section 3 and Section 5 are updated accordingly.
- Change from baseline in eGFR at 9 months assessed at the Interim Analysis is removed from the testing strategy per alignment with FDA. Relevant protocol sections have been updated accordingly (Section 2, Section 4.4, Section 12.5.1, Section 12.7, Section 12.8, Section 15).

Other changes to the protocol are:

- The exploratory PK objective is changed to evaluate PK of LNP023 in participants with SRI for whom PK information is currently not available, and potentially other subgroups if a sufficient number of participants are available for analysis at the IA. Urine PK analysis is removed from the IA as plasma analysis is prioritized to assess whether LNP023 exposure increases in SRI participants. Relevant protocol sections have been updated (Section 2, Table 2-1, and Section 12.5.3).
- Section 6.4 is updated to include further detail on the unblinding plan at the time of the Interim Analysis.
- The exploratory objective on the patient interviews at IA is removed as this objective will be analyzed when all patient interview data are available at the Final Analysis. Table 2-1 and Section 12.5.6 were updated accordingly.
- In order to allow for collection of PRO data in the case of technical failure of the electronic PRO device, the option to complete PRO questionnaires in paper format was added. Section 8.5.3 is updated accordingly.
- Removal of text related to risks of cardiovascular effects and bone marrow toxicity to align with the latest version of the Investigator Brochure Edition 9 release date 29-Jun-2022. Section 4.5 is updated accordingly.
- Changed vaccination against Streptococcus pneumoniae in inclusion criteria from recommended to required, based on newly available literature supporting increased risk of pneumococcal infection under Factor B deficiency/suppression. Section 3, Section 5.1 and Section 8.1.2 are updated accordingly.
- Adjusted wording of study rationale, exclusion criteria and medications requiring study treatment interruption or discontinuation to accommodate recent and upcoming approvals of new medications for IgAN. Section 5.2 and Section 6.2.2 are updated accordingly.

- Section 12.5.5 is updated to include other planned analyses using biomarkers collected in this and other studies, which will be specified in a separate Analysis plan, and described in a separate report.
- Wording of definition of post-menopausal woman and woman of childbearing potential have been updated to follow the latest internal guidance and template on wording for Pregnancy and assessment of fertility in Sections 5.2 and 8.4.3.

Additional minor changes were made for clarification purposes and to correct typographical errors and inconsistencies in the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, if applicable.

The changes herein are also reflected in the Informed Consent.

Amendment 2 (11-Apr-2022)

Amendment rationale

This is the second protocol amendment to the protocol. The purpose of the current protocol amendment is to implement the following:

Major changes to the protocol

The following changes have been implemented throughout the protocol:

- Change from baseline in eGFR at 9 months is moved from an exploratory endpoint to secondary endpoint at the Interim Analysis and is added to the testing strategy in order to control the study wise type I error rate for multiplicity of testing. Although the annualized total eGFR slope estimated over at least 12 months of treatment remains the preferred measure for kidney disease progression, the change from baseline in eGFR is considered relevant even at the early time point of 9 months. At the time of the Interim Analysis approximately 250 patients will have been assessed for the change from baseline in eGFR at 9 months, providing supportive evidence of efficacy to the primary analysis. Relevant protocol sections have been updated accordingly (Section 2, Section 4.4, Section 12.5.1, Section 12.7, Section 12.8).

Other changes to the protocol are:

- Wording "total score" was deleted from EQ-5D-5L and EORTC QLQ-C30 as it was a typographical inconsistency. The specific PRO tools do not yield a total score and instead comprise different sections and subscales/domains (Section 2, Tables 2.1 and 2.2).
- Reduction of urine protein excretion by measuring UPCR sampled from a 24h urine collection at month 24 is added as an exploratory endpoint at the final analysis along with the other exploratory proteinuria/albuminuria analyses at month 24 (Section 2, Table 2-2).
- Trial Feedback Questionnaire (TFQ) - TFQ data is considered outside of clinical trial data and will not be part of Clinical Database and Clinical Study Report (CSR). (Section 8, Table 8.1 Assessment Schedule and Section 8.5.3).
- Clarification added that for all estimands, background treatment with ACEi/ARB may include other background treatment for IgAN started prior to randomization (Section 2).
- Clarification added that significant non-drug therapies prior to and after the start of the study treatment are summarized by SOC and not according to ATC as it is the case for concomitant medications (Section 12.3).
- Summaries of AE by SMQ were removed as relevant AEs are captured as part of SOCs or AESI searches (Section 12.5.2).
- Clarification added that the supportive responder analysis of EORTC QLQ-C30 will be included in the program-level SAP, in a similar fashion to other supportive exploratory PRO analyses (Section 12.5.6).
- 50% increase in BUN and serum creatinine were removed from the list of clinically notable laboratory values (Section 16.1 Appendix 1) since both parameters represent kidney function, evaluated within efficacy endpoints.

Additional minor changes were made for clarification purposes and to correct inconsistencies in the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, if applicable.

Amendment 1 (30-Mar-2021)

Amendment rationale

This is the first protocol amendment to the protocol. The purpose of the current protocol amendment is to implement the following:

Major changes to the protocol

The following changes have been implemented throughout the protocol:

- Clarification that administration of steroids at pharmacological doses, immunosuppressive, or immunomodulating agents for management of IgAN, are not prohibited, but require discontinuation of study treatment for safety reasons. Section 6.2 has been revised accordingly.
- Definition of pharmacological dose of steroids changed from >10 mg/d to >7.5 mg/d prednisone/prednisolone equivalent in order to align with the current understanding of immunosuppressive steroid effects (Sections 5.2 and Section 6.2.2).
- Background medication for IgAN in addition to ACEi/ARB should also be stabilized for at least 90 days prior to the first dosing of study treatment and remain the same throughout the study. Section 3; Section 5.1; Section 6.2.1 and Section 6.6 have been revised accordingly.
- Additional intercurrent event is specified for IgAN background medication (see above) newly initiated during the study as it can confound the interpretation of the treatment strategy of interest, especially given the placebo controlled setting of the study where participants randomized to the placebo group may initiate new background therapy more often than participants randomized in the LNP023 group. Changes made to Section 2.1; Section 2.2; Section 12.4; Section 12.5 and Section 12.6 and Tables: Table 2-1 and Table 2-2.
- The alpha-spending for the study is revised so that 0.5% (one-sided) alpha is allocated at the interim analysis (IA), based on HA feedback received, and the alpha for remaining hypothesis testing is adjusted to 2% (one-sided). Section 12.8 is accordingly revised to include power at 1-sided 0.5% alpha assuming true reduction in UPCR in the range of 25%-30%, and the sequentially rejective multiple test procedure described in Section 12.5.1 and Section 12.7 to reflect the revised alpha spending for the study.
- Fibrates are added to prohibited medications during the trial as they may confound the efficacy assessment of LNP023. If the medical condition requires, medications other that fibrates should be considered. Section 6.2.3 was revised.
- Composite renal endpoint definition has been aligned with recently published International Consensus Definitions of Clinical Trial Outcomes for Kidney Failure (Levin et al 2020). The endpoint has been renamed to “Composite Kidney Failure Endpoint” – Table 2-2; Section 2.2; Section 4.1; Section 8.3.4 and Section 12.5.1 have been updated accordingly.
- One additional exploratory objective “to evaluate the effect of LNP023 vs. placebo on the change from baseline in kidney function as measured by eGFR” was added as this is a kidney function endpoint widely used by health providers. Section 2 and Section 12.6 were updated.

- Implementation of Patient Interview conducted at Month 9 in approximately 50 patients from selected countries in support of FACIT-F assessment and addition of associated exploratory objective. Section 2; Section 8.5.3; Section 12.5.6 and Section 12.6 were updated.
- Specified lab tests at screening required to exclude patients with a history of HIV infection, active HBV or active HCV infections. Additional testing and subsequent monitoring in participants in the Republic of Korea are included. Section 5.2; Section 8 and Section 9.1.1 have been updated accordingly.

Other changes to the protocol are:

- Inclusion of International Nonproprietary Name (INN) for LNP023 – iptacopan in parenthesis on the first page and in Section 1.
- Update to Section 4.5 Risks and Benefits to reflect the latest safety information.
- Allowances, clarifications and simplifications were made regarding off-site and remote visits in special circumstances (including but not limited to the COVID-19 pandemic). As a result Sections 4.6 has been added and Section 6.7, Section 7, Section 8 and Section 8.6 were updated.
- Section 6.7.2 and Section 8 were updated to remove study treatment dispensing at Week 2 visit as drug dispensed at the Randomization visit can last until Month 1 visit.
- The End of Treatment (EOT) visit has been removed as a standalone visit. Section 8 and Table 8-1 have been updated accordingly.
- Section 8.2.1 has been updated to include specifications required for biopsies for participants in India.
- Section 9.1 has been updated to clarify study treatment discontinuation, study discontinuation and withdrawal of consent and the required actions to limit missing data.

Additional minor changes were made for clarification purposes and to correct typographical errors and inconsistencies in the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, if applicable.

The changes herein are also reflected in the Informed Consent.

Protocol summary

Protocol number	CLNP023A2301
Full Title	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
Brief title	Study of efficacy and safety of LNP023 in primary IgA nephropathy patients
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The study is designed as a multicenter, randomized, double-blind, placebo controlled study to demonstrate the superiority of LNP023 at a dose of 200 mg b.i.d. compared to placebo on top of maximally tolerated or maximal locally approved ACEi or ARB on reduction of proteinuria and slowing disease progression in primary IgAN patients.. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend long-term supportive therapy with an ACEi or ARB with or without high dose CS or IS for blood pressure control and proteinuria reduction. In this double-blind, randomized study, the efficacy and safety of LNP023 will be assessed in comparison to placebo on top of the maximally tolerated or maximal locally approved doses of an ACEi or ARB.
Primary Objective(s)	The primary objective at the time of **interim analysis** is: To demonstrate superiority of LNP023 vs. placebo in the reduction of proteinuria at 9 months by measuring UPCR sampled from a 24h urine collection. The primary objective at the time of **final analysis** is: To demonstrate superiority of LNP023 vs. placebo in slowing IgAN progression measured by the annualized total slope of eGFR decline over 24 months. The primary clinical questions of interest at the Interim and Final Analysis respectively are: What is the treatment effect of LNP023 (200 mg b.i.d oral administration) vs. placebo on a) proteinuria reduction as measured by UPCR (sampled from 24h urine collection) at the Interim analysis, and b) slowing IgAN progression as measured by the annualized total eGFR slope at the Final analysis in primary IgAN patients with eGFR ≥ 30 mL/min/1.73m^2 who are on background ACEi/ARB treatment, as though corticosteroids, immunosuppressant therapy, other newly approved drugs or new background therapy for IgAN and Kidney Replacement Therapy (KRT) were not available and regardless of unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason.
Secondary Objectives	The secondary objectives at the time of **interim analysis** are: To evaluate the effect of LNP023 vs. placebo on slowing eGFR decrease as measured by the 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. To evaluate the effect of LNP023 vs. placebo on slowing IgAN progression measured by the annualized total slope of eGFR decline over 1 year. To assess the effect of LNP023 vs. placebo on the change from baseline to 9 months in the fatigue scale measured by the Functional Assessment Of Chronic Illness Therapy (FACIT-Fatigue) questionnaire. To evaluate the safety and tolerability of LNP023 vs. placebo. The secondary objectives at the time of **Final Analysis** are:

	To demonstrate superiority of LNP023 vs. placebo in the reduction of proteinuria at 9 months by measuring UPCR sampled from a 24h urine collection. 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. To demonstrate the superiority of LNP023 vs. placebo on delaying the time to first occurrence of a composite kidney failure endpoint of reaching either at least 30% decline in eGFR, eGFR <15 mL/min/1.73 m², dialysis, kidney transplantation or death from kidney failure. 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. To evaluate the safety and tolerability of LNP023 vs. placebo.
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. Thereafter, eligible participants will be randomized in a 1:1 ratio to either LNP023 200mg or matching placebo b.i.d. for a 24 month treatment period.
Study population	The study will enroll approximately 470 biopsy-confirmed IgAN participants with UPCR ≥1g/g (113 mg/mmol) calculated as the mean of two 24h urine collections despite optimal supportive treatment. Approximately 430 participants with eGFR ≥ 30 mL/min/1.73m^2 measured by central laboratory at screening and Baseline will comprise the Main Study Population. Up to approximately 40 participants with eGFR 20 - < 30 mL/min/1.73m^2 at screening and Baseline will comprise the Severely Renal Impairment (SRI) population.

Key Inclusion criteria	• Male and female patients ≥ 18 years of age with an eGFR level and biopsy-confirmed IgA nephropathy as follows
	  • For patients eGFR* ≥ 45mL/min/1.73m^2, a qualifying biopsy performed within the last 5 years is required
	  • For patients with eGFR* 30 to <45mL/min/1.73m^2, a qualifying biopsy performed within 2 years with < 50% tubulointerstitial fibrosis is required
	  • For patients with eGFR* 20 to <30mL/min/1.73m^2, a qualifying biopsy performed at any time. In all cases, if a historical biopsy is not available, one may be performed during screening.
	• Proteinuria due to primary diagnosis of IgA nephropathy as assessed at screening by UPCR ≥1 g/g (113 mg/mmol) sampled from FMV or 24h urine collection, as well as at the completion of the run-in period by UPCR ≥1 g/g (113 mg/mmol) calculated as the (geometric) mean of two 24h urine collections obtained within 14 days of each other at baseline.
	• Vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae* infection is required prior to the start of study treatment. If the patient has not been previously vaccinated, or if a booster is required, vaccine should be given according to local regulations at least 2 weeks prior to first study drug administration. If study treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment should be initiated.
	• If not previously vaccinated, vaccination against *Haemophilus influenzae* infection should be given, if available and according to local regulations, at least 2 weeks prior to first study drug administration. .
	• All patients must have been on supportive care including stable dose regimen of ACEi or ARB at either the locally approved maximal daily dose or the maximally tolerated dose (per investigators' judgment) for approximately 90 days before first study drug administration. In addition, if patients are taking diuretics, other antihypertensive medication or other background medication for IgAN, the doses should also be stabilized for approximately 90 days prior to the first dosing of study treatment.

Key Exclusion criteria	• Any secondary IgAN as defined by the investigator; secondary IgAN can be associated with cirrhosis, celiac disease, Human Immunodeficiency Virus (HIV) infection, dermatitis herpetiformis, seronegative arthritis, small-cell carcinoma, lymphoma, disseminated tuberculosis, bronchiolitis obliterans, and inflammatory bowel disease, familial mediterranean fever, etc. • Sitting office SBP >140 mmHg or DBP >90 mmHg at the randomization visit • Patients previously treated with immunosuppressive or other immunmodulatory agents such as but not limited to cyclophosphamide, rituximab, infliximab, eculizumab, canakinumab, mycophenolate mofetil (MMF) or mycophenolate sodium (MPS), cyclosporine, tacrolimus, sirolimus, everolimus, or systemic corticosteroids exposure (>7.5 mg/d prednisone/prednisolone equivalent) within 90 days (or 180 days for rituximab) prior to first study drug administration. Participants previously or currently treated with oral budesonide. Participants treated with endothelin (receptor) antagonists within 90 days prior to first study drug administration. • Prior use of LNP023 or prior enrollment in any other LNP023 clinical trial where study drug was taken, including matching placebo • History of recurrent invasive infections caused by encapsulated organisms, such as meningococcus and pneumococcus. • Active systemic bacterial, viral (including COVID-19) or fungal infection within 14 days prior to study drug administration.
Study treatment	LNP023 Placebo
Treatment of interest	The randomized treatment LNP023 (200mg b.i.d or matching placebo) regardless of unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason (treatment policy).
Efficacy assessments	• Proteinuria • Estimated Glomerular Filtration Rate • Composite Kidney Failure Endpoint • Patient Reported Outcomes (PRO) - FACIT-Fatigue
Pharmacokinetic assessments	Plasma pre-dose PK assessments will be performed in all participants at Month 3, 6 and 9. In the SRI population, 8 hour post-dose and 24 hour urine PK assessments will be performed at Month 6.
Key safety assessments	• Adverse event monitoring • Laboratory evaluations in blood and urine • Electrocardiogram (ECG) • Pregnancy and assessments of fertility • Reproductive and thyroid hormones monitoring
Other assessments	• Biomarkers • Pharmacogenetics substudy (optional) • Healthcare Resource Utilization • Patient Reported Outcomes (PRO) - EORTC QLQ-C30, EQ-5D-5L PGIS and (optional) Patient Interviews
Data analysis	All efficacy analyses will be based on the FAS and will consider only the Main Study population. **Primary efficacy estimands represented by the following endpoints:** **At the IA** • Log-ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months The hypothesis of superiority of LNP023 vs Placebo in terms of proteinuria reduction as measured by UPCR (24h) at 9 months will be tested at the one-sided 0.5% level.

	The ratio of geometric means [LNP023 vs. placebo] will be obtained from a Mixed Model of Repeated Measures (MMRM) (following the imputation approach to handle intercurrent events described in the Data analysis and statistical methods section) for the-log ratio to baseline in UPCR (24h). **At the Final analysis:** • Annualized total eGFR slope (mL/min/1.73m^2/year) estimated over 24 months The hypothesis of superiority of LNP023 vs Placebo in terms of slowing IgAN progression as measured by the annualized total eGFR slope estimated over 24 months will be tested at one-sided Type I error rate adjusted for multiplicity of testing. The difference between groups in the mean annualized total slope of eGFR decline will be obtained from a longitudinal mixed effects model (following the imputation approach to handle intercurrent events described in the Data analysis and statistical methods section). **Secondary efficacy estimands represented by the following endpoints:** **At the IA:** • Change from baseline in eGFR at 9 months • 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 FACIT-Fatigue questionnaire **At the Final analysis:** • Log-ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months • 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 ≥30% decline in eGFR relative to baseline, eGFR <15 mL/min/1.73 m², maintenance dialysis, kidney transplantation or death from kidney failure. • Change from baseline to 9 months in the total score of FACIT-Fatigue questionnaire The sequentially rejective multiple test procedures will be used for testing the hypotheses associated with the primary estimand at the Interim Analysis and the primary and the secondary estimands at the Final Analysis in order to ensure strong control of the study wise type one error for multiplicity of testing at one-sided 2.5%. The estimands of interest as well as analysis methods are described in detail in the corresponding sections.
Key words	LNP023, IgA nephropathy, IgAN, proteinuria, UPCR, eGFR, eGFR slope, kidney function decline

1 Introduction

1.1 Background

Immunoglobulin A nephropathy (IgAN), which is characterized by deposition of IgA in the glomerulus. While it is the most common type of glomerulonephritis, it is a rare disease that affects approximately 2.5 per 100,000 persons worldwide (McGrogan et al 2011), and the prevalence varies in different regions based on genetic and environmental factors, in addition to the local biopsy practice, urine screening programs and adequate registries (Coppo and Amore 2008). There is a clear West-to-East prevalence gradient, with the disease being most common in East Asia, less frequent in Mediterranean, Europe, and the Americas, and rare in Africa (Magistroni et al 2015, Schena and Nistor 2018).

IgAN is diagnosed by kidney biopsy. Immuno-fluorescence shows abundant deposition of IgA in the glomeruli, mainly in the mesangial region. The histological changes are variable but are dominated by mesangial proliferation and matrix expansion (Fogo et al 2015). It is commonly diagnosed between the ages of 16 and 35 years, usually due to the discovery of micro- or macrohematuria not attributable to other causes, with or without proteinuria. Hematuria is often recurrent and associated with respiratory infections. Most IgAN patients have a benign course. However, in approximately 25% of IgAN patients, the disease may progress slowly but persistently to end-stage renal disease (ESRD) within 10-15 years (Geddes et al 2003, Liu et al 2015). It is estimated that IgAN accounts for up to 10% of all patients in need of renal replacement therapy for ESRD in western countries, and the disease histologically recurs in up to 60% of the patients who have received kidney transplantation (Floege 2004). IgAN represents a particularly significant burden on the health care system because patients are usually relatively young when they reach ESRD.

The course of disease progression in IgAN can usually be predicted by clinical signs (hypertension, proteinuria, impaired kidney function) and histologic lesions (extent of sclerosis and tubulointerstitial damage) (Edström Halling et al 2012), among which the higher level and longer duration of proteinuria are the strongest prognosis risk factors for disease progression (Reich et al 2007). Approximately 25% of patients with IgAN will progress to ESRD within 10 - 15 years (most all of whom have proteinuria $\geq$ 1g/day), while the percentage increases to approximately 50% over 10 years for patients with proteinuria $\geq$ 2g/day (Reich et al 2007, Liu et al 2015). There was a general consensus in the nephrology research that in the past, the lack of adequately powered randomized trials in kidney disease, including IgAN, has led to a problematic imbalance between the clinical need of patients with kidney disease and the amount of reliable evidence to inform practice (Baigent et al 2017). As a part of the Kidney Health Initiative to identify (surrogate) endpoints that could be used as a basis for approval of novel therapies in IgAN, meta-analyses of RCT studies in IgAN patients with elevated proteinuria were conducted which demonstrated that reduction in urinary protein levels over a median follow-up of 9 months is predictive of long-term clinical benefit (Inker et al 2016, Thompson et al 2019). The choice of eGFR slope for confirmatory assessment of treatment benefit is supported by evidence showing that the annual eGFR slope reflects renal disease progression. eGFR slope was concluded to be an appropriate surrogate for renal outcomes based on observational and randomized clinical studies, computer simulations and analyses led by the

Kidney Health Initiative and supported by FDA, EMA and the National Kidney Foundation (NKF) (Levey et al 2020).

Treatment of IgAN has not changed significantly during the last three decades. Guidelines recommend therapy mainly based on blocking the renin-angiotensin-aldosterone system (RAAS), i.e. an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) for blood pressure control and proteinuria reduction. Even with full RAAS inhibition and optimal blood pressure control, a substantial risk of progression remains, especially for the IgAN patients with proteinuria >1 g/day. Furthermore, there are conflicting and inconsistent results on the benefit of additional therapeutic agents on top of renin-angiotensin system (RAS) blockade, such as immunosuppressive agents (including steroids), fish oil and tonsillectomy (KDIGO 2012). In some studies, steroids showed moderate evidence of efficacy but were accompanied by considerable side-effects (Floege and Rauen 2016, Fellström et al 2017, Lafayette et al 2017, Lv et al 2017). Therefore, it is a clear unmet medical need for more effective therapies to slow down or reverse IgAN progression, in particular in high-risk IgAN patients with proteinuria.

IgAN is an autoimmune disease. Its pathophysiology includes the production of galactose-deficient IgA (Gd-IgA) and the formation of immune complexes composed of IgG and Gd-IgA. Localization of these immune complexes in the glomerulus triggers local complement activation and subsequent chemotaxis of immunocompetent cells as well as local cytokine stimulation of inflammation in kidney as described in the “multiple-hit hypothesis” (Suzuki et al 2011). In recent years, mounting pathologic, biochemical, experimental, and genetic data support a pivotal role of complement activation in disease onset and progression of IgAN. The complement system, one of the major defense mechanisms of the innate immune system, is composed of the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP).The AP and LP are found to be activated in 75-90% and 17-25% of IgAN patients, respectively, while the CP does not appear to be involved in IgAN (Floege et al 2014, Maillard et al 2015).

The AP is constitutively active and plays a critical role in host defense by amplifying the complement response to mainly bacterial infection (Rizk et al 2019). Activation of the AP is believed to be important in the pathophysiology of several glomerular diseases, including IgAN, Complement-3-Glomerulopathy (C3G) as well as membranous nephropathy (MN) (Lukawska et al 2018). Complement factor B (FB) is an essential component of C3 and C5 convertases which drive the central amplification loop of the AP, therefore is a prime target for the AP inhibition (Rizk et al 2019). LNP023 (iptacopan) is a first-in-class, low molecular weight (LMW), orally active, reversible and selective inhibitor of FB and inhibits the catalytic activity of C3 and C5 convertases. LNP023 ameliorates membranous nephropathy (MN) in a rat experimental model and prevents complement activation in sera from C3G patients but also the hemolysis of human paroxysmal nocturnal hemoglobinuria (PNH) erythrocytes (Schubart et al 2019).

In the two healthy volunteer studies (CLNP023X2101 and CLNP023X1102), LNP023 was well tolerated up to a single dose of 400 mg and 200 mg b.i.d. for two weeks, and AP activity was attenuated by LNP023 measured by complement biomarker assays. While close to complete inhibition of Bb was observed at the lowest dose of LNP023 tested (i.e. 10 mg b.i.d.), a dose- and concentration-dependent inhibition of the AP was observed in Wieslab assay. In addition,

there is no ethnic sensitivity in terms of pharmacokinetic(s) (PK) exposure for LNP023 between Asian (Japanese) and Caucasian patients.

CLNP023X2203 is a two part, randomized, double-blind, placebo-controlled, dose ranging adaptive phase 2 trial that evaluates the efficacy and safety of LNP023 in IgAN patients. The primary aim of the study is to evaluate the dose response relationship of LNP023 based on reduction in proteinuria at 90 days of treatment. The safety/tolerability of LNP023 administered up to 200 mg b.i.d. is also assessed. The interim analysis (IA) at 90 days of treatment in the Part 1 study was completed on 17 December 2019. The results showed that LNP023 administered up to 200 mg b.i.d for 90 days was safe, well tolerated and was effective in reducing proteinuria. The final results from the completed Phase 2 study are described in the current Investigator's Brochure.

1.2 Purpose

This trial is a multicenter, randomized, double-blind, placebo controlled parallel group study. The purpose of the study is to evaluate the efficacy and safety of LNP023 compared to placebo on proteinuria reduction and slowing disease progression in primary IgAN patients.

The study will be the pivotal trial for registration of LNP023 in IgAN patients with the aim to demonstrate a clinically meaningful reduction in proteinuria by LNP023 vs. placebo as assessed by reduction in urine protein to creatinine ratio (UPCR) sampled from a 24 hour urine collection at an IA at 9 months. Results from the IA may serve as basis for accelerated/conditional approval. The trial will continue in a blinded fashion to confirm long-term efficacy based on a kidney function endpoint at the final analysis (annualized rate of total estimated glomerular filtration rate (eGFR) slope estimated over 24 months) to provide confirmatory evidence of LNP023 efficacy and safety in treating patients with IgAN.

The trial will enroll approximately 470 participants; 430 biopsy-proven IgAN participants with eGFR ≥30 mL /min/1.73m^2 (main study population) and up to approximately 40 participants with eGFR 20 to <30 mL/min/1.73m^2 (severe renal impairment (SRI) population). Estimated GFR will be calculated using the CKD-EPI formula (or modified MDRD formula according to specific ethnic groups and local practice guidelines at screening Imai et al 2011).

The SRI population will not be included in the efficacy analyses of the main study population; it will primarily provide additional PK and safety information for SRI participants.

2 Objectives and endpoints

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

Table 2-1 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 as 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 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. • 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 • Change from baseline in the EORTC QLQ-C30 at 9 months • 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.
• 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 **STUDY COMPLETION.**

Table 2-2 Objectives and related endpoints

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).
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 • Sustained ≥30% decline in eGFR relative to baseline, or • Sustained eGFR <15 mL/min/1.73m², or • Maintenance dialysis, or • Receipt of kidney transplant, or • 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 End Of Study (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.

Objective(s)	Endpoint(s)
	• 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 newly approved drugs for IgAN treatment due to disease progression over 24 months.	• Proportion of study 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 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. • Change from baseline to 9 and 24 months in the EORTC QLQ-C30. • 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.*
*Note that the assessment of the objective related to the semi-structured interviews will not be repeated at the study completion if all interviews planned (approximately 50, see Section 8.5.3) have been conducted and all related analyses completed at the Interim Analysis.	

2.1 Primary estimands

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 Section 12.

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. Further details about the population are provided in Section 5.
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). Further details about the investigational treatment and control treatment are provided in Section 6.

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 corticosteroid or immunosuppressant therapy (CS/IS) for IgAN treatment will be handled using the hypothetical strategy, that is as though these medications were not available. This is because LNP023 ultimately would be indicated as a chronic treatment for primary IgAN patients on top of background ACEi/ARBs treatment. Such medications 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 the analysis and will be imputed via a modeling approach accounting for the intake of CS/IS as potentially indicative of a worsening of condition (see Section 12.4.3 for detail).
- Intake of other newly approved drugs for treatment of IgAN will be handled using the hypothetical strategy, that is as though these medications were not available. The choice of strategy follows the same rationale as for the intercurrent of the intake of CS/IS. Further detail on the handling of this intercurrent event is outlined in Section 12.4.3.
- Initiation of new background therapy for IgAN treatment will be handled using the hypothetical strategy, that is as though these medications were not available. This is because 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 participants randomized to the placebo group may initiate new background therapy more often than participants randomized in the LNP023 group.
- Treatment discontinuation for any reason (other than the intake of CS/IS and/or newly approved medications for treatment of IgAN): ignore i.e. data collection will be maintained and available measurements post-treatment discontinuation will be used as if they had been

obtained under the treatment assigned at randomization (treatment policy strategy). In case measurements are missing, these will be handled as described in Section 12.4.4.

- Initiation of KRT (i.e. dialysis or transplant as defined in Section 8.3.4) will be handled using the hypothetical strategy, that is as though KRT was not initiated and disease continued to progress. This is because following initiation of KRT, eGFR and UPCR 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.

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, 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 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 that are not a part of the assigned treatment strategy. Further details can be found in Section 12.

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.

For all estimands, CS/IS and newly approved drugs for IgAN treatment (including but not limited to delayed release budesonide and endothelin inhibitors) are outlined in Section 6.2.2. Background treatment with ACEi/ARB may include other background treatment for IgAN started prior to randomization, see Section 5 for more detail.

2.2 Secondary estimands

Secondary estimands at the IA

The following secondary estimands are considered at the IA:

- Change from baseline in eGFR at 9 months, where the Population and Treatment attributes as well as strategy applied to all intercurrent events are the same as described in Section 2.1 for the primary estimand at the Interim Analysis.
- Annualized total eGFR slope (mL/min/1.73m2/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 Section 2.1).
- Proportion of participants reaching UPCR (24h) levels <1 g/g at 9 months, without receiving CS/IS, other newly approved drugs or initiating new background therapy for IgAN treatment or initiating KRT. The intake of CS/IS, other newly approved drugs for IgAN treatment and initiation of new background therapy for IgAN or KRT are handled via the composite strategy (ie. 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 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)
- Change from baseline to 9 months in the total score of 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 2.1 for the primary estimand for the Interim analysis.

Secondary estimands at the Final Analysis

The following secondary estimands are considered at the Final Analysis:

- The primary estimand at the IA, namely the log-ratio to baseline in UPCR (sampled from24h urine collection) at 9 months, will be examined as a secondary estimand at the Final Analysis in case of non-significance at the IA (see Section 12.5.1). The attributes of this estimand as well as handling strategies for remaining intercurrent events remain the same as specified at the IA.
- Proportion of participants reaching UPCR 24h levels <1 g/g at 9 months, without receiving CS/IS, 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.
- 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 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/1.73 m², 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). Further details about the investigational treatment and control treatment are provided in Section 6.

The summary measure used is: Hazard ratio between groups.

Of the intercurrent events identified in Section 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 2.1. Note that initiation of KRT is captured by the dialysis and kidney transplantation components of the Endpoint attribute (see Section 8.3.4).

- 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 2.1 for the respective secondary estimand at the IA.

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 may be supplemented by supportive as well 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.

3 Study design

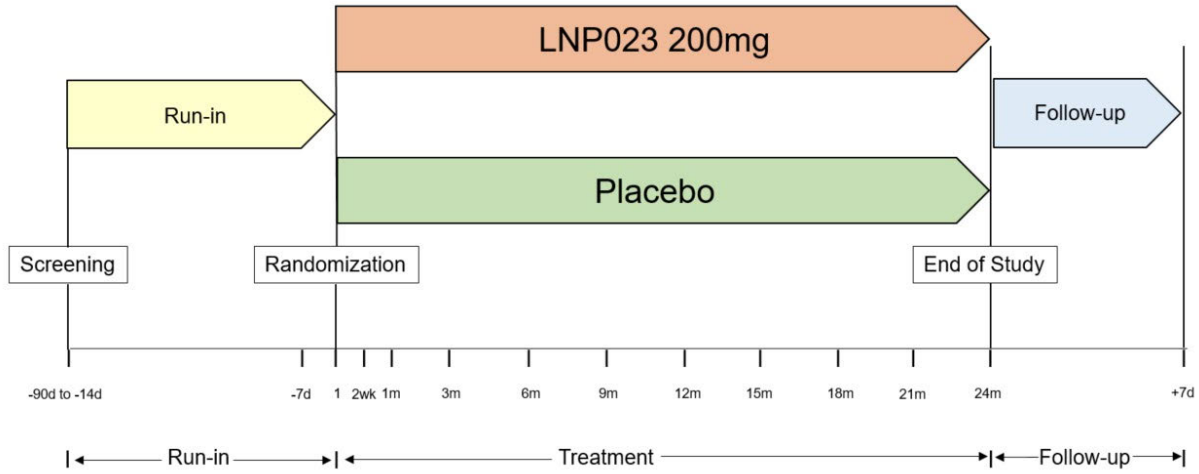
This is a multi-center, randomized, double-blinded, placebo-controlled study, which comprises a screening visit, followed by a run in period of 14 to approximately 90 days. Thereafter, eligible participants will be randomized in a 1:1 ratio to either LNP023 200mg or matching placebo b.i.d. for a 24 month treatment period. The total study duration for each participant will be a minimum of approximately 24.5 months.

The study will enroll approximately 470 biopsy-confirmed IgAN participants with UPCR ≥1g/g despite optimal supportive treatment.

- Main Study Population: approximately 430 participants with eGFR ≥ 30 mL/min/1.73m^2 and UPCR ≥1 g/g (113 mg/mmol) measured by central laboratory based on a first morning void (FMV) or a single 24 hour urine sample at screening as well as the (geometric) mean of two 24 hour urine collections at Baseline.
- Severely Renal Impairment (SRI) population: up to approximately 40 participants with eGFR 20 - < 30 mL/min/1.73m^2 at screening and Baseline.

A pre-specified IA will be performed at the time when approximately 250 participants of the Main Study Population have completed the study to the 9 month visit however all data collected up to this point will be included in the IA. The IA will include the assessment of the effect of LNP023 vs Placebo on reduction in proteinuria as measured by UPCR sampled from a 24h urine collection. 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 as measured by the annualized total eGFR slope will be evaluated.

Figure 3-1 Study Design



Screening Visit and Run-in Period

Participants will be asked to review and sign the informed consent form (ICF) prior to or at the screening visit. After signing the ICF, during this visit, inclusion and exclusion criteria will be assessed to verify the study candidates' eligibility for enrollment into the study. This will be followed by the assessments as outlined in Table 8-1, as applicable.

By signing the ICF, the study participants will provide access to the qualifying historical kidney biopsy (Section 5.1). A new kidney biopsy will be required if the historical biopsy exceeds the specified time limit described in Section 5.1.

Participants must be on ACEi or ARB at either the locally approved maximal daily dose or the maximally tolerated dose (per investigators' judgment) for approximately 90 days prior to the first dosing of study treatment and should remain on the same dose throughout the study if possible. Participants with allergies or intolerance to ACEi and ARB are eligible for the study

but the investigator should clearly document the reasons for not being on maximal ACEi/ARB dose in the source documents. In addition, if participants are taking diuretics, other antihypertensive medication or other background medication for IgAN, the doses should also be stabilized for at least 90 days prior to the first dosing of study treatment. Changes of doses in such medications should be avoided for the duration of study, if possible.

Participants who have not received the required vaccinations but have fulfilled all other eligibility criteria should be vaccinated as outlined in Section 5.1. All required vaccinations should be performed at least 2 weeks prior to the first dose of study medication. Vaccines should cover as many serotypes as possible (including meningococcal serotypes A, C, Y, W-135 and B). To minimize participant burden, the use of multivalent vaccines is recommended as locally available and per local guidelines and regulations (e.g. quadrivalent vaccines for *N. meningitidis,* which covers serotypes A, C, W and W-135 and Pneumovax-23, which covers 23 *S. pneumoniae* serotypes).

If eligibility criteria are not met, the study candidate should be considered as having failed screening and should not proceed further. The study candidate can be re-screened as described in Section 8.1.

Baseline

Approximately 7 days prior to the planned randomization visit, participants will visit the site for baseline evaluations. Participants must have completed two 24-hour urine collections on any two days within the 2 weeks preceding the baseline visit. Following all baseline evaluations as per Table 8-1, participants who are eligible based on the eligibility criteria outlined in Section 5 will continue to Randomization.

Randomization

At the time of randomization, all baseline evaluation results must be available to confirm the participant's eligibility prior to dosing. Participants should remain on their ACEi/ARBs therapy at either the locally approved maximal daily dose or the maximally tolerated dose (per investigators' judgment). In addition, if participants are taking other background medication for IgAN, they should remain on stable dose and changes in doses should be avoided for the duration of study if possible.

After meeting the eligibility criteria at baseline, participants in the Main Study Population 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 (geometric) mean 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 - <30 mL/min/1.73m^2) will be in a 1:1 ratio and 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) and continue for a total of 24 months. Participants are required to attend visits and complete the corresponding assessments as described in Table 8-1. Dose adjustment of LNP023 is not allowed during the randomized treatment period (Section 6.5) and Section 6.2.2, Section 6.6.2 and Section 9.1 provide details on interruption or discontinuation of study drug, if required.

Because of the increased risk of infections with encapsulated bacteria for participants treated with complement inhibitors, all participants will be provided with a Participant Card. Participants will be instructed to be vigilant for any clinical signs of bacterial infection and to contact the investigator or local physician immediately in case of suspicion of infection. Refer to Section 6.6.2 and Section 9.1.1 for guidance on treatment for infections.

End of study and Follow-up

The End of Study (EOS) visit will mark the end of the doubleblind 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 by the participant should be recorded in the CLNP023A2301 study CRF. The safety follow-up can be performed via a telephone call or an on-site visit. For participants who do enroll in the REP within 7 days of the EOS, the Day 1 (first study drug administration) visit of the REP will serve as the safety follow up visit for the core CLNP023A2301 study, and any adverse or serious adverse events experienced after the EOS and up to the first dose on Day 1 of the REP should be recorded in the CLNP023A2301 study CRF. If a participant enrolls in the REP directly and Day 1 (first study drug administration) in the REP is the same day as the EOS visit of the core CLNP023A2301 study, then any AEs or SAEs experienced thereafter are only captured in the REP CRF. Additional details regarding AE and SAE reporting are in Section 10.1.

4 Rationale

4.1 Rationale for study design

CLNP023A2301 is designed as a multicenter, randomized, double-blind, placebo controlled study to demonstrate the superiority of LNP023 at a dose of 200 mg b.i.d. compared to placebo on top of ACEi or ARB at either the locally approved maximal daily dose or the maximally tolerated dose (per investigators' judgment) on reduction of proteinuria and slowing disease progression in primary IgAN patients.

A multicenter setting is chosen for the study to ensure adequate recruitment and representative enrollment of patients from a wide range of geographic regions for this indication. Disease progression has shown remarkable variations in different parts of the world and across different ethnic groups (Magistroni et al 2015, Yeo et al 2019). Higher incidence and worse progression generally are observed in Asian populations. These differences are hypothesized to be due to

genetic and environmental factors, in addition to different local biopsy practices. In this study, participants will be stratified against geographic locations of Asia and non-Asia.

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend long-term supportive therapy with an ACEi or ARB with or without high dose CS or IS for blood pressure control and proteinuria reduction (KDIGO 2012). In this double-blind, randomized study, the efficacy and safety of LNP023 will be assessed in comparison to placebo on top of the maximally tolerated or maximal locally approved doses of an ACEi or ARB.

To date, the most well studied and consistent clinical risk factors of progression of IgAN are histopathology, decreased glomerular filtration rate (GFR), sustained proteinuria > 1 g/d and renal hypertension. The study population consists of patients with IgAN diagnosed by kidney biopsy. For participants with eGFR ≥ 45 mL/min/1.73m^2, the most recent biopsy should be 5 years from screening. For participants with eGFR 30 to <45 mL/min/1.73m^2, the most recent biopsy should be performed within 2 years to exclude other concomitant glomerulonephritis (GN) entities such as focal-segmental glomerulosclerosis (FSGS) or C3 glomerulopathy (C3G), and participants with ≥50% tubulointerstitial fibrosis will be excluded to ensure that patients who are most likely to derive benefit from LNP023 in the two year treatment period of the trial are included. In addition, participants with rapidly progressive glomerulonephritis (RPGN) disease, which is associated with a markedly unstable clinical course, will be excluded from the study. There is no time requirement for kidney biopsy in SRI participants (i.e. eGFR 20 to < 30 mL/min/1.73m^2) due to the consideration that the key objective in these participants is to understand the PK and safety profiles, even though severe histopathlogical presentations are not uncommon. Efficacy of LNP023 will be evaluated in the Main Study Population.

In this study, IgAN participants with UPCR ≥1 g/g at screening and baseline will be randomized. The threshold of UPCR at 1g/g is to enrich the study population with patients with elevated risk for IgAN progression and to have a population similar to that in the Inker meta-analysis where reduction in proteinuria over a median of 9 months (range, 5 to 12 months) was shown to be consistently associated with a clinically meaningful benefit in renal clinical endpoints (Inker et al 2016, Thompson et al 2019). Participants also should have adequately controlled blood pressure according to treatment guidelines (Whelton and Carey 2017), and only those with systolic blood pressure (SBP) ≤140 mmHg and diastolic blood pressure (DBP) ≤90 mmHg are eligible. The SRI population (eGFR 20 to <30 mL/min/1.73m^2) are included in order to provide additional PK and safety information for patients with very low eGFR levels.

The purpose of the run-in period is to ensure that participants have received ACEi/ARB at either the locally approved maximal daily dose or the maximally tolerated dose (per investigators' judgment) for approximately 90 days and the required vaccinations at least 2 weeks prior to first dosing. In addition, to minimize a potential carry-over treatment effect, participants who take corticosteroids or immunosuppressants for IgAN treatment should discontinue the medications at least 90 days prior to initiation of study treatment.

There will be two primary endpoints in the study: reduction in proteinuria (at 9 months) for interim analysis (IA) aiming for accelerated/conditional approval and slowing IgAN progression as measured by annualized total eGFR slope (at 24 months) at final analysis aiming for full health authority approval. The choice of proteinuria as a surrogate endpoint at 9 months is based on robust and consistent literature evidence demonstrating that urinary protein levels

correlate well with functional kidney decline and is expected to provide a sensitive and objective means to measure drug effect compared to placebo (Inker et al 2016; Thompson et al 2019). The choice of total eGFR slope for confirmatory assessment of a treatment benefit is supported by evidence showing that the annualized total eGFR slope reflects renal disease progression and long term renal survival (Levey et al 2020). The randomization treatment period of 24 months is considered appropriate to assess safety as well as the effect of LNP023 on the primary and secondary efficacy endpoints, especially the annualized total eGFR slope (Inker et al 2019).

The secondary endpoints assessed at the IA aim to delineate the potential benefits of LNP023 following at least 9 months of double-blind treatment on improving/stabilizing kidney function and reducing fatigue, which is one of the most common complaints in chronic kidney disease patients (Harwood et al 2009).

At study completion, the proportion of participants reaching proteinuria below 1g/g of UPCR, the proportion of participants who reach a composite kidney failure endpoint (≥30% reduction in eGFR, eGFR < 15 mL/min/1.73 m², maintenance dialysis, kidney transplantation, death from kidney failure) and change from baseline in the fatigue scale will be evaluated. These secondary endpoints were selected to supplement the primary efficacy endpoint and are clinically meaningful endpoints for IgAN patients.

4.2 Rationale for dose/regimen and duration of treatment

LNP023 at 200 mg b.i.d. has been selected for this study based on the totality of safety and efficacy data from the healthy volunteer studies and the Phase 2 CLNP023X2203 study Part 1 interim analysis. In addition, this dose has demonstrated a favorable benefit-risk ratio in the phase 2 studies in C3G including proteinuria reduction as well as PNH patients to maintain hemoglobin (Hb) levels.

In CLNP023X2101 and CLNP023X1102 studies, LNP023 was administered to 102 healthy volunteers in single ascending dose (SAD, 10 to 400 mg) and multiple ascending dose (MAD, 10 to 200 mg b.i.d. for 2 weeks). The results showed that LNP023 had high solubility, good permeability, a fast absorption, and was well tolerated. No deaths, serious adverse events (SAEs), or adverse events (AEs) leading to study drug discontinuation were observed. In the MAD study, dose-dependent suppression of AP activity was achieved when measured by Wieslab AP assay, with approximately 80% or greater inhibition sustained over 14 days of dosing at 100 mg and 200 mg b.i.d, while Bb level showed 30 – 40% decrease from the baseline for all LNP023 cohorts.

In the Phase 2 CLNP023X2203 Part 1 study, IgAN participants were administered LNP023 from 10 mg to 200 mg b.i.d. Treatment with LNP023 was shown to be well tolerated up to the highest dose.

In addition, the preclinical studies supported acceptable safety margins for human exposure following 200 mg b.i.d. dosing. The safety and tolerability of the LNP023 dose at 200 mg b.i.d. were supported by the Part 1 of CLNP023X2203 study in IgAN, as well as the other clinical studies in PNH and C3G for which LNP023 200 mg b.i.d. was administered for more than 12 months in some participants. In Part 1 of CLNP023X2203 study, LNP023 dose at 200 mg b.i.d. was shown to reduce proteinuria over 90 days supporting 200 mg b.i.d. of LNP023 for phase 3 development.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

At the time of study design there was no approved specific therapy for IgAN. Like in most other chronic kidney diseases (CKD) all patients are expected to receive maximally tolerated or maximal locally approved doses of ACEi/ARB as background therapy in line with KDIGO or local guideline recommendations throughout the duration of the trial to reduce proteinuria and slow IgAN progression due to their renoprotective hemodynamic effects (KDIGO 2012). Auxiliary medicinal products (AxMP) and background therapies for the trial are ACEi (Anatomical Therapeutic Chemical [ATC] Code: C09A, C09B) /ARB (ATC Code: C09C, C09D). LNP023 is the first in class Factor B inhibitor which inhibits the AP activity. Placebo is chosen as a comparator to enable a proper evaluation of the LNP023 treatment effect and safety and to facilitate the blinding which is a key measure to avoid bias in this study.

4.4 Purpose and timing of interim analyses/design adaptations

An IA will be performed when approximately 250 patients (Leading cohort of Main Study population) have completed the 9 months visit. The purpose 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 (h) urine collection at 9 months. Further efficacy evaluations include the annualized total eGFR slope estimated over 12 months, change from baseline in eGFR and FACIT-Fatigue scale at 9 months. Safety evaluations will also be conducted (both Main study and SRI populations). 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. The trial will continue in a blinded fashion to confirm long-term efficacy based on a IgAN progression endpoint (i.e., annualized rate of total eGFR slope over 24 months) to support full approval of LNP023 in treating patients with IgAN. Appropriate procedures and firewalls will be put in place to ensure the study blind as described in detail in Section 6.4.

Safety data will be analyzed by an external analysis team periodically and reviewed by the external DMC during the course of the study. Further details on the periodic safety DMC reviews will be specified in the DMC charter.

4.5 Risks and benefits

LNP023 is a small molecule Factor B inhibitor. It blocks the AP which plays an important role in the defense against microbes. The immunological response to infections, particularly those caused by encapsulated bacteria is therefore likely to be blunted. Even though the other two complement pathways (i.e. classic and lectin pathways) should not be attenuated by LNP023, there is a theoretical risk that immunological responses to infections, especially those caused by encapsulated bacteria, may be compromised in participants who take LNP023. The risks associated with the use of LNP023 are those inferred by its pharmacology and the results of preclinical safety studies as described in the Investigator's Brochure (IB). The safety results from the completed Phase 2 CLNP023X2203 study in IgAN patients and other ongoing clinical

trials in C3G patients as well as in PNH patients showed that LNP023 at a dose of 200 mg b.i.d. was safe and well tolerated.

Infections caused by encapsulated bacteria is the main risk in participants treated with complement inhibitors. Serum bactericidal activity studies of serum from vaccinated patients against meningococci showed that C5 inhibitors block killing of meningococci, whereas AP inhibitors have less inhibitory effect on meningococcal killing (Konar and Granoff 2017, Muri et al 2021). Vaccination is therefore accepted to be an effective mitigation strategy to reduce the risk of meningococcal infection for individuals treated with LNP023. Participants will be vaccinated against meningococcal, pneumococcal and H. *influenzae* infections as described in Section 5.1, since these are all encapsulated bacteria.

The risk to participants in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, provision of a Participant Card and periodic review of the safety data by an independent DMC during the study. Participants will also be closely monitored for signs and symptoms of infection (listed on a Participant Card for patient awareness) and will be instructed to contact the investigator or a local physician if they experience these symptoms. The investigator will employ clinical judgment to determine an appropriate course of treatment and report infections as an AE. Refer to Section 6.6.2 and Section 9.1.1 regarding the treatment of infections and actions to be taken with study treatment.

Other potential safety risks are based on preclinical data, including non-important potential risks of testicular effects, and thyroid effects, with no relevant findings in clinical studies performed to date.

In the clinical studies, there have been no relevant testicular adverse events or changes from baseline in reproductive hormones reported to date. Testicular effects seen in preclinical studies have been shown to be mild and reversible, with no notable effect on sperm in dogs or male fertility in the rat study. In addition, the safety margin of 17-fold was achieved when comparing unbound concentrations reached in the dog at the lowest observed adverse effect level (LOAEL) and the concentrations achieved in man at the 200 mg twice daily dose, indicating that the relevance of the preclinical findings to man is considered questionable. Testicular AEs and reproductive hormone levels will continue to be monitored in the current study.

There have been no clinically relevant thyroid adverse events or changes in thyroid hormone levels observed in clinical studies to date, suggesting a lack of translatability of the preclinical findings to human and therefore a low risk in patients. Thyroid-related AEs as well as thyroid hormone levels (T3, T4, TSH and reversed T3) will be monitored in all participants (Section 8.4.1).

Iptacopan has no known genotoxic potential. Iptacopan was tested in embryo-fetal development studies in rats and rabbits, pre- and post-natal development in rats and showed no teratogenic or embryotoxic potential. Based on lack of genotoxicity, teratogenicity and embryotoxicity from preclinical studies, men are not required to use condoms during sexual intercourse.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the

exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

A complete description of preclinical and clinical safety findings is available in the IB – Section 7.

The benefit a participant might have by participating in the study is the close monitoring of their condition and optimization of treatment of known risk factors during the full duration of the study.

In summary, potential safety risks of LNP023 which have been identified will be closely monitored in this study. In addition, an independent DMC will assess the safety of the study periodically. The overall benefit risk profile of LNP023 is positive, supporting the start of this study.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity, are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

The study will enroll a total of approximately 470 biopsy-confirmed IgAN participants with elevated proteinuria, despite optimal supportive treatment.

- **Main study population**: approximately 430 participants with eGFR ≥ 30 mL/min/1.73m^2 at baseline. This population forms the basis for the primary and secondary efficacy analysis.
  - **Leading patient cohort**: participants who are included in the interim analysis
  - **Full patient cohort**: participants who are included in the final analysis
- **Severe renal impairment (SRI) population**: up to approximately 40 participants with eGFR 20 -<30 mL/min/1.73m^2 at baseline will be enrolled into this cohort. These participants will not be included in the efficacy analyses of the main study population. They will provide additional PK and safety information for the SRI population. SRI participants will not be enrolled in the Republic of Korea.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study; patients should be able to communicate well with the investigator, understand and comply with the requirements of the study.
2. Male and female patients ≥ 18 years of age with an eGFR level and biopsy-confirmed IgA nephropathy as follows:
   - For patients eGFR* ≥ 45mL/min/1.73m^2, a qualifying biopsy performed within the last 5 years is required.

- For patients with eGFR* 30 to <45mL/min/1.73m^2, a qualifying biopsy performed within 2 years with < 50% tubulointerstitial fibrosis is required.
- For patients with eGFR* 20 to <30mL/min/1.73m^2, a qualifying biopsy performed at any time.

In all cases, if a historical biopsy is not available, one may be performed during screening. *eGFR calculated using the CKD-EPI formula (or modified MDRD formula according to specific ethnic groups and local practice guidelines)

3. Proteinuria due to primary diagnosis of IgA nephropathy as assessed at screening by UPCR ≥1 g/g (113 mg/mmol) sampled from FMV or 24h urine collection, as well as at the completion of the run-in period by UPCR ≥1 g/g (113 mg/mmol) calculated as the (geometric) mean of two 24h urine collections obtained within 14 days of each other at baseline.
4. Vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae* infection is required prior to the start of study treatment. If the patient has not been previously vaccinated, or if a booster is required, vaccine should be given according to local regulations at least 2 weeks prior to first study drug administration. If study treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment should be initiated.
5. If not previously vaccinated, vaccination against *Haemophilus influenzae* infections should be given, if available and according to local regulations, at least 2 weeks prior to first study drug administration.
6. All patients must have been on supportive care including stable dose regimen of ACEi or ARB at either the locally approved maximal daily dose or the maximally tolerated dose (per investigators' judgment) for approximately 90 days before first study drug administration. In addition, if patients are taking diuretics, other antihypertensive medication, or other background medication for IgAN, the doses should also be stabilized for approximately 90 days prior to the first dosing of study treatment.

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are **not** eligible for inclusion in this study.

1. Any secondary IgAN as defined by the investigator; secondary IgAN can be associated with cirrhosis, celiac disease, Human Immunodeficiency Virus (HIV) infection, dermatitis herpetiformis, seronegative arthritis, small-cell carcinoma, lymphoma, disseminated tuberculosis, bronchiolitis obliterans, and inflammatory bowel disease, familial mediterranean fever, etc.
2. Evidence of significant urinary obstruction or difficulty in voiding; any urinary tract disorder other than IgAN at screening and before first study drug administration.
3. Current or planned usage of any homeopathic and/or herbal medications for IgAN disease progression, such as but not limited to Lei Gong Teng.
4. Current acute kidney injury (AKI) defined by Acute Kidney Injury Network (AKIN) criteria within 4 weeks of screening (Section 16.4, Mehta et al 2007).
5. Presence of rapidly progressive glomerulonephritis (RPGN) as defined by 50% decline in eGFR within 3 months prior to screening, or presence of nephrotic syndrome.
6. Sitting office SBP >140 mmHg or DBP >90 mmHg at the randomization visit.

7. Patients previously treated with immunosuppressive or other immunomodulatory agents such as but not limited to cyclophosphamide, rituximab, infliximab, eculizumab, canakinumab, mycophenolate mofetil (MMF) or mycophenolate sodium (MPS), cyclosporine, tacrolimus, sirolimus, everolimus, or systemic corticosteroids exposure (>7.5 mg/d prednisone/prednisolone equivalent) within 90 days (or 180 days for rituximab) prior to first study drug administration. Participants previously or currently treated with oral budesonide. Participants treated with endothelin (receptor) antagonists within 90 days prior to first study drug administration.
8. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer.
9. Prior use of LNP023 or prior enrollment in any other LNP023 clinical trial where study drug was taken, including matching placebo.
10. All transplanted patients (any solid organ transplantation, including bone marrow transplantation).
11. History of recurrent invasive infections caused by encapsulated organisms, such as meningococcus and pneumococcus.
12. Major concurrent comorbidities including but not limited to advanced cardiac disease (e.g., New York Heart Association (NYHA) class IV), severe pulmonary disease (e.g., severe pulmonary hypertension (World Health Organization (WHO) class IV)), or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participant's participation in the study.
13. Any medical condition deemed likely to interfere with the patient’s participation in the study.
14. Active systemic bacterial, viral (including COVID-19) or fungal infection within 14 days prior to study drug administration.
15. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study drug administration.
16. Human immunodeficiency virus (HIV) infection (known history of HIV or test positive for HIV antibody at Screening).
17. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
18. Liver disease, such as active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection defined as Hepatitis B surface antigen (HBsAg) positive or Hepatitis C virus ribonucleic acid (HCV-RNA) positive at screening, or liver injury as indicated by abnormal liver function tests at screening and baseline as defined below:
    - Any single parameter of ALT, AST, GGT, alkaline phosphatase must not exceed 3 × upper limit of normal (ULN)
    - Serum bilirubin must not exceed 2 × ULN
19. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer treated with curative intent), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
20. Pregnant or nursing (breastfeeding) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.

21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of investigational drug and for 1 week after stopping of investigational drug. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Bilateral tubal occlusion, bilateral tubal ligation (at least six weeks before taking investigational drug)
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral salpingectomy at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository.
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral salpingectomy at least six weeks prior to enrollment on study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

6 Treatment

Study participants will be randomized to LNP023 200 mg b.i.d. or placebo in 1:1 ratio, while remaining on the maximally tolerated or locally approved maximal daily doses of ACEi or ARB throughout the treatment period.

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
LNP023200mg	Capsules	Oral use	Double blind participant-specific kits	Sponsor (global)
Placebo	Capsules	Oral use	Double blind participant-specific kits	Sponsor (global)

The investigational drug, LNP023 as 200mg and matching placebo capsules, will be prepared by Novartis and supplied to investigator sites as double blind participant kits.

6.1.2 Additional study treatments

Based on the EU CTR requirements, ACEi/ARB (background medication) are considered as AxMP and are described in this section.

Participants should take ACEi/ARB at either the locally approved maximal daily dose or the maximally tolerated dose (per investigator judgment) for approximately 90-days prior to baseline, and continue at a stable dose during the study, if possible.

In rare cases, participants cannot take ACEi/ARB because they have documented allergies or intolerance to ACEi and ARB; these participants are eligible for the study.

ACEi/ARBs are packaged and labelled according to local guidelines/practice.

6.1.3 Treatment arms/group

Participants will be assigned at the Randomization visit to one of the following 2 treatment arms/groups in a ratio of 1:1

- LNP023 200mg b.i.d
- Placebo

6.1.4 Treatment duration

The planned duration of treatment is 24 months. Study participants may be temporarily interrupted or discontinued from treatment earlier due to unacceptable toxicity, progression of underlying disease, intake of medication, described in Section 6.2.2, bacterial infection and/or treatment is discontinued at the discretion of the investigator or the participant. If a participant's study treatment is discontinued for any reason, every effort must be made to continue with the study assessments up to Month 24 as defined in Table 8-1.

Participants who have completed the study, defined as completing all study visits up to and including the End of Study visit at Month 24 will be eligible to enroll in a single-arm open-label LNP023 rollover extension program, CLNP023A2002B.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Participants should take ACEi/ARB (also considered as background medication according to EU CTR requirements) at either the locally approved maximal daily dose or the maximally tolerated dose (per investigators' judgment) for approximately 90-days prior to baseline, and continue at a stable dose during the study, if possible. In addition, if participants are taking diuretics, other antihypertensive medication, or other background medication for IgAN, the respective doses should also be stabilized for approximately 90 days prior to the first dosing of study treatment. Any changes in the doses of the aforementioned treatments should be avoided if possible. No new background treatment for IgAN should be added during study participation.

In rare cases, participants cannot take ACEi/ARB because they have documented allergies or intolerance to ACEi and ARB; these participants are eligible for the study.

The investigator must instruct the study participant to notify the study site about any new medications he/she takes after the study participant is enrolled into the study.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the study participant was enrolled into the study must be recorded on the appropriate Case Report Forms (CRFs).

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

From in vitro data examining potential iptacopan drug interactions, iptacopan was identified as a substrate of drug transporters OATP1B1/1B3 and drug metabolizing enzyme CYP2C8. In addition, iptacopan may impact pharmacokinetics (PK) of P-glycoprotein (P-gp) and OATP substrates. Thus, a drug-drug interaction study (CLNP023A2104) was conducted when iptacopan was co-administered with clopidogrel (CYP2C8 inhibitor), cyclosporine (OATP1B1/1B3 inhibitor) and digoxin (P-gp substrate), rosuvastatin (OATP substrate). The effect of clopidogrel and cyclosporine on iptacopan PK was not considered to be clinically relevant and there was a negligible impact of iptacopan on the PK of the P-gp and OATP substrates. Thus, no clinically meaningful PK drug interactions are expected with iptacopan as concluded in the current Investigator's Brochure.

Consider caution if co-administration of iptacopan with sensitive CYP3A4 or sensitive CYP2C8 substrates is required.

6.2.2 Medication requiring study treatment interruption or permanent discontinuation

Table 6-2 describes medications, which if initiated during the study, require study treatment interruption or permanent discontinuation. The guidance for managing study treatment is provided for situations when a participant requires such medications due to disease progression of IgAN and/or for treatment of other co-morbidities. Topical, inhaled and systemic corticosteroids below or equal the dose of 7.5 mg per day prednisone or equivalent are permitted

at any time during the study and do not require any action with study treatment (no interruption, no dose change).

Systemic corticosteroids in doses >7.5mg/day of prednisone or equivalent or immunosuppressive medications increase the infection risk (Lv et al 2017) and should not be co-administered with study drug during the trial due to safety reasons. Therefore, if systemic corticosteroids in the dose above 7.5 mg/day of prednisone or equivalent or other immunosuppressive compounds are required for participant treatment for any reason, study medication must be interrupted or permanently discontinued (Table 6-2).

Concomitant use of the other medications displayed in Table 6-2 is prohibited while participants are on study treatment. Should participants require the use of any of the listed medications that require permanent or temporary discontinuation of study drug, the participant should continue to attend study visits as per the visit schedule and all assessments should be completed except study drug dispensation. Participants who receive medications which require temporary study drug discontinuation can reinitiate study medication at the investigator's discretion following the guidance in Table 6-2.

Table 6-2 Medication requiring temporary interruption or permanent discontinuation of study treatment

Type of medication	Actions to be taken
Pharmacological dose of Immunosuppressive agents including but not limited to steroids (e.g. >7.5mg/d prednisone or equivalent), oral budesonide, cyclophosphamide, MMF or mycophenolate sodium, cyclosporine, tacrolimus, cyclosporin, everolimus, sirolimus.	If taken for the treatment of IgAN - permanently discontinue study treatment. Patients should continue study visits and assessments. If taken for conditions other than IgAN, study treatment should be temporarily interrupted and the Investigator should determine whether the participant can reinitiate study treatment after participant stops taking the causative medication.
Immunomodulatory agents such as but not limited to rituximab, infliximab, eculizumab, canakinumab, etc	Temporarily interrupt study treatment while taking the medication and for additional 5 half-lives (e.g. the 5 half-lives for rituximab is approximately 4 months).
Endothelin (receptor) antagonists	Interrupt study treatment for the duration of the causative medication and 90 days thereafter. Investigator should determine whether the participant can reinitiate study treatment after participant stops taking the causative medication.
CCI [redacted]	

6.2.3 Prohibited medication

Fibric acid derivatives (fibrates) are a class of medication that lowers blood triglyceride levels. Fibrates and in particular fenofibrate are known to increase serum creatinine (i.e. decrease eGFR) via a poorly understood mechanism that is not thought to be related to improvements in the disease pathway (Ting et al 2013). Their use during the trial may confound the efficacy assessment of LNP023, therefore they must not be taken during the study; if required, they must be instead replaced with another appropriate medication used for that indication.

Co-administration of iptacopan with strong CYP2C8 inhibitors (e.g., gemfibrozil) may increase iptacopan exposure. Concomitant use of strong CYP2C8 inducers (e.g., rifampin) may decrease iptacopan exposure, which may result in loss of or reduced efficacy. Thus, co-administration with strong CYP2C8 inhibitors or inducers is prohibited (Table 6-2).

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each study participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form, site should register the participant in IRT immediately and the next sequential Participant No. available will be assigned to this participant.

6.3.2 Treatment assignment, randomization

At the Randomization visit, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the study participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the study participant, which will be used to link the study participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the study participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of study participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization for the Main Study population will be stratified by 1) Geographic region (Asia, non-Asia) 2) Baseline UPCR (<2 g/g [226 mg/mmol] , ≥ 2g/g [226 mg/mmol] as measured by

the mean (geometric) of two 24 hour urine collections) and 3) Baseline eGFR (30 - <45 mL/min/1.73m^2, ≥ 45mL/min/1.73m^2).

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

The randomization scheme for study participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Participants, investigator staff, persons performing the assessments will remain blind to the identity of the treatment from the time of randomization until final database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study (2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor, (3) data with unblinding potential such as PK concentrations will be kept blind until the time of final database lock.

The randomization codes associated with participants from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until database lock.

Unblinding a single participant at site will occur in the case of participant emergencies (necessary for participant management) and at the conclusion of the study. In cases where the participant is unblinded at site for safety reasons, unblinding will occur via an emergency system in place at the site. As a result, the participant should be discontinued from the study treatment but remain in the study and attend all study visits. Appropriate procedures and firewalls will be put in place to ensure results remain concealed from individuals who are not permitted to have access as per Table 6-3 (e.g. restricted area in the analysis system and document storage system).

As noted it is expected that submission for accelerated/conditional approval may occur following the planned interim analysis. Unblinding of specific roles at the time of the interim analysis is outlined in Table 6-3 and will be defined in a separate detailed Unblinding Charter and will provide information about the persons who be unblinded and the measures taken to restrict access to participant level treatment codes during the time of and following the IA.

Table 6-3 Blinding and unblinding plan

	Time or event				
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**	**DMC safety review**	**IA for efficacy and safety**
Participants	B	B	UI	B	B
Site staff	B	B	UI	B	B
Sponsor:					
Global Clinical Supply	B	UI	UI	UI	UI
Randomization office	UI	UI	UI	UI	UI

	Time or event				
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**	**DMC safety review**	**IA for efficacy and safety**
PK sample analysts	B	B	UI	UI	UI
Unblinded Pharmacovigilance sponsor staff	B	B	UI	UI	UI
Clinical Trial Team members interfacing with sites	B	B	B	B	B
Sponsor staff involved in submission activities, decision boards and other support functions requiring unblinding, as defined in the Unblinding Charter	B	B	B	B	U
Other external groups:					
DMC	B	B	UI	UI	UI
External Independent statistical analysis CRO	B	B	UI	UI	UI
Select Steering committee members (independent from study investigators)	B	B	B	B	U
IA*: interim analysis when approximately 250 participants in the Main Study Population have 9 months of treatment UI: Allowed to be unblinded on individual participant level U: to be defined in Unblinding Charter B: Remains blinded					

6.5 Dose escalation and dose modification

LNP023 will be administered at 200 mg b.i.d. Investigational study treatment dose adjustments are not permitted.

6.6 Additional treatment guidance

Throughout the study, participants should remain on their standard guideline-based supportive care including ACEi or ARB at the maximally tolerated or locally approved maximal daily dose. In addition, if participants are taking diuretics, other antihypertensive medication or other background medication for IgAN, any changes of doses should be avoided for the duration of study if possible.

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the study participant to take the study treatment exactly as prescribed and by explaining that compliance is necessary for the study participant's safety and the validity of the study. The study participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the study participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Study participants should be counselled on the importance of adhering to study medication if compliance is noted to be <80% at a study visit.

6.6.2 Recommended treatment of adverse events

Infections

Participants and treating staff need to be instructed to be vigilant for any clinical signs of infection (e.g., malaise, chills, fever, nausea, photophobia, bone pain) and to measure the body temperature at minimum at the times of symptoms of presumed infection. Participants will be instructed to contact the study physician immediately in case of suspicion of infection or elevated body temperature for a phone directed triage.

In participants with a suspicion of or confirmed bacterial infection, cultures should be taken and treatment should be considered as per investigator’s clinical judgement, including appropriate antibiotics.

Temporary interruption and subsequent recommencement of study treatment after recovery from the infection may be considered, as per the investigator's clinical assessment of benefit and risk. Prophylactic antibiotics and early booster vaccinations should be considered in patients with recurrent infections and/or in patients taking concomitant immunosuppressants, as per the investigator's clinical judgement.

For other severe infections, including Coronavirus Disease (COVID-19), interruption of study treatment should also be considered and can be resumed once the participant has been treated and recovered, as assessed by the investigator. Every effort should be taken to keep the participant on study treatment unless the risk outweighs the benefit in the opinion of the investigator. As needed, the investigator is advised to contact the Novartis medical lead and discuss on a case-by-case basis.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the

investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT code break at any time in case of emergency. The investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time. Participants who are unblinded and therefore discontinued from study treatment are expected to remain in the study and attend all study visits. Participants who complete all study visits will be eligible to enroll in the rollover extension program.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described in Table 6-1 under investigational and control drugs section. A unique medication number is printed on the study medication label. Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the participant's source document.

As per Section 4.6, during a public health emergency that limits or prevents on-site study visits, delivery of study treatment directly to a participant's home may be permitted (if allowed by local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator decides that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The Investigator is accountable for dispatch of study treatment from the site to the participant's home. Each shipment/provisioning will be for a maximum duration of study treatment until the next site visit. During this time, regular phone calls or virtual contacts must be made by the site and for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment.

Implementation will need to be discussed with Novartis.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Operation Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded in the IRT system. Study treatment is not dispensed at Week 2 and participants should continue to take the study medication dispensed at the Randomization visit until the Month 1 visit.

Participants should take LNP023 twice per day (in the morning and in the evening) at approximately the same times each day and ideally with 12-hours interval between morning and evening dosing. At visits where PK sampling is performed (see Section 8.5.1), the participants should not take that day's morning dose until instructed by the site staff.

Participants should be instructed to swallow whole capsules and not to chew or open them and should take LNP023 without regard to food and each dose should be taken with a glass of water. If vomiting occurs during the course of treatment, participants should not take the study treatment LNP023 or matching placebo again before the next scheduled dose. Participants should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 4 hours after the approximate time of the usual daily dosing. That day's dosing should be omitted and the participant should continue treatment with the next scheduled dose.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Heath Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes the following optional subsections requiring a separate signature:
  - 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - Patient Interview, where applicable in participating countries.
  - Off-site visits: The study includes the option for the participant to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site in special circumstances (see Section 8.6). It is required as part of this protocol that the Investigator presents this option to the participant, as permitted by national and local governing regulations.
- As applicable, Pregnancy Outcomes Reporting Consent for female participants
- Optional Genetics Consent to provide a DNA sample for exploratory DNA studies

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

The study includes an optional sub studies/ DNA component which requires a separate signature if the participant agrees to participate. It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments (DNA/sub studies) will in no way affect the participant's ability to participate in the main research study.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Participants will be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits do not lead to automatic discontinuation. Participants who discontinue from study treatment need to perform all assessments required at the EOS visit in addition to the assessments required at the visit when the participant is discontinuing study treatment (see Table 8-1 footnote 2). Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF. All assessments at the Randomization visit should be conducted prior to initiation of study drug. PRO measures must be completed before any clinical assessments are performed at any given visit.

In special circumstances as described in Section 4.6 and Section 8.6, including the COVID-19 pandemic that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. Phone calls, virtual contacts (e.g. tele consult) or visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities (See Section 8.5.5) can replace on-site study visits, until the participant is able to visit the site.

Table 8-1 Assessment Schedule

Period	**Screening**	**Run-in**	**Treatment**											**Follow-up**
Visit Name	**Screening**	**Baseline**	**Randomization**	**Week 2**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**EOS[2]**	**Follow-up[3]**
Visit Numbers[1]	**1**	**20**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**
Weeks	**-13 to -2**	**-1**	**1**	**2**	**4**	**13**	**26**	**39**	**52**	**65**	**78**	**90**	**103**	**104**
Months	**-3 to -1**	**-1**	**1**	**1**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Days	**-90 to -14**	**-7 to -4**	**1**	**14 ±7**	**28 ±7**	**90 ±14**	**180 ±14**	**270 ±14**	**360 ±14**	**450 ±14**	**540 ±14**	**630 ±14**	**720 ±14**	**727 -0 +21**
Informed consent	X													
Inclusion / Exclusion criteria	X	X												
Vaccination	X													
Demography	X													
Smoking/alcohol history	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medical history/current medical conditions	X													
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	S	S						S					S	
Electrocardiogram (ECG)		X						X					X	
Kidney Biopsy[4]	X													
Pregnancy Test (serum)	S													
Pregnancy Test (Urine) [5]		S											S	
Pulse rate	X	X	X	X	X	X	X	X	X	X	X	X	X	

Period	**Screening**	**Run-in**	**Treatment**											**Follow-up**
Visit Name	**Screening**	**Baseline**	**Randomization**	**Week 2**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**EOS[2]**	**Follow-up[3]**
Visit Numbers[1]	**1**	**20**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**
Weeks	**-13 to -2**	**-1**	**1**	**2**	**4**	**13**	**26**	**39**	**52**	**65**	**78**	**90**	**103**	**104**
Months	**-3 to -1**	**-1**	**1**	**1**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Days	**-90 to -14**	**-7 to -4**	**1**	**14 ±7**	**28 ±7**	**90 ±14**	**180 ±14**	**270 ±14**	**360 ±14**	**450 ±14**	**540 ±14**	**630 ±14**	**720 ±14**	**727 -0 +21**
Blood Pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body Temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body Height	X													
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
24-hr urine collection[6]	X[7]	X					X	X					X	
First morning void urine (midstream)	X	X		X	X	X	X	X	X	X	X	X	X	
HIV screening	X													
HBV[9, 10]	X					X	X	X	X	X	X	X	X	
HCV[11, 12]	X					X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	
Estimated Glomerular Filtration Rate	X	X		X	X	X	X	X	X	X	X	X	X	
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	
Reproductive and thyroid hormone panel		X	X	X	X	X	X	X			X		X	
Blood for complement			X					X					X	

Period	**Screening**	**Run-in**	**Treatment**											**Follow-up**
Visit Name	**Screening**	**Baseline**	**Randomization**	**Week 2**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**EOS[2]**	**Follow-up[3]**
Visit Numbers[1]	**1**	**20**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**
Weeks	**-13 to -2**	**-1**	**1**	**2**	**4**	**13**	**26**	**39**	**52**	**65**	**78**	**90**	**103**	**104**
Months	**-3 to -1**	**-1**	**1**	**1**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Days	**-90 to -14**	**-7 to -4**	**1**	**14 ±7**	**28 ±7**	**90 ±14**	**180 ±14**	**270 ±14**	**360 ±14**	**450 ±14**	**540 ±14**	**630 ±14**	**720 ±14**	**727 -0 +21**
biomarkers C3/C4[14]														
Spot urine (midstream) for biomarker substudy			X					X					X	
Blood for biomarker substudy[14]			X					X					X	
Patient reported outcomes		X				X	X	X			X		X	
Patient Interview[13]								X						
Trial Feedback Questionnaire			S					S					S	
PK blood collection						X	X	X						
Pharmacogenetic sample[8]			X											
Drug dispensation			X		X	X	X	X	X	X	X	X		

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[S] Assessment to be recorded in the source documentation only. Trial Feedback questionnaire will be documented in source notes as completed however not captured in the clinical database.

[1] Visit structure given for internal programming purpose only

[2] For any participant prematurely discontinuing study treatment but remaining in the study for study visits, the assessments required at the visit the participant is discontinuing study treatment as well as any additional assessments required at the EOS visit must be performed.

Period	Screening	Run-in	Treatment											Follow-up
Visit Name	Screening	Baseline	Randomization	Week 2	Month 1	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	EOS[2]	Follow-up[3]
Visit Numbers[1]	1	20	100	110	120	130	140	150	160	170	180	190	200	210
Weeks	-13 to -2	-1	1	2	4	13	26	39	52	65	78	90	103	104
Months	-3 to -1	-1	1	1	1	3	6	9	12	15	18	21	24	25
Days	-90 to -14	-7 to -4	1	14 ±7	28 ±7	90 ±14	180 ±14	270 ±14	360 ±14	450 ±14	540 ±14	630 ±14	720 ±14	727 -0 +21

[3] A follow-up visit for AE and SAE monitoring 7 days post the EOS visit is only required for participants who either do not enter the REP, or for whom the Day 1 visit of the REP does not occur within 7 days of the EOS visit of CLNP023A2301.

[4] Kidney biopsy may be done at screening if a qualifying biopsy in the required timeframe is not available.

[5] Pregnancy tests can be performed more frequently as required by local regulations.

[6] Two 24 hour urine collections must be performed at Baseline, Month 9 and EOS, on any 2 days within 14 days prior to the visit. At Screening and Month 6 only one collection is required.

[7] Either one sample of 24 hour urine or a First Morning Void is collected at screening.

[8] Pharmacogenetic sample collection is only performed in participants who sign the PG informed consent. If the PG sample is not taken at the randomization visit, it can be taken at any visit after randomization.

[9] HBsAg at screening for all patients. For patients in Republic of Korea additionally anti-HBc is tested at screening.

[10] Patients in Republic of Korea who are HBsAg negative but anti-HBc positive at screening require HBsAg tests from Month 3 onwards.

[11] HCV-RNA at screening for all patients. For patients in Republic of Korea additionally anti-HCV is tested at screening.

[12] Patients in Republic of Korea who are HCV-RNA negative but anti-HCV positive at screening require HCV-RNA tests from Month 3 onwards.

[13] Patient Interviews will be conducted at Month 9 in select countries in approximately 50 patients.

[14] Biomarker samples at the randomization visit must be taken prior to first dose of IMP.

8.1 Screening

Once the participant has signed the informed consent form, the participant may enter the screening period.

Rescreening

Participants who fail screening or baseline can be re-screened two additional times after screen/baseline failing. A new participant ID number should be used for re-screening and the participant must be re-consented prior to performing any screening assessments. All required screening assessments must be performed for participants being rescreened.

8.1.1 Information to be collected on screening failures

Study participants who sign an informed consent form and are subsequently found to be ineligible will be considered a screen failure. The investigator must provide the following minimal set of screen failure information:

- Reason for screen failure
- Demographic information
- Informed consent
- Inclusion/Exclusion criteria which excluded the participant from the study
- Withdrawal of informed consent (if applicable)
- Any serious adverse event (SAE) refer to SAE section (Section 10.1.3) for reporting details, death (if applicable)

Data and samples collected from participants prior to screen failure may still be analyzed.

8.1.2 Vaccinations

If not vaccinated at time of screening, vaccinations should be completed as indicated in Section 5.1, once all other eligibility criteria at screening have been met. Vaccines should cover as many serotypes as possible (including meningococcal serotypes A, C, Y, W-135 and B). To minimize participant burden, the use of multivalent vaccines is recommended as locally available and according to local guidelines & regulations (e.g. quadrivalent vaccine for N. meningitidis which covers serotypes A, C, Y and W-135 and Pneumovax-23 which covers 23 S. pneumoniae serotypes). Vaccination booster requirements should be regularly assessed based on local guidelines and regulations as well as package inserts of vaccines used for initial protocol required vaccinations.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with the CRF. Participant demographic and baseline characteristic data that will be collected include: age, sex, race, ethnicity, medical history and data on current medical conditions and concomitant medications including information on the dose and duration of time before screening that the participant has been taking an ACEi/ARB, and the medications which are specified in Exclusion Criteria 7 (Section 5.2). Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or

efficacy profile of the treatment due to these characteristics. In addition, we need to assess the diversity of the study population as required by Health Authorities.

Investigators have the discretion to record abnormal test findings on the medical history eCRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.2.1 Kidney biopsy

The diagnosis of IgAN and the inclusion of an eligible participant must be based on a kidney biopsy. In India, electron microscopy results are also required for IgAN diagnosis due to local Health Authority request. Participants with an eGFR ≥45mL/min/1.73m^2 must have a qualifying biopsy performed within the last 5 years. Participants with an eGFR 30-<45mL/min/1.73m^2 must have a qualifying biopsy performed within the last 2 years and have < 50% tubulointerstitial fibrosis. Participants with an eGFR 20-<30mL/min/1.73m^2 must have had a qualifying biopsy performed to confirm the diagnosis of IgAN; however, there is no restriction as to when it was performed.

If a participant is being considered as potentially eligible for the study but without a qualified kidney biopsy result or the biopsy is not within the specified time frame, a kidney biopsy to verify his or her eligibility may be performed during screening once the informed consent form has been signed.

It is expected that the investigator has access to the biopsy slides to confirm participant eligibility. In exceptional cases where the biopsy slides are not available, the biopsy report confirming IgAN is required, however, the investigator must make every effort to obtain the biopsy slides.

8.2.2 Hepatitis and HIV screening

All participants will be tested for hepatitis B surface antigen (HBsAg) and hepatitis C RNA (HCV RNA) at screening. Participants with active, replicative HBV infection (HBsAg positive) or HCV infection (HCV RNA positive) will be excluded from the study. HBV and HCV testing will be performed by the central laboratory. In the Republic of Korea only, participants will be tested additionally for anti-HBc and anti-HCV at screening based on local Health Authority request. For participants who are HBsAg negative but anti-HBc positive at screening, HBsAg test will be performed by a local laboratory at the scheduled visits after randomization starting at month 3. In Republic of Korea only, participants who are HCV-RNA negative but anti-HCV positive at screening, HCV-RNA test will be performed by a local laboratory at the scheduled visits after randomization starting at month 3.

Evaluation for HIV seropositivity at screening will be performed by the central laboratory using a chemiluminescence (and/or other appropriate) assay.

8.3 Efficacy

Efficacy samples will be collected at the time points defined in the Assessment schedule (Table 8-1).

8.3.1 Estimated Glomerular Filtration Rate

The rate of kidney function decline will be measured by assessing the annualized total slope of eGFR. The change from baseline at 9 months in eGFR will also be assessed at the IA. Serum creatinine as measured in mg/dL as part of the Clinical Chemistry panel through the central laboratory will be used to calculate the eGFR applying the CKD-EPI formula (Levey et al 2009).

$GFR = 141 \times \min(sCR/\kappa, 1)^{\alpha} \times \max(sCR/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

where: sCR is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of sCR /κ or 1, and max indicates the maximum of sCR /κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area. At screening, a modified formula may be applied according to specific ethnic groups and local guidelines.

8.3.2 24 hour urine collection

Urine over 24 hours will be collected. Measurements include but are not limited to UPCR, UACR, total albumin and total protein. In the SRI population, urine PK parameters (eg. total amount of excreted LNP023 via the kidney) will be analyzed.

At screening, either one 24 hour urine collection or one FMV urine sample is required to assess the participant's eligibility. At the Baseline, Month 9 and EOS visits, two 24 hour urine collections must be performed on any two days within 14 days prior to the visit.

At Month 6, one 24 hour urine collection is required. In the SRI population, this 24h urine collection must begin the day prior to the study visit and end on the day of the visit.

These 24 hour urine samples should be refrigerated throughout the period of collection and before being taken to the clinic or laboratory. Where available and allowed by local regulation and if requested by the participant, these 24h urine samples may be delivered by courier from participant's homes to the clinic or laboratory.

8.3.3 First morning void urine (midstream)

First morning void (midstream) will be collected at all visits, except the Randomization visit and the Screening visit (if 24h urine is done).

At visits where only FMV is required, participants should collect the FMV on the day of the visit. At visits where both FMV and 24 hour urine samples are required, where only one 24 hour urine sample is needed (Month 6), the FMV should be collected one day prior to the clinic visit. At Baseline, Month 9 and EOS, where two 24 hour urine samples are needed, 1) If the 24 hour urines are collected on consecutive days, FMV should be collected before the start of the first of the two 24 hour urine collections; 2) If the two 24 hour urine collections are separated by a day or more, the FMV should be collected before the start of the second 24 hour urine collection. The collected urine samples should be refrigerated after collection and before being taken to the clinic or laboratory. Measurements include UPCR and UACR.

8.3.4 Composite Kidney Failure Endpoint

The study will evaluate the effect of LNP023 on delaying time to kidney failure, defined as any one of the following five events (Levin et al 2020):

- Sustained decline in eGFR of ≥30% from baseline over at least 4 weeks, or
- Sustained eGFR <15 mL/min/1.73m^2 over at least 4 weeks, or
- Maintenance dialysis (defined as dialysis performed for at least 4 weeks),
- Receipt of a kidney transplantation, or
- Death from kidney failure

Death *from* Kidney Failure is defined when the study participant dies AND kidney failure is the underlying cause of death (i.e., advanced CKD with eGFR < 15 ml/min/1.73 m² is the driver of death, meaning the disease which initiated the train of morbid events leading directly to death, irrespective of specific mechanisms, such as hyperkalemia, fluid overload, etc.) and kidney replacement therapy was never started (irrespective of reason) (Levin et al 2020). Death from Kidney Failure will NOT be considered for participants, who develop Acute Kidney Injury (AKI) without a trajectory of advanced progressive CKD, who are not offered dialysis, refuse it, or if dialysis is unavailable.

If a reduction in eGFR from baseline ≥30% or eGFR <15 mL/min/1.73m^2 is noted at any visit, a confirmatory eGFR measurement should be obtained 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. The date of the outcome is the onset of when the decline occurred first (not the date of confirmation). If the first event occurs within 4 weeks of the EOS, a confirmatory eGFR measurement is not required.

In situations where the duration of dialysis is less than 4 weeks due to reasons such as kidney transplantation or death, or unavailability of further data or discontinuation of dialysis due to either futility of therapy or resource constraints, the outcome of Kidney Failure requiring dialysis will be concluded if the start of dialysis occurred after a trajectory of progressive CKD.

8.3.5 Appropriateness of efficacy assessments

Urinary protein excretion and eGFR are widely used measures of kidney function and indicators of disease progression. Proteinuria will be assessed by collecting urine and measuring the protein to creatinine concentration ratio (UPCR); eGFR is calculated using the CKD-EPI formula. The 2 years of follow-up in the study provides an opportunity to assess the long term effect of LNP023 on kidney function.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed. For details on AE collection and reporting, refer to AE section (Section 10.1.1).

Table 8-2 Safety Assessments and Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include BP and pulse measurements. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using a validated device with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1.

8.4.1 Laboratory evaluations

A central laboratory will be used for the analysis of the specimens collected. Details of collection, shipment, and reporting by the laboratory is provided to the investigator in the Laboratory Manual.

Clinically notable laboratory findings are defined in Appendix 1 in Section 16.1.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate. Blood samples can be taken fasting or non-fasting but the fasting state should be captured in the laboratory requisition form and CRF.

Table 8-3 Laboratory tests

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelet Count, Erythrocytes, Leukocytes with differential blood count, Lymphocytes, Reticulocytes.
Chemistry	Albumin, Alkaline phosphatase (ALP), Alanine aminotransferase (ALT) , Aspartate aminotransferase (AST) , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct

Test Category	Test Name
	Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose
HIV screening	HIV chemiluminescence (and/or other appropriate) test
Hepatitis	Hepatitis B virus surface antigen, Hepatitis C virus RNA*
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen). At the discretion of the investigator, positive results may require a sample to be sent to the central laboratory for further microscopy assessment of white blood cell(s) (WBC), red blood cell(s) (RBC) and sediments. If required locally, the macroscopic panel urinalysis can be performed at the central laboratory.
Thyroid	Triiodothyronine (T3), Thyroxine (T4), Thyroid stimulating hormone (TSH) and Reverse T3
Blood hormone levels	Testosterone (total), LH, FSH and DHT.
Pregnancy Test	Serum / Urine pregnancy test
*For patients in Republic of Korea anti-HBc and anti-HCV are tested at screening. Patients in Republic of Korea who are HBsAg negative but anti-HBc positive at screening require HBsAg tests from Month 3 onwards. Patients in Republic of Korea who are HCV-RNA negative but anti-HCV positive at screening require HCV-RNA tests from Month 3 onwards.	

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

The Fridericia QT correction formula (QTcF) should be used for clinical decisions. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF according to the following formula, where QT interval is in milliseconds (ms) and RR interval in seconds (s):

$QTcF = QT / \sqrt[3]{RR}$

ECGs are to be collected with ECG machines available at the site. The original ECGs and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

In the event that a clinically significant ECG abnormality is identified at the site (See Appendix 1 in Section 16.1), the ECG should be repeated to confirm the diagnosis with the assessment sent to the Sponsor's medical monitor for expedited review if applicable. If the participant is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate. Any identifying details must be redacted (e.g. participant initials, date of birth).

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if required by local requirements. At screening, a serum pregnancy test will be performed, and a urine pregnancy test will be performed at baseline and at the end of the study.

The participant should inform the investigator if they believe they might be pregnant or have fathered a child during the study.

Assessments of fertility

Refer to Section 5.2 for criteria to determine women that are not of child bearing potential.

A woman is considered of childbearing potential from menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or bilateral salpingectomy must be retained as source documents. A postmenopausal state is defined as no menses for 12 months of natural (spontaneous) amenorrhea without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.4 Reproductive and thyroid hormones monitoring

The assessments indicated below will be carried out as per the Assessment schedule (Table 8-1), and will be assessed in all participants.

Testosterone, follicle stimulating hormone (FSH), dihydrotestosterone (DHT), luteinizing hormone (LH), thyroid stimulating hormone (TSH) and thyroid hormones (T3, T3 reverse, T4) will be regularly monitored.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are appropriate for this indication/patient population and the potential risks associated with LNP023. The risk of infection will be closely monitored throughout the study. Participant vigilance for early signs and symptoms of infection is required and supported by providing a Participant Card to enhance awareness and vigilance. Reproductive and thyroid-related hormones, vital signs and ECGs will be monitored in order to evaluate the clinical significance of findings observed in toxicity studies.

8.5 Additional assessments

8.5.1 Pharmacokinetics

The pre-dose PK plasma samples will be collected and evaluated for all participants at Month 3, 6 and 9 according to the schedules as outlined in Table 8-4 (Main Study Population) and Table 8-5 (SRI population). Participants should be instructed not to take study treatment the morning of the visit where plasma PK pre-dose samples are taken. At these visits the study

treatment should be taken at the site after the pre-dose plasma PK sample is taken. For the SRI population, in addition, post-dose plasma and urine PK samples (from the 24 hour urine collection as outlined in Section 8.3.2) will be collected at Month 6 as specified in Table 8-5.

The details of sample collection will be outlined in the Laboratory Manual regarding sample collection, numbering, processing and shipment.

Table 8-4 PK plasma sample collection schedule - Main study population

Visit*	Timepoint	Volume (mL)	Sample number	Dose Ref. ID
Month 3	pre-dose	3	101	1
Month 6	pre-dose	3	201	2
Month 9	pre-dose	3	301	4
*If the pre-dose PK sample collection is missed at any of the visits mentioned, the collection can be done at Month 12. In this case the sample number will be 401 and the Dose Ref. ID will be 6				

Table 8-5 PK plasma sample collection schedule - SRI population

Visit**	Timepoint	Volume (mL)	Sample number	Dose Ref. ID
Month 3	pre-dose	3	101	1
Month 6^	pre-dose	3	201	2
	0.25h	3	202	3
	0.5h	3	203	3
	1h	3	204	3
	2h	3	205	3
	4h	3	206	3
	6h	3	207	3
	8h	3	208	3
Month 9	pre-dose	3	301	4
**If the pre-dose PK sample collection is missed at any of the visits, the collection can be done at Month 12. In this case the sample number will be 401 and the Dose Ref. ID will be 6. ^If the PK sampling at Month 6 is missed, it can be performed at Month 9. In this case the sample numbers would be 301, 302... etc. The Dose Ref. ID would be 4 for pre-dose and 5 for post dose collections.				

Table 8-6 Urine Sample Collection Schedule - SRI population

Visit	Timepoint	Sample number	Dose Ref. ID
Month 6♦	0-24h	501	3
The 24h urine sample described in Section 8.3.2 will be used for PK analyses. The PK urine should correlate with the 0-8hr post-dose plasma sample collection. If performed at Month 9 the sample number will be 601, the Dose Ref ID will be 5.			

Concentrations of LNP023 will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 1.0 ng/mL (plasma) and 10 ng/mL (urine). Metabolites (as needed) may be determined as appropriate. 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 Section 16.3 and additional PK parameters may be calculated if deemed necessary. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report. For

participants with SRI in which extensive PK sampling will be conducted plasma protein binding of LNP023 will be explored, if feasible.

8.5.2 Biomarkers

Samples Collected in the Full Population

Blood will be collected in all participants at the Randomization visit (prior to the first dose of IMP), Month 9 and EOS to measure Cystatin C and the complement related biomarkers C3 and C4. These results will be used to determine if baseline levels change with treatment, predict participant outcomes and/or IgAN progression. Instructions for sample collection, processing, and shipment will be provided in the Laboratory Manual.

8.5.2.1 Additional biomarker assessments

A sub-study will be performed at sites selected as having the capacity to sample fragile biomarkers and where allowed locally, in as many participants as possible. Blood and urine will be collected at the Randomization visit (prior to the first dose of IMP), Month 9 and EOS. Samples will be used to measure biomarkers or proteins related to complement pathways, IgA nephropathy and LNP023 mechanism of action, such as Wieslab, sC5B9 and/or Factor Bb. The analysis of circulating markers is also planned to examine the effect of LNP023 on biomarkers/protein expression and may support the identification of biomarker signatures that characterize disease development and the response of treatment with LNP023. In the event promising biomarkers/proteins (or methods) are discovered or new information on study drug biomarker effect is obtained, additional analysis may be performed on remaining samples. Instructions for sample collection, processing, and shipment will be provided in the Laboratory Manual.

8.5.3 Clinical Outcome Assessments (COAs)

Validated Patient Reported Outcomes (PROs) questionnaires will be self-administered by participants via an electronic PRO device (ePRO) before any other procedure or assessment at the time points specified in Table 8-1.

If a participant is not able to self-administer the ePRO or refuses to complete the questionnaires, this should be documented in the source documents. Detailed instructions relating to the administrative procedures of the ePRO questionnaires will be provided to the sites.

The participant should be given an electronic device (ePRO) in the language of their choice to complete the questionnaire(s) at the scheduled visit before any other clinical assessments are performed. The participant should be given sufficient space and time to complete the questions. The participant should be made aware that completed questionnaires are not reviewed by the investigator/study personnel. The questionnaire completion date and time should be documented in study source records.

In the case of a technical failure with the electronic PRO device only, the questionnaires should be completed using a paper version of the questionnaire.

FACIT-Fatigue

The primary PRO for this study is the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (version 4). The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) is a 13-item questionnaire that assesses patient-perceived tiredness, weakness and difficulty conducting activities due to fatigue. The FACIT-Fatigue is a psychometrically sound instrument and has been widely used to measure fatigue for patients with various chronic illnesses. The purpose of FACIT-Fatigue in this study is to assess the experience and impact of fatigue on patients with IgAN.

To further understand the participants' symptoms, functioning, and overall well-being, and the meaningfulness of changes during the study, three additional patient reported outcomes questionnaires (PRO) and a Patient Interview will be used. The PROs include the following:

- EORTC QLQ-C30
- EQ-5D-5L
- Patient Global Impression of Severity of fatigue (PGIS)

A brief description of each questionnaire is given in the sections below.

EORTC QLQ-C30

The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was selected for inclusion in the study as it is responsive to clinical status and change over time. It is also widely recognized as clinically valid and reliable measure for assessing Health-Related Quality of Life (HRQoL), function, and symptoms (Aaronson et al 1993, Fayers et al 2002). The EORTC QLQ-C30 consists of 30 questions, which are incorporated into five functional domains (physical, role, cognitive, emotional, and social domains); a global health status/global quality of life scale; three symptom scales (fatigue, pain, nausea and vomiting scales); and six single items that assess additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and the perceived financial burden of treatment.

EQ-5D-5L

The EuroQol-5 Dimensions-5 Level (EQ-5D-5L) is a widely used questionnaire designed to assess health status in adults. The measure is divided into two distinct sections, the descriptive system and the EQ visual analogue scale (EQ VAS). The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Participants rate each of these items from 1 of the 5 levels: no problems, slight problems, moderate problems, severe problems, or unable to/extreme. A composite health state is then defined by combining the levels for each dimension into a 5-digit number. The second section includes the EQ visual analogue scale (EQ VAS) that measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best imaginable health state" and 0 represents the "worst imaginable health state." Respondents are asked to rate their current health by placing a mark along this continuum (Rabin and de Charro 2001, Van Reenen et al 2015).

PGIS

A Patient Global Impression of Severity of fatigue questionnaire will be used to understand the overall severity of fatigue experienced and the clinical meaningfulness of treatment effects experienced during this study. It contains the question "How would you rate your overall symptoms of fatigue during the past 7 days?" to which the participant indicates their fatigue severity by selecting one of five response options: no symptoms, mild, moderate, severe, and very severe.

Patient Interviews

Qualitative patient feedback on the meaningfulness of changes experienced during the study is of increasing interest to regulatory bodies and patient communities, as outlined in FDA's Patient Focused Drug Development Guidance (FDA, June 2020, Anthony et al 2017). To collect this patient-reported feedback, semi-structured patient interviews will be conducted at Month 9 in a representative sample of participants. These interviews are designed to further understand the extent to which participants in the study experienced meaningful changes in their IgAN-related disease experience and to obtain feedback on the patient-reported outcome (PRO) questionnaires administered in the study, to understand the relevance of the items assessed by the questionnaires and explore patient's perceptions of meaningful improvement on PRO scores.

All interviews will be conducted by researchers from a third-party vendor who are trained in qualitative interviewing techniques to ensure the quality of the interview and data protection. During each interview, interviewers will follow a semi-structured interview guide. This guide is not intended as a script to be followed verbatim but rather will be referenced during interviews to ensure that relevant and complete information related to the research question is collected in as spontaneous a manner as possible. The training of the interviewers and the open-ended approach ensures that study participants are not unduly biased and that the language study participants use to describe their experiences is elicited organically (Staunton et al 2019). Interviews will be conducted over the phone or via teleconference software, last approximately 90-minutes, and be audio-recorded for analyses purposes. These interviews will be optional, and implemented in a subset of approximately 50 participants in selected countries as allowed by local authorities.

Trial Feedback

A Trial Feedback Questionnaire (TFQ) will be provided for participants to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators. Responses would be used by Novartis to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect or adverse events and therefore would not be trial data. Should any spontaneous information be collected about AEs, this would be transferred to the safety database. TFQ data is considered outside of Clinical Trial data and will not be part of Clinical Database and Clinical Study Report.

8.5.4 Pharmacogenetics substudy (optional)

The study includes an optional genetic research component which requires a separate informed consent signature if the participant agrees to participate. As permitted by local governing regulations and by the IRB/EC, it is required as part of this protocol that the investigator presents these options to the participant.

This exploratory study will aim to identify inherited genetic factors which may (1) be related to the causes and consequences of IgAN, its pathophysiology and associated comorbidities, (2) predict response to treatment with LNP023, (3) predict genetic predisposition to side effects. The goal is to better understand the safety and treatment effect of LNP023, or to learn more about human diseases, or to help develop ways to detect, monitor and treat diseases.

Analyses may occur retrospectively after study close. As technology changes over time, the most appropriate technology will be used at the time the exploratory genetic research is performed. This may include the study of the entire genome.

Laboratory Manuals will be provided with detailed information on sample collection, handling, and shipment.

8.5.5 Healthcare Resource Utilization

Analyses will be undertaken, as appropriate, to assess the effects of treatment on Healthcare Resource Utilization (HRU) parameters. These measures may include hospitalization (e.g. number of hospital days), emergency room visits and unscheduled visits to a physician's office. The frequency and duration of any inpatient hospitalization will be recorded along with the primary reason for the hospital admission and discharge. All attempts will be made to collect HRU variables in all participants throughout the duration of the study to avoid selection bias. The information about other drugs used, laboratory tests conducted and procedures performed also will be collected.

8.6 Off-site visits

At the investigator’s direction and based on benefit-risk considerations of the participant’s clinical condition, qualifying participants may be offered the option of off-site visits to unburden the participant while ensuring participant safety, engagement and retention during situations such as a pandemic or the physical inability of a participant to visit the site. The off-site location is not a site location where the investigator will conduct the trial and where source data will be maintained, but is for example the participant’s home or another safe location if assessed as suitable by the Investigator. The off-site visits will be offered in certain countries and sites and may replace on-site visits if Sponsor, Investigator and local regulations and conditions allow.

Participants, that the Investigator identifies as suitable candidates for off-site visits, must provide consent for home visits to occur. The participant should discuss with the Investigator whether an on-site or off-site visit is more appropriate.

All off-site visits must be approved by Novartis and the off-site visit schedule will be determined in discussion between the participant, Investigator, and the Sponsor.

The following conditions must be met for off-site visits to occur:

- Off-site visits may occur during the study under exceptional circumstances and if agreed between investigator and sponsor.
- The participant must be randomized and have completed the randomization visit.
- If a participant has begun off-site visits and s/he suffers from either (1) an severe AE or an SAE (possibly related to study medication), and/or (2) any concurrent medical conditions the investigator will decide, based on a benefit-risk assessment, whether off-site visits should be continued, or not, under the circumstances.

Off-site visit personnel

The off-site visits will be conducted by a qualified member of site staff or a third-party vendor sourced by Novartis that can provide qualified off-site healthcare professionals who will perform study assessments. Where a site wishes to use off-site healthcare professionals that are not provided by Novartis this must be agreed with Novartis before use. In all cases, procedures will be performed remotely under the oversight of the investigator who will remain accountable for all medical decisions (i.e. protocol specified medical procedures, AE/SAE assessment and reporting, changes in medication, etc.) and the safety of participants. If needed, on-site staff can perform certain procedures remotely using tele-visits.

The off-site healthcare professional will perform the procedures listed in Table 8-7 as completely as possible at the visits specified in Assessment Schedule (Table 8-1). The off-site healthcare professional may collect and process laboratory samples which will then be shipped to the Central Laboratory.

Table 8-7 Assessments to be performed during off-site visits

Concomitant medications
Adverse event assessment
Pulse rate
Blood pressure
Body temperature
Blood sample collection*
Urinalysis
Patient Reported Outcomes
*Blood samples will not be collected for post-dose PK, PG or any sample requiring special handling (e.g. immediate centrifugation) which would not be possible at an off-site visit.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation

Permanent discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of medication described in the Section 6.2.2, which require study treatment discontinuation
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding
- A participant's eGFR falls to <15 mL/min/1.73m^2
- Persistent reduction in eGFR from baseline by ≥30% measured by central laboratory, and confirmed after 4 weeks
- The initiation of maintenance dialysis
- Kidney transplantation

In Republic of Korea patients, who are HBsAg negative but anti-HBc positive and patients who are HCV-RNA negative but anti-HCV positive at screening will be tested for HBsAg and HCV-RNA regularly (Table 8-1) on request of local Health Authority. If these patients are newly tested HBsAg positive or HCV-RNA positive during the study, study treatment needs to be discontinued. Additional diagnostic and treatment need to be initiated in accordance to local guidelines if required.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment agree to return for the assessments required at the visit the participant is discontinuing study treatment as well as any additional assessments required at the End of Study visit as outlined in Table 8-1 and should remain in the study and adhere to the study visit and assessment schedule (Table 8-1). If they fail to return for assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to participate in any visit(s) (including off-site as described in Section 8.6), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule. If participants are unwilling to be contacted regularly, the investigator should obtain the participant's consent to review medical records, unless the participant explicitly withdraws consent for medical record review.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to the "Emergency Breaking of Treatment Code" section (Section 6.6.3).

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and protocol-required assessments or follow-up, for any reason prior to completing the study. If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination include:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

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.

Participants who complete the study may be eligible to enroll in a single-arm open-label LNP023 rollover extension program (REP) within a given time frame. Participants who prematurely withdraw from the study for any reason are not eligible to enroll in the rollover extension program.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

The Investigator and any qualified designees are responsible for managing the safety of individual participants. They are also responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and for following up all AEs and SAEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided below (Section 10.1.1, Section 10.1.2 and Section 10.1.3).

For the investigational product and for non-authorized AxMPs (when applicable), information about adverse drug reactions and how to manage them can be found in the IB or equivalent documentation. Information about adverse drug reactions can also be found in the product information for marketed products.

Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product used in this study. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

Collecting and assessing AEs

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

The investigator will attempt to establish a diagnosis of the event (including lab abnormalities that constitute AEs) based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE.

For each AE, the investigator must assess:

1. The severity grade
    - Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
    - Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
    - Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
2. The causality

The investigator is obligated to assess the relationship between any treatment used in the study (study treatment, AxMP(s)) and each occurrence of each AE. The investigator will use clinical judgment to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.

For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken with study treatment.

All adverse events must be treated appropriately. Action taken with study treatment may include one or more of the following:

- Dose not changed
- Drug interrupted/permanently discontinued

6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

AEs should continue to be reported for participants who prematurely discontinue study treatment but remain on the study for study visits, until the EOS visit or the EOT visit +7 days, whichever is longer. Participants who complete the study but do not enroll in the REP should be contacted 7 days after the EOS visit and any AEs reported should be recorded in the CLNP023A2301 study CRF. For participants who do enroll in the REP, AEs experienced between the EOS visit of the core CLNP023A2301 study and Day 1 (first study drug administration) of the REP up to 7 days after the last dose of study drug in CLNP023A2301, should be recorded in the CLNP023A2301 study CRF. If a participant enrolls in the REP directly and Day 1 of the REP is the same day as the EOS visit of CLNP023A2301, then any AEs experienced thereafter are only captured in the CRF of the REP.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Medication used to treat AEs must be recorded on the appropriate eCRF.

Handling of AEs

All AEs must be treated appropriately. More information about how to manage AEs can be found in the IB. Information about adverse drug reactions can also be found in product information for marketed products.

Timeframe of recording of AEs

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

The Investigator must also instruct each participant to report any new AE (beyond the protocol observation period) that the participant, or the participant's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the Investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

Reporting of AEs related to AxMP(s)

The AE reporting requirements for AxMPs will apply once this trial has been transitioned under EU CTR 536/2014.

All AEs related to any AxMPs used in this study must be reported to Novartis.

In assessing causality, the investigators will use the points above.

If a suspicion that medical occurrence could be related to study treatment (and/or interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

10.1.1.1 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are of scientific and medical interest specific to Novartis's product or program, for which ongoing monitoring may be appropriate. Such events may require further investigation in order to characterize and understand them. AESI are defined on the basis of potential safety risks for the product, class effects, data from preclinical studies

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a medical occurrence in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the event (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Novartis. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Novartis. The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). (For patients with transaminases above the ULN at baseline, the Hy's law criteria is 2-fold increase above baseline values). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Serious bacterial infections caused by encapsulated bacteria will be treated as adverse events of special interest and the sponsor should be notified, as with any SAEs, within 24 hours of learning of their occurrence.

Medication used to treat SAEs must be recorded on the appropriate eCRF.

Reporting of SAEs related to AxMP(s)

All SAEs related to any AxMP (whether authorized or not) used in this study must be reported to Novartis within 24 hours of the site becoming aware of it. In assessing causality, the investigators will use the points above. If a suspicion that the medical occurrence could be related to study treatment (or an interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

If an SAE is not previously documented in the IB, or product information for marketed products, and is thought to be related to any study treatment, Novartis may urgently require further information from the investigator for HA reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment. SUSARs will be reported to the competent authorities and relevant ethics committees in accordance with national regulatory requirements in participating countries, including EU Clinical Trial Regulation 536/2014.

Screen failures

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

Run-in or Baseline failures

SAEs occurring between the time the participant has provided informed consent until the time the participant is determined to be a run-in failure must be reported.

Randomized participants

Any SAEs experienced by participants who discontinue study treatment prematurely but remain in the study for follow up, should continue to be reported in the study CRF until the EOS visit or EOT visit +7 days, whichever is longer.

Participants who do not enroll in the REP should be contacted 7 days after the EOS visit and any SAEs reported by the participant should be recorded in the CLNP023A2301 study CRF. All SAEs experienced after the 7 day period (follow-up) up to 30 days after EOS should be reported to the Novartis Safety office. Any SAEs experienced after 30 days after EOS should only be reported to the Novartis Safety office if the investigator suspects a causal relationship to study treatment. Any SAE reported after the 7 day follow-up period should be reported to the Novartis Safety office using paper SAE forms. SAEs and all related information (e.g. medications used to treat the SAE etc), should not be entered into the clinical database in cases where the SAE is more than 7 days after the date of the End of Study visit.

For participants who do enroll in the REP, SAEs experienced between the EOS visit of the core CLNP023A2301 study and Day 1 of the REP, up to 7 days after the last dose of the study drug in the CLNP023A2301, should be recorded in the CLNP023A2301 study CRF. If a participant enrolls in the REP directly and Day 1 (first study drug administration) of the REP is the same day as the EOS visit of CLNP023A2301, then any SAEs experienced thereafter are only captured in the CRF of the REP.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, under no circumstances later than within 24 hours of the investigator receiving the follow-up information. (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or

otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 1 week after stopping of investigational drug.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis as described in Section 10.1.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported. Post-natal follow up should occur at 1, 3 and 12 months after delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF if associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness (Table 10-1).

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1 in Appendix 2 (Section 16.2) for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-1. Repeat liver chemistry tests (i.e. ALT, AST, total bilirubin (TBL), prothrombin time (PT)/international normalized ratio (INR), ALP, GGT etc) to confirm elevation.

These liver chemistry repeats will be performed using a local or the central laboratory. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event

- Thorough follow-up of the liver event should include
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy.

- Exclusion of underlying liver disease, as specified in Table 16-1
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and other key variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC. Analyses reviewed by the DMC will be performed by an independent statistical group that will have access to randomization codes in accordance to procedures described in the charter and its appendices will perform the analysis which will be reviewed by the DMC.

10.2.3 Steering Committee

The Steering Committee (SC) will be established comprising medical and scientific experts who are not participating in the trial or being members of the DMC. They should not be site investigators or Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated Contract Research Organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, baseline, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant, interruptions and discontinuations will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

For interim database locks, treatment codes will be moved to restricted area to be accessed by the independent programmer and statistician. Once all the necessary actions have been completed and the database has been declared to be complete and accurate for the final analysis at the EOS, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

Continuous remote monitoring of each site's data may be performed by a centralized Novartis/Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

This section provides the complete description of the statistical methods to be used in the evaluation of data collected in the study, including derivation of endpoints, testing of the statistical hypotheses considered, and estimates of relevant treatment effects provided.

An interim Clinical Study Report (CSR) may be produced for the purpose of an early submission for conditional/accelerated approval at the time of the IA outlined in Section 4.4. The final analysis will be conducted on all participant data at the time the trial ends and will be included in the final CSR.

The following sections describe the analyses for both the Main Study population and the SRI population (see Section 5 for details). The efficacy analyses and related sample size calculations consider only the Main Study population.

The term "study treatment" refers to the randomized treatment (LNP023 or placebo) throughout this section. The stratification factors used in the statistical analysis refer to the randomization strata described in Section 6.3.2.

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.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

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.

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.

12.2 Participant demographics and other baseline characteristics

The FAS will be used for the analyses in this section.

Demographic and other baseline data including disease characteristics and kidney biopsy information will be summarized descriptively for all participants and by treatment group, for the Main study and SRI populations separately. Selected demographic and baseline characteristics will be similarly listed together with the efficacy data.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, for all participants and by treatment group, for the Main study and SRI populations separately.

12.3 Treatments

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

The duration of exposure (in weeks) to LNP023 and placebo as well as 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) will be summarized by means of descriptive statistics.

Descriptive statistics for the number and percentage of participants with a considerable dose change in their background ACEi/ARB medications during the treatment period will be provided.

Concomitant medications prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group, for the Main study population and SRI populations separately. Significant non-drug therapies prior to and after the start of the study treatment will be summarized according to System Organ Class (SOC) by treatment group, for the Main study population and SRI populations separately.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The aim of the primary estimand at the Interim analysis is answering the primary clinical question of interest in terms of proteinuria reduction (see Section 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 2.1) in order to support a full approval submission.

12.4.1 Definition of primary endpoint(s)/estimand(s)

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) or other newly approved drugs or new background therapy for IgAN and KRT were not available and regardless of unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason.

Further detail on the estimand attributes is provided in Section 2.1.

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 corticosteroids, immunosuppressant therapy or other newly approved drugs or new background therapy for IgAN and KRT were not available and regardless of unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason.

Further detail on the estimand attributes is provided in Section 2.1.

12.4.2 Statistical model, hypothesis, and method of analysis

Primary analysis at the IA

The aim at the IA is to estimate the treatment effect of the LNP023 compared to placebo, for the target population on the primary endpoint of log-transformed ratio to baseline in UPCR (24h). The log-transformation used refers to the natural log (base on e).

The following hypothesis will be tested at the one-sided 0.5% level at the time of interim analysis:

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 μ_{LNP023} is the mean of the log-transformed ratio to baseline of 24h UPCR 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 12.4.3) for the log ratio to baseline in UPCR (24h). This model will have treatment, time point (as a categorical variable), randomization strata as fixed effects, treatment*time point and time point*log(baseline 24h UPCR) as interaction terms and baseline log (24h UPCR) as fixed covariate. The correlations between visits within subjects will be modelled using an unstructured covariance matrix.

The mean difference between LNP023 versus placebo (and its 95% confidence interval) 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 95% confidence interval and one-sided p-value for the hypothesis test. The percent (%) reduction of LNP023 vs placebo will also be presented.

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 12.4.3 for detail). Similar approaches will be followed for values collected after the initiation of new background therapy for IgAN treatment and initiation of KRT (see Section 12.4.3. for detail).

At each visit where UPCR 24h is collected, the mean (geometric) of two UPCR 24h values obtained from two distinct 24 hour urine collections, as described in Section 8.3.2, 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. The UPCR (24h) measurement for the Baseline visit (Visit 20) will be used as the baseline for the analysis.

Primary analysis at the Final analysis

The aim at the final analysis is to estimate the treatment effect of LNP023 compared to placebo, for the target population on the primary endpoint of annualized total eGFR slope over 24 months.

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 β_{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 ACEi/ARB and any other background treatment for IgAN during the run-in phase of the study.

The overall study Type I error will be controlled at one-sided 2.5%. The one-sided α to be used for the final analysis will be adjusted for multiplicity of testing according to the testing procedure described in Section 12.5.1.

Statistical analysis will be carried out using a longitudinal mixed effects model (following the imputation approach to handle intercurrent events described in Section 12.4.3) 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 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 intake of CS/IS and/or other newly approved drugs for treatment of IgAN. The handling of measurements following the intake of such medications or initiation of new background therapy for IgAN treatment and KRT in the analysis is the same as for the primary estimand at the IA (see Section 12.4.3). The eGFR value for the baseline visit (Visit 20) will be used as the baseline for the analysis.

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

Primary analyses outlined above will consider only the Main Study population, and will be based on the FAS according to the randomized treatment group and strata as assigned at randomization.

12.4.3 Handling of remaining intercurrent events of primary estimand

The remaining intercurrent events 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 2.1 as follows:

- **Intake of corticosteroid or immunosuppressant therapy (CS/IS) for treatment of IgAN :** The "jump-reference" ("J2R") imputation approach (Kenward 2015) will be used to impute values after the intake of CS/IS for treatment of IgAN 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. Values for the placebo group will be imputed

under the MAR assumption. The analysis models described in Section 12.4.2 for the interim and final analyses respectively will be then applied to the imputed dataset. This process will be repeated multiple times and final inferences will be obtained using Rubin's rules (Carpenter et al 2007).

- **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.
- **Initiation of new background therapy for IgAN treatment**: values following the initiation of such therapy 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.
- **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.
- **Initiation of kidney replacement therapy (KRT) i.e. dialysis or transplant:** the "J2R" imputation approach will be used to impute values after initiation of KRT, in a similar fashion as for the intercurrent event of the intake of CS/IS for treatment of IgAN.

12.4.4 Handling of missing values not related to intercurrent event

In cases that participants who discontinue treatment for any non-administrative reason 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 caused due to administrative reasons will be implicitly handled under the primary analysis models.

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, where possible, to allow for the protocol assessments to be conducted (e.g. off-site visits, see Section 8.6 for detail). In case missing values do occur for such reasons, data 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.

12.4.5 Supplementary analysis

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 IgAN, KRT, unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason.

Likewise, 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 IgAN, KRT, unforeseen changes in permitted/concomitant medications or treatment discontinuation for any reason.

To evaluate these supplementary estimands, the population, endpoint and summary measure attributes will be the same as for the primary estimands at the Interim and Final analysis respectively. 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 as needed i.e in this supplementary estimand, the intake of CS/IS or other newly approved drugs for treatment of IgAN will be handled with the treatment policy approach. Thus, data collected after the intake of such medications will be included in the analysis that will otherwise follow the same principles as outlined in Section 12.4.2. Similarly, the initiation of new background therapy for IgAN and KRT will be handled via the treatment policy approach.

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 alternative measurement for quantifying proteinuria, which is more frequently assessed during the study and thus may offer increased precision in the analysis.

The potential impact of a wave of pandemic-related infections affecting measurements has been minimized by the implementation of measures proposed in Section 8.6. Nevertheless, impact due to pandemic-related intercurrent events cannot be precluded at this stage. In case a considerable number of unforeseen pandemic-related intercurrent 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 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 intercurrent events, as well as associated analysis methodology will be defined in the Statistical Analysis Plan (SAP) or an amendment to the SAP should new infection waves of a pandemic occur.

Subgroup analyses to assess the homogeneity of the treatment effect across subgroups of interest will be performed. The subgroups examined may include age categories, sex, ethnicity and the stratification factors specified in Section 6.3.2 (geographic region, baseline UPCR

category and baseline eGFR category). The full list of subgroups to be considered will be described in the SAP.

12.4.6 Supportive analyses

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, separately for each of the two primary estimands.

12.4.7 Sensitivity analyses for primary endpoint/estimand

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 may include, for example:

- imputation using the "*copy-reference*" approach in order to reflect the assumption that participant profiles in the LNP023 arm will slowly regress back to the mean of the placebo arm following the occurrence of both these intercurrent events.

- imputation under the MAR assumption following the intake of newly approved drugs in the LNP023 arm in order to reflect the assumption that 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.

Further sensitivity analysis of the primary estimands with respect to the treatment of missing data will be detailed in the SAP.

12.5 Analysis of secondary endpoints/estimands

The attributes of the secondary estimands at the IA and Final analysis and remaining intercurrent events are outlined in Section 2.2. All analysis described in the following section will be based on the FAS set.

For all secondary estimands the same intercurrent events as for the primary estimands apply, apart from cases where the intercurrent event itself forms part of the endpoint attribute. In general, the same strategies described in Section 12.4.3 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.

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

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

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), the primary (H_2) and the secondary estimands (H_3, H_{41} and H_{42}) at the Final analysis in order to ensure strong

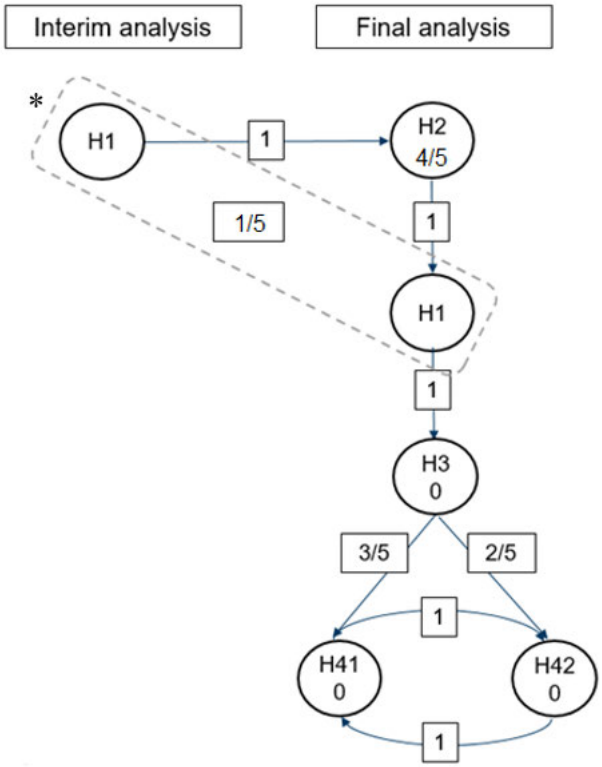
control of the study wise type one error for multiplicity of testing at one-sided 2.5%. Hypothesis identifiers are provided in Table 12-1. The hypotheses associated with the secondary estimands at the Final analysis will be tested only if the null hypothesis associated with the primary estimand at the Final analysis is rejected.

- The initial allocation of (local) significance levels is 1/5, 4/5, 0, 0, and 0 of the overall study wise 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 2011).

Table 12-1 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 total score

Figure 12-1 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 remaining secondary estimands at the Interim analysis 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.

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

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 2.2 and Section 12.4.4 respectively) with treatment and randomization strata as fixed effect factors, and baseline log (24hr UPCR) 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.

Missing data will be, in general, handled as described in Section 12.4.4 for the primary estimands (i.e. will be imputed on the continuous scale and used to derive this binary endpoint). In case of missing data due to death from kidney failure, participants will be considered as non-responders (i.e. have not reached UPCR (24hr) <1g/g).

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/1.73 m², 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 6.3.2. 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. The Kaplan-Meier curves will be presented by treatment group.

H_{42}: Analyses for the change from baseline to 9 months in the FACIT-Fatigue total score are described in detail in Section 12.5.6.

Secondary analyses at the IA

An MMRM as described in Section 12.4.2 for UPCR 24h will be used for the analysis of the change from baseline in eGFR at month 9, with the distinction that a log-transformation will not 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 12.4.3 and Section 12.4.4). The eGFR value for the baseline visit (Visit 20) will be used as the baseline for the analysis.

The mean difference between LNP023 versus placebo will be presented for the 9 month time point, together with its two-sided 95% CI.

- 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.
- The annualized total eGFR slope over 12 months will be evaluated using the same statistical analysis and missing data handling approaches as the primary estimand at the Final analysis (see Section 12.4.2, Section 12.4.3 and Section 12.4.4). All eGFR values (measured at the central lab for scheduled and unscheduled visits) of participants who have completed the Month 12 visit at the time of the IA will be included in the analysis.
- Analyses for the change from baseline to 9 months in the FACIT-Fatigue total score are described in detail in Section 12.5.6.

12.5.2 Safety endpoints

For all safety analyses, the Safety set will be used. All listings and tables will be presented by treatment group, for the Main study and SRI populations separately. The following section outlines key safety analyses and provides a non-exhaustive description of associated outputs. Detail on further safety summaries will be provided in the SAP, as needed.

Safety summaries (tables, figures) include only data from the on-treatment period 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, with a start date during the on-treatment period (treatment-emergent AEs). In addition, a separate summary for death including on treatment and post treatment deaths will be provided as appropriate.

The on-treatment period lasts from the date of first administration of study treatment to 7 days after the date of the last actual administration of any study treatment in the core CLNP023A2301 study or until the date of first administration of study treatment in the REP, whichever occurs first.

At the time of the IA all safety data available will be included in the analysis. Differences in participant exposure-times at the IA will be appropriately considered in the analysis and associated outputs e.g. via the provision of exposure-adjusted AE/SAE incidence tables. Full detail of the IA safety analyses will be provided in the SAP.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation of treatment or study.

The number (and proportion) of participants with adverse events of special interest/related to identified and potential risks will be summarized by treatment.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

Summary statistics will be provided for all vital signs data by treatment and visit/time. Where ranges are available, abnormalities will be listed by treatment group, participant, and visit/time. If appropriate, summary statistics of the occurrence of abnormalities may be provided by treatment.

12-lead ECG

ECG parameters, including PR, QRS, QT, QTcF, and RR intervals, will be obtained for each participant during the study. ECG data will be read and interpreted as described in Section 8.4.2.

Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced by treatment group.

Summary statistics for all ECG data will be provided by treatment and time point; the number of participants with values above key threshold values will be displayed. Where normal ranges

are available, abnormalities in ECG data will be listed by treatment group, participant, and visit/time. Graphical displays of selected ECG parameters over time will be provided by treatment group.

Clinical laboratory evaluations

Summary statistics for all laboratory data will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification may be used, as appropriate, to compare baseline to the worst on-treatment value. Where normal ranges are available, abnormalities in laboratory data will be listed by treatment group, participant, and visit/time.

Graphical displays of selected safety parameters (e.g. hematological parameters, thyroid and reproductive hormone levels) over time will be provided by treatment group.

12.5.3 Pharmacokinetics

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 timepoints specified in Section 8.5.1. At the time of the IA, only the PK of LNP023 in participants with SRI and potentially other participant subgroups will be evaluated.

LNP023 plasma concentration data will be summarized by visit/sampling time point, including the frequency (n, %) of concentrations below the lower limit of quantification (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. For trough levels, mean and individual plasma concentrations will be presented in both semi-log and linear scales per visit/sampling timepoint, if feasible.

Pharmacokinetic parameters will be calculated as described in Section 8.5.1/Appendix 16.3 for the SRI population only, apart from Cmin that will be assessed in all participants. 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.

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.

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.

12.5.4 DNA

Exploratory DNA studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests are used for the analyses. Additional data, from other clinical trials, are often needed to confirm associations. Alternatively, if the number of participants enrolled in the study is too small to complete proper statistical analyses, the data may be combined, as appropriate, with those from other studies to enlarge the dataset for analysis. Detail on exploratory DNA analyses will be provided in a separate analysis plan.

Data generated on hypothesis-free platforms will be reported separately (e.g. CSR addendum).

12.5.5 Biomarkers

All biomarker data (including but not limited to C3 and C4) will be summarized via descriptive statistics by treatment and timepoint. In the summary tables, the frequency (n, %) of values below the LLOQ and above the ULOQ respectively will be included. Further displays may be considered and will be described in detail in the SAP.

Other planned analyses using biomarkers collected in this and other studies in participants with IgAN will be specified in a separate Analysis plan and described in a separate report. The FAS will be used for all analyses in this section.

12.5.6 Patient reported outcomes

The main PRO of interest for this study is the FACIT-Fatigue Scale (see Section 8.5.3). The Endpoint attribute for the PRO estimand is the change from baseline to 9 months in the FACIT-Fatigue total score. The Population and Treatment attributes as well as intercurrent events and their handling strategies are the same as for the primary estimands in Section 2.1.

Statistical analysis will be carried out using a Mixed Model of Repeated Measures (MMRM) for the change from baseline to 9 months in the FACIT-Fatigue total score. This model will have treatment, time point, randomization strata as fixed effects, treatment*time point and time point*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. Alternative covariance matrix structures to consider in case of convergence issues will be described in the SAP.

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

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. Given the greater variability at the subject-level, a 5-point change is recommended as a meaningful important difference. Response data will be analyzed using Generalized Linear Mixed Model (GLMM) including treatment, time point, randomization strata as fixed effects, treatment*time point as interaction term, and baseline FACIT-Fatigue total score as fixed covariate, with logit as link function. Subject-level random effects will be included in the model. The odds ratio between treatment arms at the 9 month

time point will be estimated together with its two-sided 95% confidence interval. Sensitivity analyses considering responder definitions based on improvements of at least 3 points and above may also be conducted and will be specified in a program-level SAP.

Analyses will include all participant data from baseline up to the intercurrent event of intake of CS/IS and/or other newly approved drugs or initiation of new background therapy for treatment of IgAN or initiation of KRT. 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 (see Section 12.4.3 and Section 12.4.4). 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. The FACIT-Fatigue value for the baseline visit (Visit 20) will be used as baseline for the analysis.

Descriptive statistics and graphical displays by visit will be also produced.

The above analyses for FACIT-Fatigue will be conducted both at the Interim as well as Final analysis, considering all participant data collected to the EOS. A further exploratory analysis will be conducted at the final analysis, following the same analysis principles as specified above 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. PGIS will be used as anchor instrument to calibrate the scale of the FACIT-Fatigue assessments and support the determination of the minimum important change for FACIT-Fatigue in IgAN patients. Of the EORTC QLQ-C30 domains/scales described in Section 8.5.3, the physical domain, global health status and fatigue scales will be used to provide complementary information to FACIT-Fatigue on participant-reported symptoms and overall well-being. EQ-5D-5L will be used to support Health Technology Assessment evaluations.

PGIS

To further calibrate the performance of the FACIT-Fatigue in the context of treatment with LNP023 and determine within-subject, 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 subject. 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. A full description of the anchor-based evaluation will be included in a project-level SAP.

EORTC QLQ-C30

Changes from baseline to 9 and 24 months in the EORTC QLQ-C30 domain/scales identified above will be analyzed following the same approach as for FACIT-Fatigue total score. A supportive responder analysis will similarly be included in the program-level SAP. Descriptive summary statistics will also be provided.

EQ-5D-5L

Changes from baseline to 9 and 24 months in the EQ VAS scale will be analyzed following the same approach as for FACIT-Fatigue total score. Descriptive summary statistics will also be provided.

For the analysis of the three additional exploratory PROs at the Interim analysis, the changes from baseline to 9 months will only be considered.

Patient Interviews

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 the program-level SAP. Analyses will be done at the time of Final Analysis.

12.6 Analysis of exploratory endpoints

The following exploratory endpoints will be analyzed based on the FAS:

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

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.
- 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 initiation of new background therapy for treatment of IgAN or initiating KRT.
- 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 and 24 months, and UPCR (sampled from 24h urine collection) at 24 months.
- Time-averaged proteinuria [average of UPCR values (sampled from 24h urine collection)] from baseline to 24 months.

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

Note that exploratory objectives related to biomarker, PK and PRO endpoints are described in the relevant sub-sections (Section 12.5.3, Section 12.5.6).

All exploratory endpoints will be summarized descriptively. Comparisons between treatment groups on a clinically relevant subset of the above endpoints will be implemented. Further detail will be provided in the SAP.

12.7 Interim analyses

An interim analysis is planned when approximately 250 participants in the Main Study population have completed the 9 months visit. The primary purpose of this interim analysis is to demonstrate superiority of LNP023 vs placebo on proteinuria reduction, based on a primary endpoint of percentage change from baseline in 24h UPCR (i.e. log-transformed ratio to baseline in 24h UPCR), in order to support accelerated/conditional marketing authorization (see Section 4.4 for further detail). Table 2-1 outlines the objectives and associated endpoints to be assessed at the IA. The results of the IA will further inform decision making for the current study e.g. continue or stop for safety reasons. Further detail for this interim analysis is provided in Section 4.4 and Section 6.4.

To ensure strong control of the study wise type one error for multiplicity of testing, the sequentially rejective multiple test procedures (Bretz et al 2009) 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 (see Section 12.5.1). At the interim analysis, H_1 will be tested at alpha/5. Note that if H_1 cannot be rejected at the IA but H_2 is rejected at the final analysis, H_1 will be re-tested (now with full sample size). To adjust for multiplicity in the group-sequential test of H_1 alone, alpha for the test of H1 is split to (alpha/5, $alpha_F$), and $alpha_F$ is obtained (via a numerical search) such that P_{H1}(H_1 rejected at interim)+P_{H1}(H_1 not rejected at interim, H_1 rejected at final)=alpha, given a correlation of $\sqrt{n_{IA}/n_{final}}$ in the group-sequential test at currently planned n_{IA}=250 and n_{final}=430 (see Section 12.5.1) (Willi and Frank Bretz 2013).

Periodic safety DMC reviews for the monitoring of safety data by the external DMC (see Section 4.4) will be performed by an external analysis team during the course of the study. Such safety analyses do not inflate the type I error for the primary efficacy hypothesis testing and thus no adjustment for multiplicity is required.

12.8 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.

12.8.1 Primary endpoint(s)

Interim analysis

The log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) will be used to estimate 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 LNP023 and placebo groups. 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 12.5.1.

12.8.2 Secondary endpoint(s)

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.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.)

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

Monitoring strategy, methods, responsibilities, and requirements are provided in the monitoring plan and contracts. Details may include definition of study critical data items and processes

(e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring)

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

Clinically notable laboratory abnormalities for selected tests based on a percent change from Baseline:

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% of erythrocytes (absolute value & not change from baseline)

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

Uric acid >50% increase

Along with investigators, the clinical trial team from Novartis will receive alerts for clinically notable values via fax/e-portal (or appropriate means agreed with central labs and Novartis).

ECG alert values

Resting heart rate sinus rhythm < 30 or a HR decrease from baseline ≥ 25% or

HR > 130 [bpm]

QRS >120 or increase >25% compared to predose baseline [msec]

QTcF >500 or increase >60 compared to predose baseline [msec]

Ventricular tachycardia

New complete heart block (Grade III AV block) or Mobitz II AV block

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Definitions of Triggers, Actions and Follow-up requirements for liver events

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case (Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN – or 3 x ULN in the presence of bone pathology) (In patients with transaminases above the ULN at baseline, the Hy's Law criteria is 2-fold increase above baseline values)	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Report as an SAE (even before all other possible causes of liver injury have been excluded) Establish causality (investigate alternative etiologies)[a] Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory value) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP, GGT, CK and GLDH (frequency at Investigator discretion) Monitor for symptoms[b] Report outcome[c]
ALT or AST		
> 8 × ULN	Interrupt the study treatment Hospitalize if clinically appropriate Establish causality (investigate alternative etiologies)[a] Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT (frequency at Investigator discretion) Monitor for symptoms[b] Report outcome[c]
> 5 to ≤ 8 × ULN If elevated at baseline: > 3 x baseline or > 300 U/L (whichever occurs first)	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for more than 2 weeks, discontinue the study drug Establish causality (investigate alternative etiologies)[a] Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
> 3 × ULN to ≤ 5 × ULN (accompanied by symptoms)[b] If elevated at baseline: > 2 x baseline	Perform INR within 48 hours Interrupt the study treatment Hospitalize if clinically appropriate Establish causality (investigate alternative etiologies)[a] Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion) Monitor for symptoms[b] Report outcome[c]

Criteria	Actions required	Follow-up monitoring
or > 300 U/L (whichever occurs first)	Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	
> 3 to ≤ 5 × ULN (patient is asymptomatic)[b] If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	Perform INR within 48 hours • If INR > 1.5, follow the guidance in row above for symptomatic patients. • If INR ≤ 1.5: Repeat LFT within the next week If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology) >3 x ULN if bone pathology is present	Repeat LFT within 48 hours If elevation persists, establish causality (investigate alternative etiologies)[a] Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality (investigate alternative etiologies)[a] Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at Investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)[b]	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Interrupt the study treatment Hospitalize the subject Establish causality (investigate alternative etiologies)[a] Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion) Monitor symptoms[b] Report outcome[c]
Any AE potentially indicative of a liver toxicity[d]	Consider study treatment interruption or discontinuation Hospitalization if clinically appropriate Establish causality (investigate alternative etiologies)[a] Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	Investigator discretion

Criteria	Actions required	Follow-up monitoring
[a] Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease [b]Severe fatigue, malaise (general), abdominal pain (right upper quadrant), nausea, vomiting or rash with eosinophilia [c]Resolved = return to Day 1 values; Condition unchanged = stable values at three subsequent monitoring visits at least 2 weeks apart; Condition deteriorated = values worsen or liver transplantation; and Fatal. [d]These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms. TBL: total bilirubin; ULN: upper limit of normal		

16.3 Appendix 3: Non-compartmental pharmacokinetic parameters

Table 16-2 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).
These parameters will be measured in plasma and urine for the SRI population only, apart from Cmin that will be assessed in all patients.	

16.4 Appendix 4: Classification/staging system for Acute Kidney Injury as described by AKIN

Table 16-3 Classification/staging system for Acute Kidney Injury* (Mehta et al 2007)

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 µmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 mL/kg per hour for more than 6 hours
2[a]	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline	Less than 0.5 mL/kg per hour for more than 12 hours
3[b]	Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl [≥ 354 µmol/l] with an acute increase of at least 0.5 mg/dl [44 µmol/l])	Less than 0.3 mL/kg per hour for 24 hours or anuria for 12 hours

*Modified from RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria. The staging system proposed is a highly sensitive interim staging system and is based on recent data indicating that a small change in serum creatinine influences outcome. Only one criterion (creatinine or urine output) has to be fulfilled to qualify for a stage.
[a]200% to 300% increase = 2- to 3-fold increase.
[b]Given wide variation in indications and timing of initiation of kidney replacement therapy (KRT), individuals who receive KRT are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of KRT.