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LNP023

Clinical Trial Protocol CLNP023X2203 / NCT03373461

An adaptive seamless randomized, double-blind, placebo-controlled, dose ranging study to investigate the efficacy and safety of LNP023 in primary IgA nephropathy patients

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO& PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse event
ACEi	angiotensin converting enzyme inhibitor
[redacted]	[redacted]
AhR	aryl hydrocarbon receptors
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	complement alternate pathway
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
b.i.d.	Bis In Die (Twice daily)
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulations
CK	creatinine kinase
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease – Epidemiology Collaboration
CP	classical pathway
CMO&PS	Chief Medical Office & Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	coefficient of variation
[redacted]	[redacted]
DAR	dose administration record
DDI	Drug Drug Interactions
DHT	Dihydrotestosterone
DMC	Data Monitoring Committee
DNA	Deoxyribonuclein acid
DRF	dose range finding
ECG	Electrocardiogram
EDC	Electronic Data Capture

eGFR	Estimated Glomerular Filtration Rate
EOS	End of study
EOT	End of treatment
FE	food-effect
ELISA	Enzyme-linked immunosorbent assay
eSAE	Electronic Serious Adverse Event
ESRD	End Stage Renal Disease
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FMV	First Morning Void
FSH	Follicule-Stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
HA	Health Authority
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	chorionic gonadotropin
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
hpf	high-power-field
HV	healthy volunteers
IA1	Interim analysis 1
IA2	Interim analysis 2
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board

IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
KIM-1	Kidney Injury Molecule-1
LDH	lactate dehydrogenase
LFT	Liver function test
LH	Luteinizing hormone
LLOQ	lower limit of quantification
LMW	low molecular weight
LOAEL	Lowest Observed Affect Effect Level
LP	lectin pathway
MAC	Membrane Attack Complex
MAD	multiple-ascending dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MCP	Multiple Comparison Procedure
MMRM	Mixed Model of Repeated Measures
MMF	Mycophenolate Mofetil
[redacted]	[redacted]
NOAEL	No Observed Adverse Effect Level
OATP	Organic anion-transporting polypeptide
OC	oral contraceptives
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PRO	Patient reported outcome
PT	prothrombin time
PXR	pregnane X receptor
RAAS	renin-angiotensin-aldosteron-system
RBC	red blood cell(s)

RNA	Ribonuclein acid
SAD	single-ascending dose
SAE	Serious adverse event
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOM	Site Operations Manual
SUSAR	Suspected unexpected serious adverse reactions
TBL	total bilirubin
TDI	time dependent inhibition
TID	ter in die (three times a day)
TSH	Thyroid stimulating hormone
UA	Urine Albumin
UACR	Urine Albumin to Creatinine Ratio
UI	Unblinded (individual)
UG	Unblinded (group)
UP	Urine Protein
UPCR	Urine Protein to Creatinine Ratio
ULN	upper limit of normal
ULoQ	upper limit of quantification
WBC	white blood cell(s)
WoC	Withdrawal of Consent
WOCBP	Women of child bearing potential

Pharmacokinetic definitions and symbols

Ae0-t	Amount of drug (or defined metabolite) excreted into the urine from time zero to time 't' where t is a defined time point after administration [mass units or % of dose]
AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
AUCtau,ss	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time / volume]
Cav,ss	The average steady state plasma (or serum or blood) concentration during multiple dosing
CL	The systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration [volume / time]
CLr	The renal clearance from plasma (or serum or blood) [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Cmax,ss	The observed maximum plasma (or serum or blood) concentration following drug administration at steady state [mass / volume]
Cmin,ss	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
Racc	The accumulation ratio
Tmax	The time to reach the maximum concentration after drug administration [time]
Vss	The volume of distribution at steady state following intravenous administration [volume]
Vz	The volume of distribution during the terminal elimination phase following intravenous administration [volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
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.
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)
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
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.
Patient	An individual with the condition of interest
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Run in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject’s medications or other intervention)
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
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
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)

Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Amendment 6 (September 2020)

Amendment rationale

The main purpose of this amendment is to update the unblinding plan for the study.

The grouped level results from the Part 1 interim analysis (IA1) and Part 2 interim analysis (IA2) will be communicated to support continued development of LNP023 (e.g. initiation of phase 3 IgAN study).

- The aggregate unblinded results at the group level from IA1 Part 1 of the trial can be communicated once all patients have completed Part 1 of the study and all Part 2 patients have been enrolled (entered run-in phase). Investigators, patients and Novartis study team will remain blinded to the individual patient treatment codes until final database lock.
- The IA2 (carried out when all patients in Part 2 have completed to Day 90) will include the planned primary analysis based on all patients in the trial. The aggregate unblinded results at the group level from IA2 can be communicated upon finalization of these results. Investigators, patients and the Novartis study team will remain blinded to the individual patient treatment codes until final database lock.

Major changes to the protocol

The following changes have been implemented throughout the protocol:

1. Part 2 interim analysis will be performed when all patients in Part 2 have been randomized and completed Day 90. However, for patients who are not able to attend the visit until after the Day 90 visit cutoff for the Part 2 interim analysis (IA2), the data will considered missing for the purposes of the interim analysis.(Section 3.5 and Section 11.9).
2. The unblinding plan for the study has been updated (Section 6.4 and Table 6-2). The update to this plan will allow sharing of unblinded group level results from IA1 and IA2 to support initiation of phase 3 IgAN study.
3. Section 8.5.2 has been updated to confirm that Soluble Biomarker analysis will be conducted at selected sites only.

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. 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 5 (April 2020)

Amendment rationale

The main purpose of this amendment is to confirm the final number of patients recruited into Part 2 of the study and the doses to be investigated based on the results of the Part 1 interim analysis (IA1). Based on the available data from interim analysis Part 1 (IA1) of the trial, part 2 of the study will recruit approximately 50 randomized patients. In addition and as specified in the protocol, a 4th active dose was to be included in part 2, either 25 mg b.i.d or 100 mg b.i.d. After review of the Part 1 interim analysis, the DMC recommended inclusion of 100 mg b.i.d. dose. The next interim analysis (IA2) will hence be planned to take place when approximately 50 patients from Part 2 have completed the 90 day visit. The totality of evidence from approximately 100 patients (pooled from Part 1 and Part 2) is expected to provide sufficient information. Additionally, approximately 50 patients will provide additional information to evaluate the proteinuria reduction from month 3 to month 6.

The changes are summarized in more detail below**.**

Major changes to the protocol

The following changes have been implemented throughout the protocol:

1. As a result of the available data from the interim analysis of Part 1 (IA1) of the trial, Part 2 of this study will recruit approximately 50 randomized patients. (Section 3.5, Section 11.7 and Section 11.9)
2. Post interim analysis part I (IA1), the DMC has recommended to add 100 mg dose to part 2 of the study. (Section 3.1, Section 3.5, Section 6.2)
3. At the time of IA2, the sponsor (The Novartis Decision Making Team) will become unblinded to the patient treatment codes to allow decision making for next steps of the clinical development. This is considered reasonable as the impact of this knowledge biasing the overall study results is thought to be minimal due to the objective nature of the endpoints. In addition, the time point for primary analysis of the study for dose response, combining Parts 1 and 2, is the 90 day visit. Notably, the investigator and patient will remain blind until the end of the trial. In addition, after the last patient in Part 1 completed his/her final study visit, the Novartis Decision Making Team will have access to the individual unblinded results of IA1. (Section 6.4 and Table 6-2)
4. A one-sided type I error rate of 10% will be used for all efficacy analyses in the final analyses (Section 11.4)
5. Based on new available data from pre-clinical and clinical studies, the following sections have been updated: Section 1.2.2, Section 3.3, Section 3.6.2 and Section 3.6.3
6. Adjustments to run-in criteria and discontinuation of study drug due to COVID-19 (Section 3.1, Section 3.2 and Section 7.2)

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. 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 (May 2019)

Amendment rationale

The main purpose of this amendment is to increase the duration of treatment phase from 90 days to 180 days in Part 2 of the trial in order to gather information about longer term treatment effects and safety information for LNP023.

In addition, the description and implementation of the planned adaptations to Part 2 of the trial has been further clarified/modified.

The changes are summarized below.

Major changes to the protocol

The following changes have been implemented throughout the protocol:

- Interim reports from the main study phase of LNP023 chronic toxicology studies (26-week rat; 39-week dog study) are available. Supported by these results, the treatment in Part 2 is extended from 90 days to 180 days in order to assess efficacy and safety for a longer treatment duration (Section 3.1, Section 3.2, Section 3.3, Section 11.4, Section 11.5, Section 11.9, Table 6-2, and Table 8-2).
- Added one secondary objective for Part 2 of the study assessing the effects of LNP023 on renal function up to 180 days of treatment.
- Severe anemia with marked bone marrow fibrosis was observed in 1 out of 12 dogs in the 39-week dog toxicology study at 150 mg/kg dose. Reticulocyte count will be included in hematology assessment, and will be measured at all visits including the 3-month safety follow-up period.
- Clarified that patients who have received LNP023 previously will not be able to participate in Part 2 of the study.
- Clarified that patients who have enrolled in Part 2 will remain in screening or run-in phases and will not receive blinded study treatment until the DMC recommendation is available (Section 3.1, Section 6.2 and Section 8.2).
- Table 8-2 is added to define the assessment schedule for patients participating in Part 2, while Table 8-1 is for Part 1 of the study only.
- In Section 7.5, the study stopping rules have been modified based on trial status so that, should the pre-specified safety event occur, the independent Data Monitoring Committee (DMC) will be contacted in a timely manner to assess the patient safety and if changes in trial conduct are warranted.
- In Section 8.7, PK samples on Day 30 will be collected from all of the patients in Part 1, and at least 48 patients in Part 2.
- The total sample size of Part 2 will be calculated which provides at least 80% power assuming a 1-sided alpha of 5% for the final analysis.

- Clarified that a new renal biopsy should be performed at screening if the most recent renal biopsy was performed more than three years ago.
- In Section 8.5, Table 8-1 and Table 8-2, the instructions on how to collect both 24 hour urine and first morning void on Visits 20, 140, 160 and 180 have been added.
- Results of rabbit embryo-fetal development study are available. The findings support removing the statement limiting duration of treatment and changing the contraception methods from "highly effective" to "effective" (Section 1.2, Section 3.6, Section 4.2, Section 5.1, Section 6.2 and Section 9.6).

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The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent/Assent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 3 (September 2018)

Amendment rationale

The purpose of this amendment is to modify the inclusion criteria at screening and to simplify the investigations performed during patient visits in an attempt to improve patient recruitment and to reduce burden to the patients. This is in response to data received on patient screen failures and feedback from sites.

The changes are summarized below.

Major changes to the protocol

The following changes have been implemented throughout the protocol:

1. The number of 24h urine collections is reduced in the assessment schedule Table 8-1.
2. Inclusion criteria 6 in Section 4.1: the urine protein level required at screening for inclusion is decreased from ≥1g/24h to ≥0.75g/24h from a 24h urine collection, or a urine protein to creatinine ratio (UPCR) ≥0.8g/g (90mg/mmol) from first morning void sample. For consistency, this change is reported in other sections of the protocol.
3. PK sampling, and PD [redacted] were removed from Day 1 in the assessment schedule Table 8-1. The volume of blood collected was updated accordingly in Section 3.6.1. The PK objectives were updated accordingly in Section 2.2 Secondary objectives and Section 8.7 Pharmacokinetics.
4. [redacted]
5. In Section 11.4.2, the statistical hypotheses have been reworded using the technical formulation in Bretz et al 2005 and Pinheiro et al 2014; specifically, the previously written H_1 indicated a decrease in proteinuria, but has now been edited to reflect the same primary objective of proteinuria reduction in terms of achieving a positive dose response relationship.
6. Based on new available data from clinical and pre-clinical studies, the following sections have been updated: Section 1.2.3 Non-clinical pharmacology and pharmacokinetics Section 1.3.2 Human pharmacokinetic data, Section 3.3 Rationale for dose/regimen, route of administration and duration or treatment and Section 5.2 Prohibited treatment.
7. The temperature and blood pressure measurements were modified according to standard clinical practice at study centers, inclusion criteria 11 in Section 4.1 was modified.
8. Section 7.3 Withdrawal of informed consent was updated according to the new GDPR regulation. Glossary of terms was adapted accordingly.
9. In the perspective to open sites in Japan, the possibility to use the modified MDRD formula according to specific ethnic group (Imai et al 2011) was added for the calculation of estimated GFR. See inclusion criteria 5 in Section 4.1 and Section 8.5.3.

10. Biomarkers in Section 2.3 [redacted] Secondary objectives.
11. The synopsis is updated to reflect the above changes as appropriate.
12. Minor changes were made throughout the protocol for improved clarity, better alignment between different protocol sections and to correct minor inconsistency errors.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent/Assent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2 (March 2018)

Amendment rationale

The purpose of this amendment is to allow including patients with a pulse rate below 50 if the patient is otherwise in a physically good and stable condition without any other significant ECG abnormalities as judged by the investigator.

The purpose of this amendment is to address questions raised by different Health Authorities. The changes are summarized below.

Major changes to the protocol

The following changes have been implemented throughout the protocol:

1. Revised wording of inclusion criterion 11 about pulse rate lower limit in Section 4.1
2. LNP023 is neither teratogenic nor embryo/feto toxic, and since very significant exposure margins exist, it is considered that there is no risk to a developing fetus related to paternal transfer of the drug via seminal fluids. Therefore no male contraception is needed and as consequence the consent to collect pregnancy outcome information of a female partner who becomes pregnant becomes obsolete.
   In Section 5.1 "contraception requirements" and Section 9.6 "Pregnancy reporting" the statement about collection of information of pregnancy outcome of the female partner of a male participant has been deleted.
3. In Section 6.3 further clarification is added regarding the Ancestry (Asian/non-Asian) being used as a stratification factor in the randomization and which is included in the IRT specifications.
4. In Section 7.5 the study stopping rules have been adapted based on feedback by Health Authorities.
5. Endocrine parameters such as testosterone, FSH, LH, DTH, T3, T4 and TSH are checked regularly. Checks on Day 15 and 30 were added to allow for a potential early detection of possible effects. Assessment schedule in Section 8.1 has been updated accordingly.
6. Additional pregnancy test on participating patients of childbearing potential will be performed on Day 90 and during the EOS visit as requested by a Health Authority. Assessment schedule in Section 8.1 has been updated accordingly.
7. Exceeding twice the upper normal limit for the serum bilirubin should lead to the exclusion from exclusion. Exclusion criterion 6 in Section 4.2 has been adapted accordingly.
8. In Section 6.4 it has been clarified that site staff will be blinded to study treatment throughout the study and is not able to see the treatment arm assignment.
9. The baseline visit has been extended to -7 to -4 days in order to get the proteinuria results from central lab in time to check for eligibility. The Assessment Schedule in Table 8-1 has been updated accordingly.
10. The synopsis is updated to reflect the above changes as appropriate.

11. Minor changes including Section 8.6.7 and Section 10.3 were made throughout the protocol for improved clarity, better alignment between different protocol sections and to correct minor consistency errors

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent/Assent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (December 2017)

Amendment rationale for non-substantial changes

The purpose of this non-substantial amendment is to address questions raised by the British Health Authority (MHRA).

The protocol synopsis recommended that women use contraception until the end of the study, while Section 4.2 stated that women of child bearing potential are only advised to continue using contraception for one week after the last dose. This inconsistency was corrected, taking into account the advice in the synopsis being considered acceptable to the MHRA.

Criteria for choosing between the two scenarios for Part 2, which are described in the DMC charter were added to the protocol as requested.

Major changes to the protocol

The following changes have been implemented throughout the protocol:

1. Section 3.1 study design was slightly adapted to refer to Section 3.5 for more details on the criteria considered for choosing between the two scenarios.
2. Clarification on criteria for choosing between the two scenarios for Part 2 in Section 3.5.
3. Revised wording of Section 4.2 to clarify inconsistency with regards to the advice given to women of child bearing potential was corrected in line with the advice described in the synopsis
4. Minor changes were made throughout the protocol for improved clarity, better alignment between different protocol sections and to correct minor consistency errors

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

Protocol summary

Protocol number	CLNP023X2203
Full Title	An adaptive seamless randomized, double-blind, placebo-controlled, dose ranging study to investigate the efficacy and safety of LNP023 in primary IgA nephropathy patients
Brief title	Study of safety and efficacy of LNP023 in patients with IgA nephropathy
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	The aim of the study is to assess whether LNP023, an oral small molecule that inhibits the complement alternative pathway known to be activated in the kidney of most patients with IgA nephropathy (IgAN), reduces the renal inflammation, proteinuria, and improves renal function in patients with confirmed IgA nephropathy and to evaluate dose responses to support dose selection for subsequent clinical development of LNP023 for IgAN and potentially other indications.
Primary Objective(s)	To evaluate the dose response relationship of LNP023 on the reduction in proteinuria versus placebo after 90 days of treatment in patients with IgA nephropathy.
Secondary Objectives	• To evaluate the safety and tolerability of LNP023 • To assess the effect of LNP023 on renal function • To assess the pharmacokinetics of LNP023 • To assess the effect of LNP023 on alternative complement pathway • To estimate the lowest dose that provides maximal reduction of proteinuria
Study design	This is an adaptive seamless randomized, double-blind, placebo-controlled, dose ranging study evaluating the efficacy and safety LNP023 following 90-180 days of treatment. In Part 1, 4 groups of IgAN patients will be randomized to three doses (10 mg, 50 mg and 200 mg b.i.d) of LNP023 or Placebo. At the end of Part 1, a pre-specified interim analysis will be performed to evaluate the initial response to therapy and to make design choices for Part 2 using predefined rules. The trial may either be stopped for futility, or continued with some design adaptations (increase of the sample size and addition of a dose arm of either 25 mg or 100 mg b.i.d) for the treatment phase of Part 2. Hence, patients in Part 2 will be randomized to placebo, 10 mg, 50 mg, 200 mg b.i.d and a 4th active dose of either 25 mg b.i.d or 100 mg b.i.d. 100 mg dose was chosen by the DMC after the interim analysis Part 1. The treatment phase will be extended to 180 days in Part 2 compared to Part 1, during which additional efficacy and safety data will be collected. Data from Part 1 and Part 2 of the study up to approximately Day 90 will be pooled and used for the interim analysis Part 2 (IA2).

Population	A total of up to approximately 48 (Part 1) male and female patients with a biopsy-verified IgA nephropathy will be enrolled. The number of patients in Part 2 will be determined from the results of Part 1 (N = 48-100 patients randomized). As a result of available data from interim analysis Part 1 (IA1) of the trial, part 2 of the study will recruit approximately 50 randomized patients. Patients must have been on stable therapy with an Angiotensin-converting-enzyme inhibitor (ACEi) or Angiotensin II Receptor Blockers (ARB) at the maximally tolerated dose to achieve adequate blood pressure control for at least 90 preceding days before randomization. The urine protein to creatinine ratio (UPCR) should be ≥0.8 g/g (≥90 mg/mmol) sampled from first morning void (FMV) or urine protein ≥0.75 g/24hr from a 24h urine collection at screening and urine protein ≥0.75 g/24hr from a 24h urine collection at the completion of the Run-in Phase.
Key Inclusion criteria	• Female and male patients ≥18 years of age with a biopsy-verified IgA nephropathy and where the biopsy was performed within the previous three years. If the most recent renal biopsy was performed more than three years ago, a new biopsy should be performed. • Patients must weigh at least 35 kg to participate in the study, and must have a body mass index (BMI) within the range of 15 - 38 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2 • Measured Glomerular Filtration Rate (GFR) or estimated GFR calculated using the CKD-EPI formula (or modified MDRD formula according to specific ethnic groups and local practice guidelines) ≥30 mL/min per 1.73 m^2 • UPCR ≥0.8 g/g (≥90 mg/mmol) sampled from first morning void (FMV) or urine protein ≥0.75 g/24hr from a 24h urine collection at screening and urine protein ≥0.75 g / 24h from a 24h urine collection at the completion of the run- in period • Vaccination against *Neisseria meningitidis* types A, C, Y and W-135 is required at least 4 weeks prior to first dosing with LNP023. Vaccination against *N. meningitidis* type B, *S. pneumoniae* and *H. influenzae* should be conducted if available and acceptable by local regulations, at least 4 weeks prior to first dosing with LNP023 • All patients must have been on supportive care including a maximally tolerated dose of ACEi or ARB therapy for the individual, antihypertensive therapy or diuretics for at least 90 days before dosing
Key Exclusion criteria	• Presence of crescent formation in ≥50% of glomeruli assessed on renal biopsy • Patients previously treated with immunosuppressive agents such as cyclophosphamide, mycophenolate mofetil (MMF) or mycophenolate sodium, cyclosporine, tacrolimus, sirolimus, or systemic corticosteroids within 90 days prior to start of LNP023/Placebo dosing • All transplanted patients (any organ, including bone marrow) • History of immunodeficiency diseases, or a positive Human Immunodeficiency Virus (HIV; ELISA and Western blot) test result. • Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a patient. Patients with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded • Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may

	jeopardize the subject in case of participation in the study. The Investigator should make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following: • A history of invasive infections caused by encapsulated organisms e.g. meningococcus or pneumococcus • Splenectomy • Inflammatory bowel disease, peptic ulcers, severe gastrointestinal disorder including rectal bleeding; • Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection; • Pancreatic injury or pancreatitis; • Liver disease or liver injury as indicated by abnormal liver function tests. ALT (SGPT), AST (SGOT), GGT, alkaline phosphatase and serum bilirubin will be tested. • Any ***single parameter*** of ALT, AST, GGT, alkaline phosphatase or serum bilirubin must not exceed 2 x upper limit of normal (ULN) • Prothrombin Time / International normalized ratio (PT/INR) must be within the reference range of normal individuals Evidence of urinary obstruction or difficulty in voiding any urinary tract disorder other than IgAN that is associated with hematuria at screening; [If necessary, laboratory testing may be repeated on one occasion (as soon as possible) prior to randomization, to rule out any laboratory error] • Pregnant or nursing (lactating) 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. • A history of clinically significant electrocardiogram (ECG) abnormalities, or any of the following ECG abnormalities at Screening or Baseline: • PR > 200 msec • QRS complex > 120 msec • QTcF > 450 msec (males) • QTcF > 460 msec (females) • History of familial long QT syndrome or known family history of Torsades de Pointes • Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study • History of severe allergic reactions as per Investigator decision • Female patients who are pregnant or breastfeeding, or intending to conceive during the course of the study • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception from first dosing until an additional one week following cessation of study drug. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases • History of any porphyria metabolic disorder

Study treatment	LNP023 is available at dose strength of 5 mg, 25 mg, 100 mg and matching placebo capsules. Patients will be randomized to either 0 mg (matching Placebo), 10 mg, 50 mg, or 200 mg b.i.d. in Part 1. Either the dose of 25 mg or 100 mg b.i.d will be added in Part 2 based on the interim analysis results in Part 1. 100 mg was chosen by DMC after interim analysis part 1.
Pharmacokinetic assessments	PK parameters of LNP023 in plasma and urine, including but not limited to Cmax,ss, Tmax,ss, AUCtau,ss and Cmin,ss for every dose group.
Efficacy/PD assessments	• UACR and UPCR, 24h urine excretion of albumin and protein • eGFR • complement alternative pathway biomarkers [redacted]
Key safety assessments	• Physical examination • Body Temperature • Blood pressure and pulse rate • Hematology • Blood chemistry • Urinalysis • Pregnancy test • ECG evaluation • Blood hormones (T3, T4, Thyroid stimulating hormone (TSH), reversed T3, Luteinizing hormone (LH), Follicule-Stimulating hormone (FSH), testosterone and Dihydrotestosterone (DHT) • Adverse Events / Serious Adverse Events (AEs/SAEs)
Other assessments	[redacted] • Soluble biomarker, circulating fragment of factor B (Bb) and sC5b-9 [redacted]
Data analysis	The primary variable is the change from baseline of log transformed UPCR derived from the 24h urine collections at baseline and day 90. An interim analysis will be performed when approximately 48 patients have been randomized in Part 1 and have completed treatment to Day 90 (or withdrawn from the trial). The intention of this analysis is to provide preliminary evidence of dose-response relationship for proteinuria, to determine the sample size for Part 2, and to determine the additional treatment arm of either 25 mg or 100 mg b.i.d to be studied in Part 2. Three decision steps will follow from this interim analysis. Step 1. Assess futility: If the maximum observed effect is not greater than a 20% reduction in UPCR, or the one-sided p-value for the multiple contrast test is ≥ 0.1 then do not continue to Part 2. Step 2. Sample size re-estimation for Part 2: The total sample size will be calculated which provides sufficient information for primary analysis. Step 3. Select doses to be studied in Part 2. At the time of second interim analysis (IA2) all data from Part 1 and Part 2 of the study up to Day 90 will be pooled and analyzed for primary analysis. A final data analysis will be performed once the last patient in Part 2 has completed treatment (Day 180).

	The primary endpoint will be analyzed using MCP-Mod procedure (Bretz et al 2005). A two stage approach will be taken for this analysis: first, change from baseline in log transformed UPCR at multiple timepoints will be analyzed using a Mixed Model of Repeated Measures (MMRM) model. UPCR is derived from the 24h urine collections at baseline, day 30 and day 90. The results will be back transformed and presented on the original scale. The model will include treatment, time point (as study day relative to start of study treatment) study part (Part 1 or Part 2) and ancestry (Asian/non-Asian) as fixed effects and baseline log UPCR as fixed covariate. Treatment-by-time point and time point-by baseline log UPCR will be included as interaction terms. Time point will be included as a repeated factor with an unstructured covariance matrix to allow adjustment for correlations between time points within patients. Secondly, the following global hypothesis will be tested for the day 90 time point using the generalized MCP-Mod approach at the one-sided 10% significance level to assess whether LNP023 is different from placebo: H0: $c^T_m \mu = 0$ for all m in {1, ⋯6} H1: $c^T_m \mu > 0$ for at least one m in {1, ⋯6} Where μ is the vector of adjusted means for each treatment group from the analysis of the primary endpoint at day 90 i.e. $\mu = (\mu_{Placebo}, \mu_{LNP023\ dose\ 1}, \ldots, \mu_{LNP023\ dose\ n})T$ and c^T_m m is the vector of optimal contrasts coefficients for the m^{th} candidate dose response shape m, as described below. • Model 1: Linear • Model 2: Emax with ED50 at 5mg • Model 3: Emax with ED50 at 50mg • Model 4: Sigmoidal emax with ED50 at 25mg and Hill parameter=3 • Model 5: Sigmoidal emax with ED50 at 50mg and Hill parameter=3 • Model 6: Exponential with delta =50 The dose response curve and the ED90 will be estimated with 80% confidence intervals.
Key words	IgAN patients, chronic kidney disease, glomerulonephritis, complement alternative pathway, proteinuria, renal biopsy, UACR and UPCR

1 Introduction

1.1 Background

Approximately 10% of the population worldwide is affected by chronic kidney disease (CKD) and millions die each year due to the lack of available or effective treatment of end stage renal disease (ESRD) (NKF 2017).

IgA nephropathy (IgAN) is a form of glomerulonephritis characterized by deposition of IgA in the glomerulus. IgAN is the most common type of glomerulonephritis, but the exact incidence and prevalence numbers are elusive due to differences in biopsy practice, diagnostic criteria and lack of adequate registries. IgAN is considered as an orphan disease by Health Authorities (HA) in Europe and the US.

Renal biopsy is required for diagnosis of IgAN. 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). Co-localized with IgA are C3 fragments (iC3b, C3c and C3dg) and Factor P (properdin) that are components indicative of complement Alternative Pathway (AP) activation that are present in >90% of patients (Figure 1-1). While activation of the classical pathway (CP) is highly unusual, the lectin pathway (LP) is also activated in 17-23% of IgAN patients (Floege et al 2014, Maillard et al 2015).

IgAN is commonly diagnosed between the ages of 16 and 35 years usually due to the discovery often associated with respiratory infections. Most IgAN patients have a benign course. However, ~25% of IgAN patients will reach ESRD within 10-15 years.

Treatment of idiopathic (primary) IgAN has not changed significantly during the last three decades and effective, approved therapy is still lacking. Guidelines recommend therapy mainly based on angiotensin converting enzyme inhibitor (ACEis) or angiotensin receptor blocker (ARBs) with or without high dose steroids and cytotoxic agents, for blood pressure control and proteinuria reduction, and are based on weak evidence (KDIGO 2012). However, there are conflicting and inconsistent results on the beneficial use of immunosuppressive agents (including steroids), showing moderate evidence of efficacy but considerable side-effects (Fellström et al 2017, Floege and Rauen 2016, Lafayette et al 2017). The TESTING trial showed renal survival benefit of methyl-prednisolone, but at the cost of serious adverse events, including fatalities in young patients, which triggered early termination of the trial for safety reasons (Lv et al 2017).

Approximately 25% of patients develop proteinuria and hypertension, and are at risk of CKD and fast progression to ESRD. In many of these patients, ESRD develops within 10 years (Liu et al 2015). As shown in many IgAN patient studies, urine protein or albumin levels are predictive of long-term outcome, as are reductions in proteinuria (Inker et al 2016, Thompson et al 2019). In addition, complement factors in urine are important biomarkers of disease activity (Maillard et al 2015). For example, high urinary levels of factor H (which is involved in decay of convertase and C3b inactivation) are associated with poor outcome (Liu et al 2015).

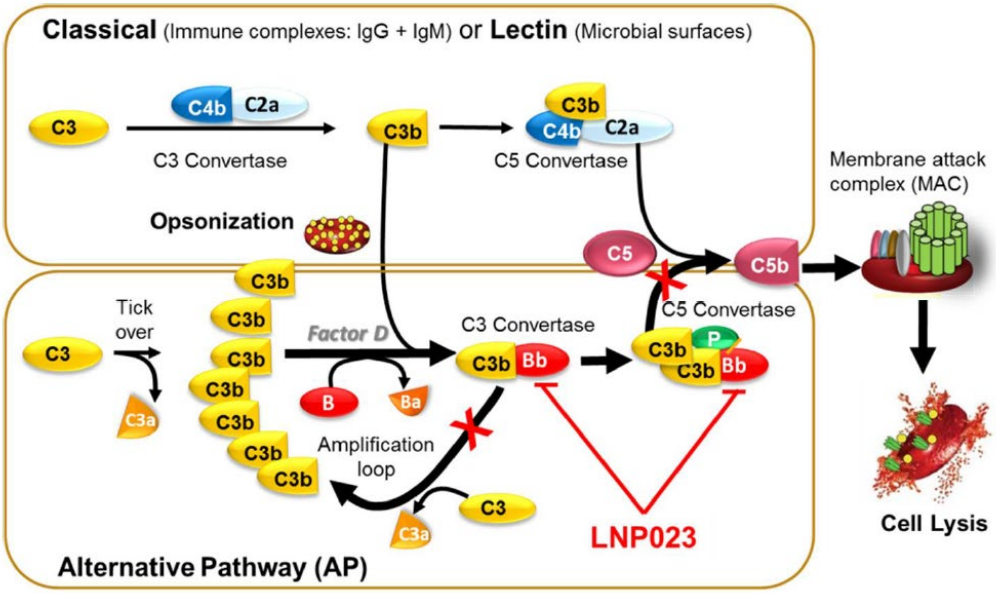
For approximately 25% of patients with IgAN, progression to ESRD is relatively rapid. To give perspective, the rate of progression of these at-risk IgAN patients is more rapid than patients with membranous nephropathy with similar levels of urinary protein or autosomal dominant polycystic kidney disease (Chapman 2012, Roscioni et al 2014).

The seriousness of this disease, the lack of adequate treatment and the recent recognition of the importance of the AP complement system (Koscielska-Kasprzak et al 2014) suggest that there is both a need and an opportunity for new therapies for IgAN.

Inherited and acquired dysregulation of the complement alternative pathway (AP) plays an important role in many renal diseases, almost all of which show signs of complement AP hyperactivation in renal biopsies (Cook 2013, Mathern and Heeger 2015). In a small open label study, reductions in proteinuria were reported in four patients after lectin pathway inhibition (Omeros 2017).

LNP023 is a first-in-class, oral, low molecular weight (LMW) inhibitor of Factor B (FB); a key protease of the complement alternative pathway (AP). Inhibition of FB prevents amplification of all pathways as well as AP-induced assembly of C3- and C5-convertases (Figure 1-1). A translational assay demonstrated that LNP023 blocks both hemolysis and C3 deposition in PNH-like erythrocytes. At the same time, LNP023 has only limited effect on classical-pathway induced activation of the terminal pathway.

Figure 1-1 Overview of the complement system with the site of action of LNP023



The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure.

1.2 Nonclinical data

LNP023 is an oral potent and selective small molecule factor B (FB) Inhibitor with the following characteristics:

- It inhibits alternative pathway mediated Membrane Attack Complex (MAC) formation in 50% serum and whole blood in many species
- It fully inhibits C3 deposition on, and hemolysis of, PNH-like human erythrocytes
- A dose-dependent sustained inhibition of AP activation and activation-dependent products (Ba, C3d) was observed *in vivo* (mouse LPS model)
- The PK properties allow for complete and sustained inhibition of FB over the dosing period
- Overall LN023 has a low potential for drug-drug Interactions (DDI) with minimal inhibition or induction of CYP450 or efflux/uptake transporters at anticipated exposures in human. In addition, LNP023 is cleared by multiple disposition pathways suggesting that drug interactions (as victim) are unlikely to increase LNP023 plasma exposure to a clinical relevant extent.

1.2.1 Teratogenicity and reproductive toxicity data

LNP023 has no known genotoxic potential. An embryo-fetal development study in rats with a combined dose range finding (DRF) / preliminary-fetal development study in rabbits were performed to enable enrollment of women of child bearing potential (WOCBP) in Phase II studies providing they use effective contraception methods, during study drug treatment and an additional one week following cessation of study drug.

LNP023 was well tolerated in the rat embryo-fetal toxicity study with no significant maternal toxicity observed. No effect on pregnancy or fetal growth was noted at any dose. A finding not considered adverse was a slight dose-dependent delay observed in the ossification of the parietal and interparietal bones of the skull, which is expected to resolve with further development of the fetus or after littering. In a single litter of animals administered 1000 mg/kg/day, a soft, skin covered cyst was recorded in the parietal region of the head for two fetuses. This finding could have been indicative of litter-related effect; however, an association with treatment could not be fully excluded. No observed adverse effect levels (NOAEL) for fetal toxicity was established at 300mg/kg/day, with total AUC-based exposure margins of 3, as compared to the highest anticipated clinical dose of 200 mg b.i.d. LNP023 was not mutagenic or clastogenic in *in vitro* and *in vivo* genotoxicity studies.

In summary, LNP023 is not considered teratogenic or embryo lethal. No LNP023-related adverse fetal findings were detected in any of the studies. NOAEL for fetal toxicity was established at the highest dose in both studies, with total AUC-based exposure multiples of 7.5 and 19, respectively for the rat and rabbit study, as compared to the highest anticipated clinical dose of 200 mg b.i.d.

1.2.2 Non-clinical safety program

The safety pharmacology and toxicology program conducted for LNP023 is consistent with all relevant ICH Guidelines on non-clinical safety (as outlined in ICH M3). LNP023 was tested in single administration and repeat-dose studies in rats and dogs of up to 13-week duration with an 8 week recovery period, and also in rats (26 weeks) and dogs (39 weeks) with a 27 weeks recovery period (still ongoing as of March 2019) to assess the long-term safety of LNP023 at a range of doses. In addition to the general toxicology program, genotoxicity studies, safety pharmacology studies, studies on phototoxicity and embryo-fetal development studies have been performed.

Based on current knowledge, four potential risks have been identified for LNP023, including 'Infections', 'Testicular effects', ‘Bone marrow toxicity and severe anemia’ and ‘Follicular cell hypertrophy’. The risk for infections is based on the mode of action for LNP023 as a FB inhibitor and in theory the risk is lower with selective inhibition of AP than with compounds blocking all complement pathways. Testicular effects have been observed in the toxicology studies conducted in rats and dogs, and determined the NOAEL in both species. However the effects were minimal and fully reversible, with no effect on sperm in the chronic (39-week) dog study and no effect on male fertility in the rat fertility study. The risk for male reproductive adverse effects in patients in the phase II trials is considered minimal, for details see Section 3.6.2.2. Bone marrow toxicity and severe anaemia were observed in a single male dog in the highest dose group (150 mg/kg/day) in the 39-week dog study. Moderate hyporegenerative anemia was noted at the end of the 9-month (39-week) treatment period, which further progressed to severe non-regenerative anemia despite discontinuation of treatment. The main finding in histopathology was marked bone marrow fibrosis, while bone marrow cytology indicated dyserythropoiesis. No other cases have been observed in pre-clinical or clinical studies. No bone marrow effects were previously observed pre-clinically or clinically, or are expected based on the LNP023 mode of action (complement FB inhibition). However, a LNP023-related effect cannot be excluded at this stage. As a safety margin of 14 times higher than the highest clinical dose of 200 mg b.i.d., the risk for patients is considered low. Pathogenesis of this isolated finding is not fully understood and will be explored further. Hematological parameters including reticulocyte count will be monitored in all patients treated with LNP023. In addition, thyroid follicular cell hypertrophy was observed consistently in the preclinical studies in rats and dogs, correlating with increased thyroid weight and changes in thyroid hormone levels. The effects were fully reversible after the recovery period, and not considered adverse in the absence of clinical signs of hypo- or hyperthyroidism.

Other non-clinical safety findings of undetermined relevance are cardiovascular effects, hyperbilirubinemia and proteinuria. Thus far, these findings have not been seen in the clinical setting.

In vitro phototoxicity studies have indicated a weak potential risk for photosensitization. Considering the weak *in vitro* phototoxicity response, the absence of a dose-dependence and the low incidence and transient nature of erythema formation, *in vivo* photo-activation of the compound is considered to be unlikely and therefore human risk is low.

1.2.3 Non-clinical pharmacology and pharmacokinetics

LNP023 is a potent and selective FB Inhibitor. It inhibits alternative pathway mediated Membrane Attack Complex (MAC) formation or C3 deposition in 50% serum and whole blood in many species. A dose dependent and sustained inhibition of AP activation and activation-dependent products (Ba, C3d) was observed *in vivo* (mouse LPS model).

LNP023 has a high solubility and moderate permeability. In animal pharmacokinetic (PK) studies, the PK profile of LNP023 was characterized by good absorption and a low to medium clearance across all species investigated with a systemic half-life of about 6-7 h and a Tmax observed between 0.5 and 2 h. In animals, LNP023 showed an approximate dose-linear exposure with little accumulation on multiple dosing and no or minor gender differences. In the rat, the predominant clearance mechanism was hepatic metabolism with only a small contribution from direct renal and biliary excretion. LNP023 was mainly excreted via feces with >90% of the dose recovered within 24 h. LNP023 has shown a marked concentration dependence across all species with respect to plasma protein binding ranging from 60% to >99%. Mechanistic studies suggested that this is due to saturable binding to the target (i.e. FB) which is highly abundant (300 mg/L) in the systemic circulation.

1.3 Clinical data

1.3.1 Human safety and tolerability data

The first in human Phase I trial (CLNP023X2101) was designed to assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of LNP023 after single and multiple oral dose administration to healthy volunteers (HV).The results are briefly summarized hereunder.

The study consisted of three parts:

- Part 1: single-ascending dose (SAD) escalation evaluating seven single doses of LNP023 at 5, 10, 25, 50, 100, 200 and 400 mg
- Part 2: multiple-ascending dose (MAD) escalation evaluating 14-day administration of LNP023 at four dose levels 25 mg, 50 mg, 100 mg and 200 mg (b.i.d. each)
- Part 3: single dose of LNP023 at 100 mg administered under fed and fasted conditions for the food-effect (FE)

Based on available data from LNP023X2101 single doses of LNP023 up to 400 mg and multiple doses up to 200 mg b.i.d. in HV appeared safe and were well tolerated.

1.3.2 Human pharmacokinetic data

The disposition of LNP023 in human is predicted to depend predominantly on the metabolism by CYP2C8, glucuronidation (UGT1A1), and direct biliary excretion via the efflux transporter P-gp as well as direct renal excretion. As the fractional contribution of all known individual disposition pathways does not exceed 50%, the likelihood that co-medications may have a major impact on the systemic exposure of LNP023, is currently considered low. At relevant concentrations of LNP023 no induction of the human CYP1A (AhR) or CYP3A4 (PXR) were detected in respective reporter gene assays For PXR a mild induction effect in human hepatocytes has been detected at concentrations well above Cmax at 200 mg b.i.d. suggesting low risk for interactions with oral contraceptives (OC). *In vitro*, LNP023 has been found not to inhibit any CYP enzymes as well as efflux transporters with the exception of possible inhibition of intestinal P-gp at the highest dose (200 mg b.i.d.). Organic anion-transporting polypeptide (OATP) uptake transporters may be inhibited at concentrations currently expected to be more than 10-fold above the predicted human Cmax. Concomitant use of LNP023 with respective inhibitors or inducers may cause only a small net effect on LNP023 exposure. The PK profile observed after single dose as well as after multiple (b.i.d.) administration of LNP023 was characterized by a fast absorption and a non-linear and under-proportional dose exposure relationship which is in contrast to what has been seen in animals. This may be due to on-target plasma protein binding to the highly expressed (300 mg/L) FB impacting liver uptake and thus clearance. After single and multiple dose, a dose dependent increase in the CL was observed which again may be related to an increased unbound fraction when the target (i.e FB) becomes saturated. The terminal half-life of LNP023 was around 20 hrs. In line with its favorable biopharmaceutical properties (i.e high solubility across the whole pH range) no food effect on Cmax or AUC was observed after a single dose of 100 mg of LNP023.

1.3.3 Human pharmacodynamic data

The administration of LNP023 in healthy volunteers led to rapid suppression of the complement AP activity (measured by the Wieslab AP assay) across all single ascending dose cohorts (5, 10, 25, 50, 100, 200 and 400 mg) in the phase I study (CLNP023X2101). Compared to baseline, approximately 80% or greater inhibition of the AP activity was achieved at two hours post-dose for subjects receiving LNP023 at 25 mg or higher doses. Duration of sustained inhibition was dose-dependent. The AP activity largely returned to baseline level by 48 hours post-dose.

The PD effect was also evaluated by quantifying activation-dependent fragment Bb. After a single dose administration of LNP023, the level of Bb continued to decrease until 12 hours post-dose. Approximately 30% to 50% decrease of Bb, relative to baseline, was achieved for subjects receiving LNP023 at 25 mg or higher doses. The response was sustained beyond 48 hours post-dose for high-dose cohorts (100 mg, 200 mg and 400 mg).

In the multiple ascending part (25, 50, 100 and 200 mg b.i.d.), dose-dependent suppression of AP activity was also achieved when measured by the Wieslab AP assay, with approximately 80% or greater inhibition sustained over 14 days of dosing at 100 mg and 200 mg b.i.d. However, the sustained effect on Bb level was approximately 30 to 40% decrease (compared to baseline) for all MAD cohorts with no clear dose-dependency.

1.4 Study purpose

The purpose of this Phase IIa/IIb dose ranging study is to generate human data in the intended patient population with IgAN to establish clinical proof-of-concept and to evaluate dose responses to support dose selection for subsequent clinical development of LNP023 for IgAN and potentially other indications.

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	Endpoints related to primary objective(s)
To evaluate the dose response relationship of LNP023 on the reduction in proteinuria versus placebo after 90 days of treatment	The primary variable for the statistical analysis is the ratio to baseline of urine protein to creatinine concentration ratio (UPCR based on 24h urine collection) at 90 days

2.2 Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)
To evaluate the safety and tolerability of LNP023	Assessment of safety based on vital signs, physical examination, ECGs, laboratory assessments, and collection of AEs assessed from baseline until the end of the study visit.
To assess the effect of LNP023 on renal function up to 90 days of treatment (combining Part 1 and Part2 of the study)	Estimated glomerular filtration rate (eGFR; estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation) Serum creatinine Hematuria (number of erythrocytes/high-power-field (hpf) measured through microscopic examination) 24h-UP, 24h-UA, UACR (urine albumin to creatinine concentration ratio) UPCR (urine protein to creatinine concentration ratio) from first morning void.
To assess the pharmacokinetics of LNP023	Plasma: Non-compartmental parameters related to total parent drug, including but not limited to Tmax, Cmax, AUClast and AUCtau will be calculated for each dose level. Urine: Non-compartmental parameters, including but not limited to total cumulative urinary excretion (Ae) and renal plasma clearance (CLr)
To assess the effect of LNP023 on alternative complement pathway	Plasma levels of alternative pathway biomarkers including Bb and sC5b-9
To estimate the lowest dose that provides maximal reduction of proteinuria	Ratio to baseline of UPCR

Secondary objective(s)	Endpoints related to secondary objective(s)
To assess the effect of LNP023 on renal function up to Day 180 (Part 2 of the study)	Estimated glomerular filtration rate (eGFR; estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation) UPCR from 24 hour sample and first morning void Hematuria (number of erythrocytes/high-power-field (hpf) measured through microscopic examination) UACR (urine albumin to creatinine concentration ratio).

3 Investigational plan

3.1 Study design

This is a multicentre, randomized, double blinded (investigator, subject and sponsor blinded), placebo-controlled, dose-ranging, parallel-group adaptive design.

The study comprises a run-in phase of at least 30 days, a 90 days treatment phase in Part 1; a 180 days treatment phase in Part 2 and a 90 days follow-up phase in both Parts 1 and 2.

At screening, patients must have UPCR ≥0.8 g/g (≥90 mg/mmol) sampled from first morning void (FMV) or urine protein ≥0.75 g/24hr from a 24h urine collection. Patients will remain on their supportive therapy, i.e. ACEi or ARB with or without diuretics, statins or antihypertensive therapy for the duration of the trial. Patients who complete the Run-in Phase with a 24-hr urine protein excretion of ≥0.75 g/24hr will be eligible for randomization and entry into the Treatment Phase of the trial. To be dosed, patients must have been on stable therapy with an ACEi or ARB for at least 90 days at the maximally tolerated dose (KDIGO 2012, see Section 4.2 Exclusion criteria below). If dose adjustments of ACEi/ARB, or diuretics are required, the Run-in Phase needs to be extended to ensure stable ACEi/ARB and diuretic medication. Run-in phase can be extended to minimize patient risk of visit sites during the COVID-19 pandemic._During the Treatment Phase, no change in these medications is allowed except for safety reasons.

Patients enrolled into Part 1 of the study will initially be randomized to one of four treatment arms and treated for 90 days with placebo, or active therapy with LNP023 at doses of: 10 mg, 50 mg or 200 mg twice daily (b.i.d.).

At the end of the 90 day treatment phase of Part 1, a pre-specified interim analysis will be performed to evaluate the initial response to therapy and validate the plan for the overall number of patients and dose cohorts. Predefined rules will be used to adapt the protocol. The trial may either be stopped for futility, or continued with some design adaptations for the treatment phase in Part 2. Allowable pre-specified adaptations include calculation of the sample size for Part 2 (ranging from 48 - 100 patients) and addition of a dose arm (either 25 mg or 100 mg b.i.d) according to pre-defined criteria, as described in the interim analysis section (Section 3.5). As a result of available data from interim analysis Part 1 (IA1) of the trial, part 2 of the study will recruit approximately 50 randomized patients. Based on IA1 results, an additional 100 mg dose was chosen by the DMC to be added into Part 2. No further adaptations of the study are planned. Treatment arms in Part 2 will include placebo and four doses of LNP023 given twice daily.

For both parts, each patient will participate in a run-in period, during which a full physical examination, medical history, concomitant medication vital signs, ECG evaluation, vaccination, BP control assessment, repeated 24h-UP, eGFR assessment, safety laboratory tests [redacted] will be performed.

If not previously vaccinated, all patients will receive vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Hemophilus influenzae* within the screening window according to local regulation and practice. All required vaccinations should be done at least 30 days prior to start of treatment. If there is doubt about the success of vaccination, antibody titers can be measured according to local practice. The run-in period may be extended to allow vaccination procedures to be completed before first dose.

Patients who meet the eligibility criteria at screening and following the run-in period will be admitted to the study site on Day -7 /-4 for baseline evaluations (please refer to Assessment schedule, Table 8-1 and Table 8-2).

All baseline safety evaluation results must be available prior to dosing.

Drug administration and treatment period will start on Day 1.

Safety assessments during the treatment period include for each visit

- Blood pressure
- Infection surveillance
- Hematology and serum chemistry
- Urine chemistry and urinary microscopy
- Physical examination
- T3, T4, TSH, reversed T3, FSH, LH, testosterone and DHT
- Vital signs
- 12-lead ECG (PR interval, QRS duration, heart rate, RR, QT, QTcF)
- AEs

Efficacy (proteinuria; renal function), PK, [redacted] will also be conducted through the study.

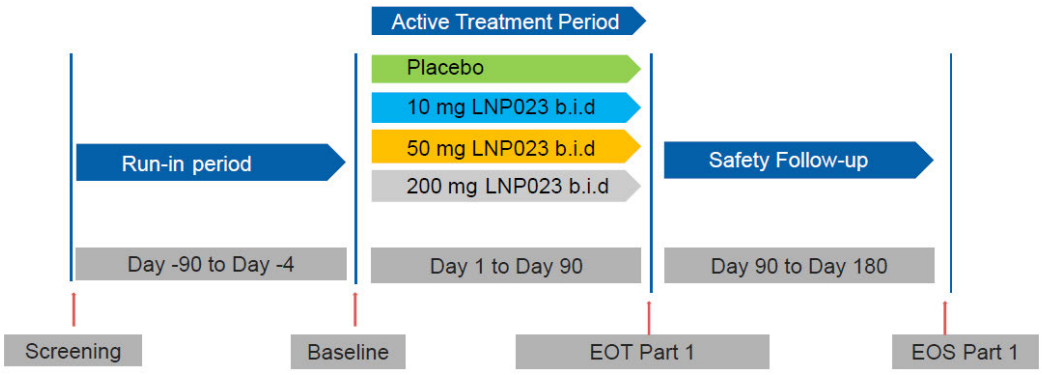
Patients should return to the site on a regular basis for follow up assessments and approximately 90 days after last dosing for study completion evaluations (EOS).

Design of Part 1:

Approximately forty-eight patients will be enrolled in Part 1 to allow for 40 patients to complete this part of the study. These patients will be randomized to treatment groups as follows: 14 to placebo, 10 to LNP023 10 mg, 10 to LNP023 50 mg and 14 to LNP023 200 mg, all b.i.d.

Study duration for patients enrolled in Part 1 will be of approx. 270 days.

Figure 3-1 Part 1



Design of Part 2:

An interim analysis will be performed when approximately 48 patients have been randomized in Part 1 and have completed treatment to Day 90 (or withdrawn from the trial), as described in the interim analysis section (Section 3.5).

The design and doses tested for Part 2 will be determined according to pre-specified rules that will be defined in full in the Data Monitoring Committee (DMC) charter. First, a sample size re-estimation will be performed to determine the number of patients to be randomized in Part 2 and secondly, a decision will be made on which dose (either 25 mg or 100 mg b.i.d) is to be added in Part 2. The sample size for Part 2 will be chosen to be in the range of 48 to 100 patients (i.e. to aim for 40 – 85 patients completing the 90 day treatment period in Part 2 of the study). Patients who are enrolled in Part 2, either in screening or run-in phase will not receive blinded study treatment until the interim analysis on Part 1 is completed and DMC recommends to proceed to Part 2 of the study. As a result of available data from interim analysis Part 1 (IA1) of the trial, part 2 of the study will recruit approximately 50 randomized patients.

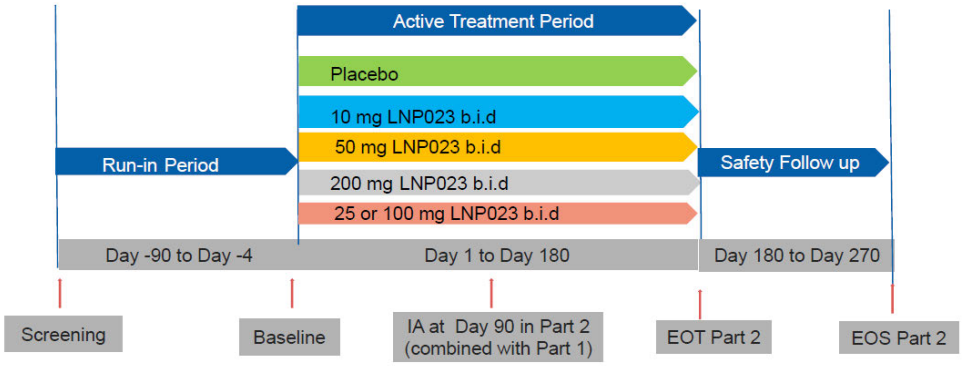
The selection of doses to be used in Part 2 will be guided by the results seen in Part 1. Two scenarios will be considered:

1. placebo, 10 mg, 50 mg, 100 mg and 200 mg b.i.d.
2. placebo, 10 mg, 25 mg, 50 mg and 200 mg b.i.d.

Scenario 1 using an additional 100 mg dose was chosen by the DMC after interim analysis part 1. LNP023 or matching placebo will be administered twice daily for 180 days in a blinded manner Study duration for patients enrolled in Part 2 will be approx. 360 days.

See Section 3.5 for more details. Decisions will be based on safety as well as efficacy information. Patients in Part 2 will be allocated across the five treatment groups. The randomization ratio (or combination of) will be chosen to aim for an approximately equal allocation of patients to the treatment groups across the whole study (Parts 1 and 2 combined).

Figure 3-2 Part 2



3.2 Rationale for study design

The design of the study addresses the primary objective of assessing efficacy in terms of the reduction of proteinuria in patients with IgAN and takes into account the rarity of this disease and the objective nature of the measurement.

In this trial, LNP023 is compared to placebo, both given in addition to supportive care for these patients (including stable doses of ACEi or ARB). Placebo is chosen to enable a proper evaluation of the LNP023 treatment effect, safety and to facilitate the blinding that is a key measure to attempt to avoid bias in this study.

The rationale for including only patients with UPCR ≥0.8 g/g (≥90 mg/mmol) sampled from first morning void (FMV) or urine protein ≥0.75 g/24hr from a 24h urine collection, is that these patients have increased risk of rapid progression towards ESRD. The current supportive care includes blockade of the renin-angiotensin-aldosteron-system (RAAS) using either an ACEi or an ARB at a dose recommended by KDIGO guidelines. RAAS blockade is given to reduce proteinuria and protect renal function.

The purpose of the minimum one-month run-in period is to ensure that the level of proteinuria is stable (based on a stable dose of ACEi/ARB for at least 90 days prior to treatment), that the RAAS blockade is at guideline-recommended levels, and that all subjects have been vaccinated. As a result of the COVID-19 pandemic, run-in period can be extended to minimize patient risk of visit to sites. Three LNP023 dose arms are included in Part 1 of the study to enable an early assessment of the efficacy dose-response relationship and to provide a link between the PK/PD relationship observed in healthy volunteer studies and the PK/PD/efficacy relationship in IgA nephropathy patients.

The study design follows an adaptive approach in which information from Part 1 will be used to adapt the design of Part 2 as described in the Section 3.1 Study design. This provides an opportunity both to stop the trial early for futility should efficacy not be demonstrated, and to ensure that at the end of Part 2 sufficient patients have been allocated to each of the LNP023 dose groups to enable a sufficiently precise estimation of the lowest dose that provides the maximal reduction of proteinuria.

The sample size re-estimation at the end of Part 1 is included because this is the first study of LNP023 in any patient population and the treatment effect is not yet known. Should the treatment effect be smaller than predicted in Part 1, the process of sample size re-estimation allows for an increase in the size of Part 2 to increase the power.

After treatment, patients will be in a safety follow up period of 90 days, which is longer than normally required for a small molecular weight compound. The rationale for choosing 90 days is that it gives an opportunity to follow if changes in proteinuria are sustained or if it returns to baseline levels during the follow up period.

Proteinuria is considered as the key measure of efficacy based on evidence that a reduction in proteinuria is associated with reduced risk of ESRD in patients with IgAN (Thompson et al 2019). A meta-analysis of trials for IgAN assessed the effect of treatment intervention on proteinuria in predicting the effect of that intervention on clinical outcomes. The study demonstrated that a treatment-induced decrease in proteinuria resulted in a comparable reduction in the risk of end-stage renal disease (Inker et al 2016). Of the various methods for assessing proteinuria UPCR sampled on a 24-hour urine collection is selected as the primary endpoint.

Vaccination strategy

In this study, LNP023, a small molecule oral FB inhibitor, is used to block the complement AP that is important for the defense against microbes. Thus, the immunological response to infections is likely to be blunted and treatment with LNP023 is considered to be associated with a risk for infections. To adequately mitigate the risk for infections, patients will be vaccinated. Further details and the vaccination strategy are outlined in Section 3.6.2.1.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

PK profiles in human obtained for LNP023 after b.i.d. dosing from 10 - 200 mg revealed a non-linear dose-exposure relationship with increases in AUCtau of <1.5 in response of an escalation factor of 2. The current assumption is that for full efficacy greater than 80-90% inhibition of alternative complement pathway is required at Ctrough. Based on the readout from biomarkers (Wieslab, AP assay and Bb) indicating target occupancy or inhibition of alternative pathway, the anticipated human efficacious dose ranges between approximately 10 mg b.i.d. and 100 mg b.i.d. for a 60 kg individual. This would advocate evaluating doses that would: (i) clearly indicate target occupancy (25 mg b.i.d.); (ii) provide maximal exposure in terms of AUC and coverage at Ctrough (200 mg b.i.d.).

The currently suggested plan includes a broad dose range of 10 mg (b.i.d), 50 mg (b.i.d) and 200 mg (b.i.d.) as different biomarkers (see above) indicated full efficacy at very different dose levels and the under-proportional dose-exposure relation observed for LNP023 requires administration of fairly different doses to achieve a significant and wide enough exposure range to clearly correlate human exposures with the respective clinical outcome.

Further, the maximal suggested dose of 200 mg b.i.d. is expected to exceed the current NOAEL of the most sensitive species (dogs) in 13-weeks GLP studies with total drug concentration based safety margins of 0.7 (AUC based) and 1.1 (Cmax based). The exposure at 200 mg b.i.d will stay 2.9-fold below the exposure at which minimal testicular effects were observed in the 13-weeks dog study (LOAEL).

Safety margins based on unbound drug lead to a calculated ratio of 2.2 (AUC and Cmax based) for the more sensitive species (dog) for the NOAEL.

In a pre-clinical toxicity study, LNP023 was tested in single administration and repeat-dose studies in rats and dogs of up to 26 and 39-week duration, respectively. Interim reports from the main study phase are provided in January 2019 and the results were included in the IB (version 6, March 2019). Supported by these results, the treatment in Part 2 is extended from 90 days to 180 days in order to assess efficacy and safety for a longer treatment duration. The multiple dose administration of 90 days in Part 1, and 180 days in Part 2 should provide an adequate exploration of the efficacy, safety, PK, and PD in this study which may inform the design of the phase 3 study.

3.4 Rationale for choice of comparator

As there is no approved therapy for IgA nephropathy, and LNP023 is the first in class Factor B inhibitor, patients will be randomized to receive either LNP023 or placebo treatment. Whilst IgAN patients may receive steroid or immunosuppressant treatments, these are not widely accepted as standard of care and are associated with unacceptable adverse events (Lv et al 2017).

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis will be performed when approximately 48 patients have been randomized in Part 1 and have completed treatment to Day 90 (or withdrawn from the trial). The intention of this analysis is to provide preliminary evidence of dose-response relationship for proteinuria, to determine the sample size for Part 2, and to determine the additional treatment arm of either 25 mg or 100 mg b.i.d to be studied in Part 2.

Three decision steps will follow from this interim analysis:

Step 1 Assess futility: Data from Part 1 will be analyzed using the MCP-Mod procedure Bretz et al 2005. If the maximum observed effect (i.e. the maximum of the point estimates from the analysis) is not greater than a 20% reduction in UPCR, or the one-sided p-value for the multiple contrast test is ≥ 0.1 then do not continue to Part 2.

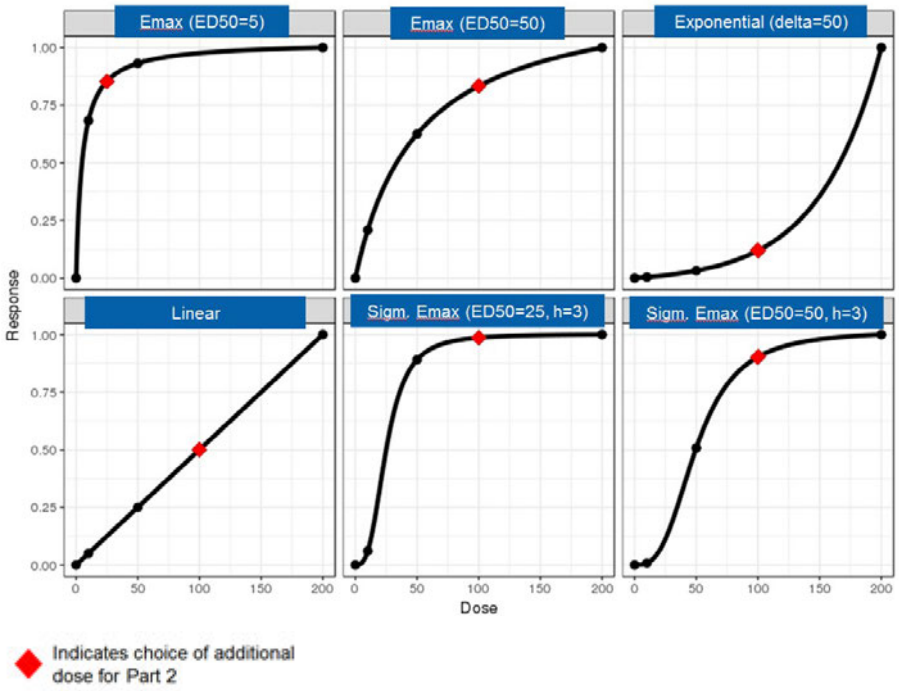
Step 2 Sample size re-estimation for Part 2: The total sample size will be calculated which provides sufficient information for primary analysis (see Section 11.9).

Step 3 Select doses to be studied in Part 2. The Mod step (from MCP-Mod) will determine which of the candidate models (as described in Section 11.4.2) is likely to represent the best fit to the data. Based on this, Figure 3-3 provides the general decision rule for recommendation of dose selection for Part 2 of the trial.

However the DMC will additionally take into consideration all the efficacy and safety data assessed at the IA for their recommendations.

As a result of available data from interim analysis Part 1 (IA1) of the trial, part 2 of the study will recruit approximately 50 randomized patients. Based on IA1 results, an additional 100 mg dose was chosen by the DMC to be added into Part 2.

Figure 3-3 Dose selection guideline based on primary endpoint



A further interim analysis will be performed when patients enrolled in Part 2 have been randomized and completed Day 90 in Part 2 (or withdrawn from the trial) in order to inform future development. However, for patients who are not able to attend the visit until after the day 90 visit cutoff for the part 2 interim analysis, the data will be considered missing for the purposes of the interim analysis. This second interim analysis (IA2) will consider the pooled data from Part 1 and Part 2 of the study (up to Day 90), the safety follow-up data from Part 1 and Part 2 patients who have consented to receive treatment as per protocol version 03 or earlier (up to Day 180), and any additional data of patients who have consented to receive randomized treatment in Part 2 as per study protocol version 04. This second interim analysis will constitute the final analysis for the primary endpoint (which is based on all data from Part 1 and Part 2 up to and including the Day 90 visit). A third interim analysis may be performed once the last patient has completed Day 180 to support future development. Depending on the size of Part 2, an interim safety review may be done in consultation between the DMC and Novartis.

3.6 Risks and benefits

LNP023 has not been previously administered with therapeutic intent to patients with IgAN. Therefore, no statement can be made at this time on the actual clinical benefits of LNP023 in this patient population. However, given the mechanism of action of LNP023 targeting the complement system as discussed in the background (Section 1.1), there is good rationale to believe that a therapeutic response can be achieved with the compound in patients with IgAN.

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, early stopping rules, periodic review of the safety data by an independent DMC, and guidance for the investigators in the IB.

Women of child bearing potential (WOCBP) 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 effective contraception requirements and an additional one week following cessation of study drug as outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

There may be unknown risks of LNP023 which may be serious.

3.6.1 Blood sample volumes

A maximum of 350 mL and 450 mL of blood is planned to be collected over a period of approx. 270 days in Part 1 and 360 days in Part 2 of the study respectively, from each subject as part of the study. Additional samples may be required for safety monitoring.

The timing of blood sample collections is outlined in the Assessment schedule (Section 8.1).

A summary blood log is provided in the Site Operations Manual. Instructions for all sample collection, processing, storage and shipment information are also available in the SOM and central Laboratory Manual.

See Section 8.9 regarding the potential use of residual samples.

3.6.2 Potential risks

The potential risks of LNP023 can only be assessed indirectly by analyzing the pharmacological profile, preclinical safety studies and clinical studies.

A FIH trial (LNP023X2101) has been conducted in healthy volunteers (HV) with 7 SAD cohorts with LNP023 doses of 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg and 400 mg; 4 MAD cohorts with LNP023 given b.i.d. for 2 weeks at doses of 25 mg, 50 mg, 100 mg and 200 mg and where the effect of food intake was studied after single doses of 100 mg. In the trial, LNP023 dose-dependently inhibited the AP complement system. There were no SAE's; few AEs, most of mild intensity, and the incidence of AEs was similar in subjects receiving LNP023 as those given placebo (see IB). No clinically relevant change was observed for systolic or diastolic blood pressure or for supine pulse rate in the LNP023 and placebo treatment arms. ECG was carefully monitored using Holter 12-lead ECG and no change was observed in LNP023- or placebo-treated subjects.

3.6.2.1 Risk of infections

In this study, LNP023 is used to block the complement AP. Patients with factor B (FB) deficiency are generally perfectly healthy, but have impaired resistance against bacterial infections (Slade et al 2013). Of particular concern are rare, but serious, meningococcal or pneumococcal infections. In the general population the annual incidence of invasive infections with *Neisseria meningitidis* is between 0.1-2.0 cases per 100,000 with great variation between regions (Sridhar et al 2015). For infections with *Streptococcus pneumoniae*, the annual risk is 35 cases per 100,000 for individuals <2 or >65 years of age, while it is 4 cases per 100,000 in individuals between 18 and 35 years of age (Alanee et al 2007). The current risk for invasive infections with *Hemophilus influenzae* is 1.6 per 100,000 in the US (MacNeil et al 2011).

Translational research has shown that the serological response to meningococcal infection is maintained during AP blockade, but that it is markedly reduced after blockade of the CP with C5-blockers like eculizumab (IB, Section 7.2). Vaccination is predicted to be an effective mitigation strategy to reduce the risk for individuals treated with LNP023.

After a single injection of meningococcal vaccine, high titers are achieved after two weeks, but in most studies data on titers at Day 28 are reported (Gossger et al 2012, Keyserling et al 2005). Similar effects are seen with the pneumococcal vaccines (McFetridge et al 2015, Bryant et al 2015). Important vaccinations should be performed prior to initiation of LNP023. Importantly, no live vaccines should be given to individuals on LNP023.

During the run in phase, vaccination will be done according to local regulation and practice at least 4 weeks prior to the first dose to effectively increase the serological titers and reduce the risk for the individual in the unlikely event of bacterial infection with *N. meningitidis*, *S. pneumoniae* or *H. influenzae*. The vaccines and the vaccination procedures recommended vary between countries.

Patients will be closely monitored for signs and symptoms of infection. Patients will be instructed to contact the investigator if they suspect infection/experience potential symptoms of infection between visits. The investigator will employ clinical judgement to determine an appropriate course of treatment and report infections as an AE. If symptoms of severe bacterial infections are reported, LNP023 treatment will be interrupted, bacterial cultures taken, and treatment with appropriate antibiotics immediately initiated.

With the vaccinations and close monitoring described above, the risk for serious infection during LNP023 treatment is considered to be low. In addition, prophylactic antibiotics (eg penicillin V or erythromycin) may be given at investigator's discretion.

3.6.2.2 Risk of testicular effects

Findings of tubular degeneration in the testis were seen in toxicology studies conducted in rats and dogs, associated with minimal endocrine disturbances of the pituitary-testis axis in both species, for details see Section 1.2.2.

The risk for male reproductive adverse effects in patients in the phase II trials is considered minimal as:

- The findings are not expected to occur at the proposed clinical exposures. At the proposed maximal clinical dose of 200 mg b.i.d., patient total drug exposures are expected to exceed the established NOAEL exposure levels by 1.14-fold (safety margins of 0.8), and stay 3.6-fold below the LOAEL exposure levels established in toxicology studies. Current projections based on free plasma concentration of LNP023 in animals versus human reveal safety margins of 2.2 for the NOAEL and 17 for the LOAEL
- The testicular and epididymis changes driving NOAEL were minimal in nature
- The non-clinical evaluations indicated full reversibility, no effect on sperm parameters in the male dog (motility, morphology or numbers) and no effect on male fertility in the rat

In the current study, biomarkers of testicular function [testosterone, follicle stimulating hormone (FSH), dihydrotestosterone (DHT) and luteinizing hormone (LH)], TSH and thyroid hormones (T3, T3 reversed, T4) will be regularly monitored.

3.6.2.3 Risk of bone marrow toxicity and severe anaemia

In one male animal receiving high dose of LNP023 (150 mg/kg/day) in the 39-week dog study, moderate hyporegenerative anemia was noted at the end of the 9-month (39-week) treatment period, which further progressed to severe non-regenerative anemia despite discontinuation of treatment. The main finding in histopathology was marked bone marrow fibrosis, while bone marrow cytology indicated dyserythropoiesis. Due to the isolated nature of this finding seen at high exposures, the risk for patients is considered low. Pathogenesis of this isolated finding is not fully understood and will be explored further. Hematological parameters including reticulocyte count will be monitored in all patients. See Table 8-2.

3.6.2.4 Risk of thyroid follicular cell hypertrophy

Dose and treatment duration-dependent incidence and severity of thyroid follicular cell hypertrophy was observed in preclinical studies, correlating with increased thyroid weight and changes in thyroid hormone levels. These were consistently observed in the rat and the dog toxicity studies. The effects were fully reversible after a recovery period, and not considered adverse in the absence of clinical signs of hypo- or hyperthyroidism. Thyroid function and related AEs are being closely monitored in LNP023 studies, as are thyroid hormone levels (T3, T4, TSH and reversed T3). See Section 8.6.13.

3.6.2.5 Non-clinical safety findings of undetermined relevance

In toxicology studies with LNP023, a few findings were observed that are considered of undetermined relevance based on current knowledge. These have not been seen in the clinical setting thus far, and there is no evidence to conclude that these have a causal association with LNP023 exposure or an impact on the risk-benefit balance of LNP023.

Cardiovascular effects: LNP023 in medium to high doses in dogs elicited peripheral vasodilatation, reducing the total peripheral resistance and blood pressure in addition to causing compensatory heart rate increase. At the highest doses, pathological changes were noted in the dogs. The response may be present in humans, even though it was not seen in other species. Small QTc effects were observed at high doses and exposures in nonhuman primates, but in no other species. The risk for humans is considered to be small, but vital signs, ECGs and cardiac AEs will be closely monitored. See Section 8.6.7

Hyperbilirubinemia: In the 4-week GLP toxicological study, a significant dose-dependent effect was observed on the conjugated bilirubin levels in rats and dogs. The effect was considered to be minimal to mild. No change was observed in liver enzymes and the effect was reversible in all animals. Increased bilirubin was accompanied by bile duct hyperplasia in one high-dose dog. At this point it is not known if the hyperbilirubinemia is translatable to humans. Liver function tests and hepatic AEs will be closely monitored in the LNP023 program. See Section 8.6.8.

Proteinuria: This finding was observed in rats treated with high doses of LNP023 (1,000 mg/kg), but electron microscopy did not reveal any morphological changes. The effect was fully reversible, and morphological changes and proteinuria were not observed in dogs. Urine and renal function will be closely monitored. See Section 8.8.4

3.6.3 Risk mitigation strategy

Safety and tolerability data for LNP023 doses up to 200 mg b.i.d. have been collected in study LNP023X2101 in HV, Section 3.6.2. There are four potential risks that have been identified namely 'infections' and 'testicular effects', 'bone marrow toxicity and severe anaemia' and 'thyroid follicular cell hypertrophy'. Infection is mitigated by vaccinations against encapsulated bacteria as described in Section 3.6.2.1. The testicular risk is carefully monitored by analyzing the level of relevant hormones (see Section 3.6.2.2). The bone marrow risk is monitored by review of haematological laboratory values and AEs._Thyroid function will be regularly measured by TSH, T3, T4 and reversed T3. Furthermore, there are preclinical findings of undetermined clinical relevance that will be mitigated by careful clinical monitoring. Thus, blood pressure and 12-lead ECG will be monitored before and after the first dose and before and after a dose at steady state (Day 30) and at other visits throughout the study. Bilirubin and liver enzymes will be carefully monitored together with other laboratory parameters. Finally, urine will repeatedly be collect for analysis of proteinuria as well as other biomarkers in urine.

Patients will return to the clinic on a regular basis. During these visits safety, tolerability, efficacy and PK/PD data will be collected. Standard safety assessments will include vital signs, physical examinations, ECGs, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), and AEs as outlined in the Assessment schedule (Table 8-1).

A priori defined stopping criteria and guidelines (Section 7.5) in addition to the clinical opinion of the Investigator will be used to protect individual patient safety during the trial.

Finally, key safety data will be reviewed by the Sponsor and DMC in a blinded manner on an ongoing basis.

4 Population

4.1 Inclusion criteria

IgA nephropathy patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any study-specific assessment is performed.
2. Female and male patients ≥18 years of age with a biopsy-verified IgA nephropathy and where the biopsy was performed within the previous three years. If the most recent renal biopsy was performed more than three years ago, a new biopsy should be performed.
3. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
4. Patients must weigh at least 35 kg to participate in the study, and must have a body mass index (BMI) within the range of 15 - 38 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2
5. Measured GFR or estimated GFR calculated using the CKD-EPI formula (or modified MDRD formula according to specific ethnic groups and local practice guidelines (Imai et al 2011)) ≥30 mL/min per 1.73 m^2

6. Urine protein to creatinine ratio (UPCR) ≥0.8 g/g (≥90 mg/mmol) sampled from first morning void (FMV) or urine protein ≥0.75 g/24hr from a 24h urine collection at screening and urine protein ≥0.75 g / 24h from a 24h urine collection at the completion of the run-in period.
7. Vaccination against *Neisseria meningitidis* types A, C, Y and W-135 is required at least 4 weeks prior to first dosing with LNP023. Vaccination against *N. meningitidis* type B should be conducted if available and acceptable by local regulations, at least 4 weeks prior to first dosing.
8. Vaccination for the prevention of *S. pneumoniae* and *H. influenzae*, if available and acceptable by local regulations, at least 4 weeks prior to first dosing.
9. All patients must have been on supportive care including a maximally tolerated dose of ACEi or ARB therapy for the individual, antihypertensive therapy or diuretics for at least 90 days before dosing.
10. Laboratory values must meet the following criteria:
    hemoglobin ≥ 9.0 g/dL
    platelet count ≥ 100,000/mm3
11. Vital signs should be within the following ranges
    body temperature between 35.0-37.5 °C
    systolic blood pressure, 90-160 mm Hg
    diastolic blood pressure, 50-90 mm Hg
    pulse rate, 40-90bpm, below 50bpm if no other clinically significant ECG abnormalities as per Investigator decision. For subjects with heart rates less than 50 bpm, evidence should be provided that they have no history of *(i)* moderate or severe valvular disease; *(ii)* history of coronary artery disease, myocardial infarction, hypertension or diabetes mellitus; *(iii)* history of cardiomyopathy, congenital heart defect, open heart surgery, or ongoing arrhythmia; (iv) family history of sudden death in a first degree relative.

4.2 Exclusion criteria

IgA nephropathy patients fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

1. Presence of crescent formation in ≥50% of glomeruli assessed on renal biopsy
2. Patients previously treated with immunosuppressive agents such as cyclophosphamide, mycophenolate mofetil (MMF) or mycophenolate sodium, cyclosporine, tacrolimus, sirolimus or systemic corticosteroids exposure within 90 days prior to start of LNP023/Placebo dosing
3. Patients who previously have received LNP023. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.
4. All transplanted patients (any organ, including bone marrow)
5. History of immunodeficiency diseases, or a positive HIV (ELISA and Western blot) test result.

Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a patient. Patients with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded

6. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The Investigator should make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following:
   - A history of invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus
   - Splenectomy
   - Inflammatory bowel disease, peptic ulcers, severe gastrointestinal disorder including rectal bleeding;
   - Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
   - Pancreatic injury or pancreatitis;
   - Liver disease or liver injury as indicated by abnormal liver function tests. ALT (SGPT), AST (SGOT), GGT, alkaline phosphatase and serum bilirubin will be tested.
   - Any ***single parameter*** of ALT, AST, GGT, alkaline phosphatase or serum bilirubin must not exceed 2 x upper limit of normal (ULN)
   - PT/INR must be within the reference range of normal individuals
   - Evidence of urinary obstruction or difficulty in voiding any urinary tract disorder other than IgAN that is associated with hematuria at screening and before dosing; [If necessary, laboratory testing may be repeated on one occasion (as soon as possible) prior to randomization, to rule out any laboratory error]
7. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
8. A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening or baseline:
   - PR > 200 msec
   - QRS complex > 120 msec
   - QTcF > 450 msec (males)
   - QTcF > 460 msec (females)
   - History of familial long QT syndrome or known family history of Torsades de Pointes
   - Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study
9. History of severe allergic reactions as per Investigator decision
10. Plasma donation (> 200 mL) within 30 days prior to first dosing.
11. Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation

12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception from first dosing until an additional one week following cessation of study drug. *Effective contraception methods include:*
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation 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 subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - 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 placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure <1%), for example hormone vaginal ring or transdermal hormone contraception

    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.

    If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the ICF.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. 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.
13. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
14. History of any porphyria metabolic disorder
15. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline.
16. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes

The investigator must ensure that all subjects being considered for the study meet the above eligibility criteria. No additional criteria should be applied by the investigator in order that the study population will be representative of all eligible subjects.

Patient selection is to be established by checking through all eligibility criteria at screening and baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a subject from enrollment into the study.

5 Restrictions for Study Subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

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, they should agree that in order to participate in the study they must adhere to the effective contraception requirements outlined in the Section 4.2 (Exclusion Criteria).

If there is any question that a subject will not reliably comply, the subject should not be entered or continue in the study.

5.2 Prohibited treatment

Preclinical studies have shown that systemic disposition of LNP023 is primarily mediated by metabolism clearance, in particular by the CYP450 family (primarily CYP2C8) as well as by direct glucuronidation. In addition, some minor contribution from direct renal and intestinal excretion is anticipated, and some role of the organic anion-transporting polypeptide (OATP) in hepatic uptake cannot be fully ruled out. Unless a drug interaction involves inhibition of several of the above mentioned pathways, a major impact on exposure of LNP023 is unlikely. However, to ensure patient's safety, co-medications that inhibit multiple disposition mechanisms of LNP023 (e.g. Gemfibrozil) should be avoided. The same applies to strong CYP2C8 inhibitors such as Clopidogrel.

P-glycoproteins having a **narrow therapeutic** index (e.g. digoxin, quinidine, paclitaxel, fentanyl, phenytoin) should also not be administered with LNP023. However, if no alternative treatment or other adaptations are available, a staggered dosing (co-medication given >3 hrs following oral administration of LNP023) is recommended to avoid increases in systemic exposure (AUC>2) due to P-gp inhibition by LNP023 at the intestinal level.

The investigator should consult with the Novartis medical expert prior to treating a patient with this type of co-medication.

Use of the treatments displayed in the table below is NOT allowed.

Table 5-1 Prohibited medication

Prohibited medication	Prohibited period	Action to be taken
Live Vaccination	From randomization until the end of treatment period	Discontinue study treatment during treatment period
Immunosuppressive agents such as but not limited to cyclophosphamide, MMF or mycophenolate sodium, cyclosporine, tacrolimus, sirolimus, systemic corticosteroids	Three months prior to dosing and treatment periods including 90 days follow-up.	Discontinue study treatment during treatment period
Biological agents such as rituximab, infliximab, canakinumab, etc.	Six months prior to dosing and treatment periods including 90 days follow-up.	Discontinue study treatment during treatment period
Gemfibrozil	5 half-lives of Gemfibrozil prior to administration of LNP023	Discontinue study treatment during treatment period
Strong CYP2C8 inhibitors	5 half-lives of the inhibitor prior to administration of LNP023	Discontinue study treatment during treatment period
P-gp substrates with narrow therapeutic index	1 day prior to administration of LNP023	Discontinue study treatment during treatment period or apply staggered dosing regimen

5.2.1 Drugs to be used with caution

Substrates for Organic Anion-Transporting Peptides (OATP)

LNP023 was identified *in vitro* as a weak inhibitor of the uptake transporter OATP1B1, but not of OATP1B3. The *in vivo* inhibition potential of LNP023 on OATP1B1 is considered low, however, an increase in systemic exposure (<1.25 fold) of OATP1B1 substrates co-administered with LNP023 cannot be entirely ruled out. Investigators may permit OATP substrates with a narrow therapeutic index (e.g. high-dose simvastatin) with caution and when clinically indicated. In any case, the respective label information for the co-medication needs to be taken in consideration.

5.3 Dietary restrictions and smoking

There are no specific dietary restrictions.

5.4 Other restrictions

No applicable

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual.

6.1.1 Investigational treatment and control drug(s)

The investigational drug, LNP023 as 5 mg, 25 mg, 100 mg and matching placebo capsules will be prepared by Novartis and supplied to investigator sites as double blind patient kits. The capsules all look identical.

Table 6-1 Overview of study medication

Study Drug Name	Formulation	Unit dose	Packaging	Provided by
LNP023	Capsules	5 mg	Double Blind Patient Specific Kits	Novartis
LNP023	Capsules	25 mg	Double Blind Patient Specific Kits	Novartis
LNP023	Capsules	100 mg	Double Blind Patient Specific Kits	Novartis
Placebo	Capsules	0 mg	Double Blind Patient Specific Kits	Novartis

6.1.2 Bio-batch retention samples

Not applicable for this study.

6.1.3 Additional study treatment

No additional study treatment beyond investigational drug and placebo are included in this trial.

6.2 Treatment arms

Patients enrolled into the Part 1 of the study will be randomized to one of four treatment arms and treated for 90 days - placebo, or active therapy with LNP023 at doses of: 10 randomized to 10 mg, 10 to 50 mg, 14 to 200 mg LNP023 and 14 to placebo twice daily (b.i.d.). The patients who have been randomized to Part 1 will not be able to participate in Part 2 of the study.

Patients can be screened and enter the run-in phase in Part 2 of the study but will not receive blinded study treatment until the interim analysis of Part 1 is completed and DMC recommends to proceed to Part 2 of the study.

The patients enrolled in Part 2 of the study will be randomized to one of the following sets of doses and treated for 180 days (see Section 3.5):

1. placebo, 10 mg, 50 mg, 100 mg and 200 mg LNP023 b.i.d. or
2. placebo, 10 mg, 25 mg, 50 mg and 200 mg LNP023 b.i.d.

Based on the interim analysis results following Part 1 scenario 1, an additional 100 mg dose was chosen by the DMC. LNP023 or matching placebo will be administered twice daily for 180 days in a blinded manner. Study duration for patients enrolled in Part 2 will be approximately 360 days.

6.3 Treatment assignment and randomization

Upon signing the informed consent form, the patient is assigned the next sequential number available in electronic data capture (EDC) system. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number in the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the appropriate screening period CRF.

All eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will use the IRT system after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm, and will specify a unique medication number for the first package of investigational treatment to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. Patients will be randomized to treatment, within the ancestry strata (Asian/non-Asian), to provide the required overall balance of subjects to treatment group in Part 1. The Part 2 randomization will ensure that, at least 48 subjects are included in Part 2, and the number of subjects randomized to each treatment group included in the study (combining Part 1 and Part 2) will be approximately equal. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject 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 Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s). The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office. Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

The investigator will enter the screening number in the eCRF.

6.4 Treatment blinding

This is a subject, investigator and sponsor-blinded study. Subjects, investigators and sponsor will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at a site for safety reasons (necessary for subject management) will occur via the process defined in place at the site (see Section 6.7).

Medication will be supplied as double blind patient kits. The blinded investigator or his/her delegate performs the randomization in IRT system.

Sponsor staff

Sponsor clinical staff is required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly.

The sample analysts handling pharmacokinetic samples will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team in a way that does not unblind individuals who are meant to be blinded.

Personnel involved in interim analysis at Part 1 and DMC:

An independent data analysis team of statisticians and programmers will be employed to produce the interim analyses results and to communicate with DMC at the time of interim analyses and safety review, as outlined in Table 6-2. The Sponsor pharmacometrician, PK and Biomarker experts, independent of investigator site interface will also have access to the unblinded individual level data in order to conduct the modeling analysis of PK and PD data, and will only share summary group level results with the Novartis decision making team.

Sponsor staff responsible for decision making at the clinical program development level (the Novartis decision making team) will receive the aggregated unblinded results at the treatment group level at the time of the interim analyses, as outlined in Table 6-2.

The Novartis decision making team will become unblinded to the patient treatment codes at the time of IA2. In addition, after the last patient in Part 1 completed his/her final study visit, the Novartis decision making team will have access to the individual unblinded results of IA1 as outlined in Table 6-2.

In order to support initiation of the phase 3 trial of the IgAN program, the interim analyses results (IA1 and IA2) will be communicated according to the following plan, as per Table 6-2:

- The aggregate unblinded group level interim analysis results from IA1 at Part 1 of the trial (IA at Part 1 EOT, see Table 6-2) can be communicated once all patients have completed Part 1 of the study and all Part 2 patients have been enrolled (entered run-in phase).
- The aggregate unblinded group level interim analysis results (including the pre-specified primary analysis) from IA2 at Part 2 of the trial (IA at Part 2 Day 90) can be communicated upon finalization of these results.
- Note that the Part 1 and Part 2 investigators, patients and the Novartis study team will remain blinded to the individual patient treatment codes until the final database lock.

DMC

The DMC will be provided with unblinded results to facilitate the review of safety information (see Table 6-2) and to review the interim analysis results of Part 1 of the trial.

More details will be provided in the DMC charter about the unblinding plan and data flow.

See Table 6-2 for an overview of the blinding/unblinding plan.

Table 6-2 Unblinding plan for the study

Role	Randomization list generated	Treatment allocation & dosing	Safety event	IA at Part 1 EOT (Day 90)	DMC Safety review	IA at Part 2 (Day 90)*
Patients	B	B	UI	B/UG[#]	B	B/UG
Site staff	B	B	UI	B/UG[#]	B	B/UG
Novartis study team	B	B	UI	B/UG[#]	B	B/UG
Drug supply and randomization Office	UI	UI	UI	UI	UI	UI
DMC	B	B	UI	UI	UI	UI
Independent analysis team	B	B	UI	UI	UI	UI
Pharmacometrician/PK and Biomarker Experts	B	B	B	UI	B	UI
Novartis decision making teams	B	B	B	UG/UI[†]	B	UI

IA Interim Analysis; B Blinded; UG Unblinded at the group level; UI Unblinded at the individual level

*An optional IA once the last patient in Part 2 has completed treatment (Day 180) may be done, following the same unblinding plan as the IA in Part 2 (Day 90).

[†] After the last patient in Part 1 completes his/her final study visit.

[#]After the last patient in Part 1 completes his/her final study visit and after the last patient has been enrolled (entered run-in phase) in Part 2.

6.5 Treating the subject

LNP023 will be administered to the subject via the oral route of administration. The study drug will be given to the patients to be taken at home twice a day.

See the Site Operations Manual for further details.

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

6.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number assigned by Novartis. The Subject Number is composed of a site number and a sequential number. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number available in electronic data capture (EDC) system. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number in the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the appropriate screening period CRF.

To differentiate the patients enrolled into Part 2 from Part 1, the subject numbers for the patients in Part 1 will start with “001”, and the subject numbers for the patients in Part 2 will start with a preceding number “5”.

6.6 Permitted dose adjustments and interruptions of study treatment

Dose adjustments and/or interruptions of study drug treatment are not permitted.

If symptoms of severe bacterial infections are reported, LNP023 treatment will be interrupted, bacterial cultures taken, and treatment with appropriate antibiotics immediately initiated.

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject 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 subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study 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 at any time in case of emergency. The investigator will need to provide:

- protocol number
- study drug name (if available)
- subject number

In addition, the investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject

and, if applicable, whether the subject can continue into the next trial phase (e.g., an unblinded extension).

6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with LNP023, as detailed in Section 8.7.

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject 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 subject using a diary. 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.

6.9 Recommended treatment of adverse events

At present, there is insufficient information to provide specific recommendations regarding treatment of AEs. There is no treatment that can reverse the activity of LNP023. LNP023 is a small molecule with a half-life of 12 hours. Potential AEs should therefore be treated symptomatically at the discretion of the Investigator. Medication used to treat AEs must be recorded on the concomitant medications/significant non-drug therapies CRF.

6.10 Rescue medication

Not applicable.

6.11 Concomitant treatment

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

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded in the appropriate CRF.

Prophylactic antibiotics (eg penicillin V or erythromycin) may be given at investigator's discretion.

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.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication (see Section 5.2). If in doubt, the investigator should contact Novartis before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes their Study Completion visit (EOS), and any repeat assessments associated with this visit have been followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All randomized and/or treated subjects should have a safety follow-up visit 90 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 9.2 and the Site Operations Manual. Documentation of attempts to contact the subject should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the subject or the investigator.

Study treatment must be discontinued under the following circumstances:

- Subject decision - subjects may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the subject's safety.
- Pregnancy (see Section 8.6 (Safety) and Section 9.6 (Pregnancy reporting))
- Use of prohibited treatment as outlined in Table 5-1.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
- Clinically symptomatic and suspected COVID-19 (+) and/or COVID-19 (+)

The appropriate personnel from the site and Novartis will assess whether investigational drug treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

If discontinuation of study treatment occurs, investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the appropriate CRF.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3, Withdraw of Informed Consent). Where possible, they should return for EOS visit within 14 days after last study medication administration. If they fail to

return for EOS visit for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 7.4. (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

7.3 Withdrawal of informed consent

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

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

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

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 subject are not allowed unless safety findings require communicating or follow-up.

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

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study Stopping rules

The DMC will perform safety reviews of blinded data throughout the study. The first blinded data safety review will occur one month after the first dose of study drug and then monthly thereafter. If the DMC decides that an un-blinded safety data review is necessary, a copy of the randomization list will be requested from (and provided by) the Independent Programmer and Independent Statistician. The DMC charter provides complete details of this process.

In addition, DMC will conduct ad hoc safety evaluation in a timely manner and provide its recommendation on study conduct should the circumstance below arise:

- One fatal or life-threatening SAE occurs, that is considered by the Investigator as potentially or possibly related to LNP023.
- The Sponsor or DMC considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify an ad hoc safety evaluation.

If a full safety review is triggered, the DMC will be asked to perform a review of the safety data in an unblinded manner (SAEs and other safety information as necessary), the DMC can recommend (i) for the study to continue without amendment, (ii) to continue the study with modifications to the protocol (iii) to stop the study.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely discontinued subject. 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 subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. The assessment schedule is applicable for both Part 1 and 2 of the study.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects 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.

Table 8-1 Assessment Schedule for Part 1 of the Study

Period	Screening		Treatment																Safety Follow Up	EOS
Visit Name	Screening	Baseline	Treatment																	
Visit Numbers[1]	1	20	110			120		130	140								150	160	170	1999
Days	run-in phase	-7 to -4	1			8 ±1		15±2	30 ±3								60±3	90±3[15]	120±5	180±5
Time (post-dose)	-	-	Pre-dose	1h	2h	Pre-dose	1h	-	Pre-dose	0.25h	0.5h	1h	2h	4h	6h	8h	-	-	-	-
Informed consent	X																			
[redacted]																				
Inclusion / Exclusion criteria	X	X																		
Vaccination	X																			
Medical history/current medical conditions	X																			
Pregnancy and assessments of fertility[14]	S	S							S								S	S		S

Period	Screening		Treatment																Safety Follow Up	EOS
Visit Name	Screening	Baseline	Treatment																	
Visit Numbers[1]	1	20	110			120		130	140								150	160	170	1999
Days	run-in phase	-7 to -4	1			8 ±1		15±2	30 ±3								60±3	90±3[15]	120±5	180±5
Time (post-dose)	-	-	Pre-dose	1h	2h	Pre-dose	1h	-	Pre-dose	0.25h	0.5h	1h	2h	4h	6h	8h	-	-	-	-
Hepatitis and HIV Screen	S																			
Demography	X																			
Pulse rate[2]	X	X	X	X	X	X	X	X	X				X				X	X	X	X
Blood Pressure[2]	X	X	X	X	X	X	X	X	X				X				X	X	X	X
Body Temperature[2]	X	X	X			X		X	X								X	X	X	X
Physical Examination[2]	S	S						S										S	S	S
Body Height	X																			
Body Weight	X	X	X			X		X	X								X	X		
Electrocardiogram (ECG)	X	X	X	X			X	X	X				X				X	X		
Alcohol Test and Drug Screen	S	S																		
24h urine collection[3]	X[18]	X							X									X		
First morning void urine (midstream)[4]	X	X	X			X		X	X								X	X	X	X
Estimated Glomerular filtration rate[5]	X	X	X			X		X	X									X	X	
Hematology[2]	X	X	X			X		X	X								X	X	X	

Period	Screening		Treatment															Safety Follow Up	EOS
Visit Name	Screening	Baseline	Treatment																
Visit Numbers[1]	1	20	110			120		130	140							150	160	170	1999
Days	run-in phase	-7 to -4	1			8 ±1		15±2	30 ±3							60±3	90±3[15]	120±5	180±5
Time (post-dose)	-	-	Pre-dose	1h	2h	Pre-dose	1h	-	Pre-dose	0.25h	0.5h	1h	2h	4h	6h	8h	-	-	-	-
Clinical Chemistry[2,7]	X	X[17]	X			X		X	X								X	X[17]	X	X
PK blood collection						X		X[16]	X	X	X	X	X	X	X	X	X[16]	X[16]		
[redacted]																				
blood levels of testosterone, FSH, LH, DHT and thyroid hormones[6]		X						X	X								X	X		X
Safety Urinalysis[2, 13]	X	X	X			X		X	X								X	X	X	X
[redacted]																				
PD [redacted][9]		X				X		X	X						X		X	X		

Period	Screening		Treatment																Safety Follow Up	EOS
Visit Name	Screening	Baseline	Treatment																	
Visit Numbers[1]	1	20	110			120		130	140								150	160	170	1999
Days	run-in phase	-7 to -4	1			8 ±1		15±2	30 ±3								60±3	90±3[15]	120±5	180±5
Time (post-dose)	-	-	Pre-dose	1h	2h	Pre-dose	1h	-	Pre-dose	0.25h	0.5h	1h	2h	4h	6h	8h	-	-	-	-
[redacted]																				
Concomitant medications	X																			
Study drug administration[11]			X																	
Study Drug Dispense			X			X		X	X								X			
[redacted]																				
Adverse Events	X																		X	X
Study phase completion information																				X

Table 8-2 Assessment Schedule for Part 2 of the Study

Period	Screening		Treatment															Safety Follow Up	EOS
Visit Name	Screening	Baseline																	
Visit Numbers[1]	1	20	110		120	130	140							150	160	175	180	190	2999
Days	run-in phase	-7 to -4	1		8±1	15±2	30 ± 3							60±3	90±3[15]	135±7	180±7[15]	210±7	270±7[15]
Time (post-dose)	-	-	Pre-dose	1h	-	-	Pre-dose	0.25 h	0.5 h	1h	2h	4h	6h	8h	-	-	-			-
Informed consent	X																			
[redacted]																				
Inclusion / Exclusion criteria	X	X																		
Vaccination	X																			
Medical history/current medical conditions	X																			
Pregnancy and assessments of fertility[14]	S	S					S								S	S		S		S
Hepatitis and HIV Screen	S																			
Demography	X																			
Pulse rate[2]	X	X	X	X	X	X	X				X				X	X	X	X	X	X
Blood Pressure[2]	X	X	X	X	X	X	X				X				X	X	X	X	X	X

Period	Screening		Treatment																Safety Follow Up	EOS
Visit Name	Screening	Baseline																		
Visit Numbers[1]	1	20	110		120	130	140								150	160	175	180	190	2999
Days	run-in phase	-7 to -4	1		8±1	15±2	30 ± 3								60±3	90±3[15]	135±7	180±7[15]	210±7	270±7[15]
Time (post-dose)	-	-	Pre-dose	1h	-	-	Pre-dose	0.25 h	0.5 h	1h	2h	4h	6h	8h	-	-	-			-
Body Temperature[2]	X	X	X		X	X	X								X	X	X	X	X	X
Physical Examination[2, 20]	S	S				S										S	S	S	S	S
Body Height	X																			
Body Weight	X	X	X		X	X	X								X	X	X	X		
Electrocardiogram (ECG)[2]	X	X	X	X		X	X				X				X	X	X	X		
Alcohol Test and Drug Screen	S	S																		
24h urine collection[3]	(X)[18]	X					X									X		X		
First morning void urine (midstream)[4]	(X)[18]	X	X		X	X	X								X	X	X	X	X	X
Estimated Glomerular filtration rate[5]	X	X	X		X	X	X								X	X	X	X	X	X
Hematology[2; 21]	X	X	X		X	X	X								X	X	X	X	X	X

Period	Screening		Treatment															Safety Follow Up	EOS
Visit Name	Screening	Baseline																	
Visit Numbers[1]	1	20	110		120	130	140								150	160	175	180	190	2999
Days	run-in phase	-7 to -4	1		8±1	15±2	30 ± 3								60±3	90±3[15]	135±7	180±7[15]	210±7	270±7[15]
Time (post-dose)	-	-	Pre-dose	1h	-	-	Pre-dose	0.25 h	0.5 h	1h	2h	4h	6h	8h	-	-	-			-
Clinical Chemistry[2,7]	X	X[17]	X		X	X	X								X	X[17]	X	X[17]	X	X
PK blood collection					X[16]	X[16]	X	X	X	X	X	X	X	X	X[16]	X[16]	X[16]	X[16]		
[redacted]																				
blood levels of testosterone, FSH, LH, DHT and thyroid hormones[6]		X				X	X								X	X	X	X		X
Safety Urinalysis[2, 13, 19]	X	X	X		X	X	X								X	X	X	X	X	X
[redacted]																				

Period	Screening		Treatment														Safety Follow Up	EOS
Visit Name	Screening	Baseline																
Visit Numbers[1]	1	20	110		120	130	140							150	160	175	180	190	2999
Days	run-in phase	-7 to -4	1		8±1	15±2	30 ± 3							60±3	90±3[15]	135±7	180±7[15]	210±7	270±7[15]
Time (post-dose)	-	-	Pre-dose	1h	-	-	Pre-dose	0.25 h	0.5 h	1h	2h	4h	6h	8h	-	-	-			-
[redacted]																				
PD [redacted][9]		X			X	X	X						X		X	X	X	X	X	
[redacted]																				
Concomitant medications			X																	
Dispense Study Medications			X			X	X							X	X	X				
Study drug administration[11]			X																	
[redacted]																				
Adverse Events			X															X		X

Period	Screening		Treatment															Safety Follow Up	EOS
Visit Name	Screening	Baseline																	
Visit Numbers[1]	1	20	110		120	130	140							150	160	175	180	190	2999
Days	run-in phase	-7 to -4	1		8±1	15±2	30 ± 3							60±3	90±3[15]	135±7	180±7[15]	210±7	270±7[15]
Time (post-dose)	-	-	Pre-dose	1h	-	-	Pre-dose	0.25 h	0.5 h	1h	2h	4h	6h	8h	-	-	-			-
Study phase completion information																			X

[1] Visit structure given for internal programming purpose only
[2] Unless specified otherwise, these procedures, including infection surveillance, are performed before the morning dose (i.e. predose) at each visit
[3] The 24hour urine collection should start one day prior to the clinic visit, **AFTER** the patient urinates for the first time, then all urine in the next 24 hours will be collected and refrigerated before being taken to the clinic. Assessments may include but not limited to UACR and UPCR, 24h urine excretion of albumin and protein, renal function biomarkers, PK (except at Baseline)
[4] A midstream urine sample will be obtained from the first morning void (FMV) on the visit day. For Visits 20, 140, 160 and 180 when both FMV and 24-hour urine samples are required, FMV should be collected one day prior to the clinic visit. The collected urine sample should be refrigerated before being taken to the clinic. Assessments may include but not limited to UACR and UPCR, renal function biomarkers.
[5] Estimated Glomerular Filtration Rate (eGFR) is calculated according to CKD-EPI. Modified MDRD formula according to specific ethnic groups and local practice guidelines (Imai et al 2011) may be used at Visit 1 only.
[6] including thyroid function surveillance (T3, reversed T3, T4, Thyroid Stimulating Hormone - TSH-DHT level assessment)
[7]Clinical chemistry includes total protein, albumin, creatinine, glucose, sodium, potassium, lipids, and liver safety monitoring (ALT, AST, ALP, TBL, PT/INR, GGT levels assessment) etc.
[redacted]
[9] May include but not limited to sC5b-9, Bb, [redacted]
[redacted]
[11] LNP023 to be administered b.i.d. daily from Day 1 to Day 90 in Part 1, Day 1 to Day 180 in Part 2. At days of the study visit, the morning dose of study medication will be administered at the study center after pre-dose sampling, evening dose can be taken at home.
[redacted]
[14] Serum pregnancy test required at screening, urine pregnancy test at further time points
[15] For Part 1, Day 90 (Visit 160) is End of Treatment (EOT) and Day 180 (Visit 1999) is End of Study (EOS); for Part 2, Day 180 (Visit 180) is End of Treatment (EOT) and Day 270 (Visit 2999) is End of Study (EOS).
[16] To be collected pre-dose.
[17] Total Cholesterol, LDL, HDL, Triglycerides, Glucose under fasting condition will be measured at baseline (Visit 20), EOT (Visit 160) in Part 1, Visit 160 and EOT (Visit 180) in Part 2.
[18]. At screening UPCR can be measured from first morning void OR 24h urine collection.
[redacted]
[20]. Complete physical examination at Visit 20, Visit 160 and Visit 1999 (EOS) in Part 1 and Visit 2999 (EOS) in Part 2. Abbreviated physical examinations will be performed at the other visits.
[21]. Hematology analysis includes red blood cell count (RBC), white blood cell count (WBC), platelet counts, hematocrit, hemoglobin, reticulocytes, neutrophils, etc.
X = assessment to be recorded in clinical database S = assessment to be recorded in source documentation only

8.2 Informed consent procedures

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

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

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 subject source documents.

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject 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 subject.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

[redacted]

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

Refer to the Site Operations Manual for a complete list of Informed Consent Forms (ICF) included in this study.

Patients who agree to participate in Part 2 of the study may sign the ICF, enter screening and run-in phases prior to the interim analysis in Part 1; however, patients will only be randomized in Part 2 after the DMC recommendation becomes available.

8.3 Subject screening

It is permissible to re-screen a subject if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent.

Subject demographics will include age, sex, race, ethnicity, height, weight and BMI. Other baseline disease characteristics include relevant medical history, current medical conditions, results of laboratory screens, transplant history, donor characteristics (e.g., age, sex, race, type) and any other relevant information. Information on the duration of time before screening that the patient has been taking an ACEi/ARB, and whether ACEi/ARB has been stable will also be collected.

Details are outlined in the Site Operations Manual.

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

8.4.1 Renal biopsies

The diagnosis of IgAN and the inclusion of an eligible patient must be based on a renal biopsy. The slides of the renal biopsy must be digitalized and submitted to a central database. If the most recent renal biopsy was performed more than three years ago, a new biopsy should be performed.

Details are outlined in the Site Operations Manual.

8.5 Efficacy / Pharmacodynamics

Efficacy / Pharmacodynamic samples will be collected at the time points defined in the Assessment schedule. Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment.

8.5.1 Clinical Outcome Assessments (COAs)

[redacted]

8.5.2 Soluble Biomarkers

Soluble complement biomarkers in plasma will be evaluated as potential pharmacodynamics and mode-of-action markers. They may include, but are not be limited to:

- Circulating fragment of factor B (Bb)
- sC5b-9 (terminal complement complex)

The list may be changed or expanded further as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the study or of other LNP023 studies. Detailed descriptions of the assays will be included in the bioanalytical data reports.

This assessment will be conducted at selected sites only.

8.5.3 Estimated Glomerular filtration rate

Estimated glomerular filtration rate (eGFR) is calculated applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al 2009).

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

where: S_{cr} 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 S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/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, modified formula may be applied according to specific ethnic groups and local guidelines.

Details are outlined in the Site Operations Manual.

8.5.4 First morning void urine (midstream)

First morning void (FMV) midstream urine will be obtained at all visits. On Visits 20, 140, 160 and 180 at which both FMV and 24 hour urine samples are required, FMV should be collected one day prior to the clinic visit. The collected urine sample should be refrigerated before being taken to the clinic. Measurement includes UACR, UPCR, [redacted]

8.5.5 24h urine collection

Urine over 24 hours will be collected. Measurement includes, but is not limited to, UACR and UPCR, 24h urine excretion of albumin and protein, creatinine clearance, and PK.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule (Section 8.1) detailing when each assessment is to be performed.

8.6.1 Blood Pressure

Systolic and diastolic blood pressure will be measured using an automated validated device (e.g., OMRON) with an appropriately sized cuff. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

The repeat sitting measurements will be made at up to 5 minute intervals and measurements will be recorded on the Vital Signs eCRF.

8.6.2 Pulse rate

Pulse rate will be measured.

8.6.3 Urinalysis and urine microscopy

Dipstick measurements for leucocytes and blood will be performed. Any positive result will require a sample to be sent for further Microscopy assessment of WBC, RBC and sediments. Results for both the positive dipstick parameters and the microscopy will be recorded.

8.6.4 Body Weight

- Body weight will be measured
- Body mass index (BMI) will be calculated as (Body weight (kg) / [Height (m)]^2)

8.6.5 Body Height

Height will be measured.

8.6.6 Body Temperature

Body temperature should be measured as per local practice – the same method to be used consistently for all patients at each site.

8.6.7 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the Site Operations Manual.

All ECGs are done as 12-lead triplicate ECGs. All ECGs evaluations will be done by the investigators.

PR interval, QRS duration, heart rate, RR interval, QT interval, QTc.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

As applicable, QTcF and QTcB may be calculated in-house. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess patient eligibility. See the Site Operations Manual for additional details.

Clinically significant abnormalities must be reported in the AE CRF.

8.6.8 Clinical Chemistry

The following measurements will be done: Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Triglycerides, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose.

8.6.9 Hematology

Hemoglobin, hematocrit, reticulocyte count, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured. Coagulation testing including prothrombin time (PT) also reported as INR and activated partial thromboplastin time (aPTT) will be measured.

8.6.10 Pregnancy and assessments of fertility

Pregnancy Testing

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment schedule (Section 8.1), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements*. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

*Additional pregnancy testing might be performed if requested per local requirements.

Refer to Section 9.6 for details on Reporting Pregnancy.

Assessments of Fertility

Refer to Section 4.2 for criteria to determine women that are not of child bearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained at source. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject, who states that they are of non-child bearing potential, regardless of reported reproductive/menopausal status at Screening/Baseline.

8.6.11 Physical Examination

A complete physical examination should include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. Information for all physical examinations must be included in the source documentation at the study site and will not be recorded on the CRF. Significant findings that are present prior to informed consent are included in the CRF capturing Medical History. Significant findings observed after informed consent signature which meet the definition of an AE must be appropriately recorded on the appropriate CRF capturing AEs.

8.6.12 Vaccination

If prior vaccination cannot be confirmed e.g. documented in subject's medical notes, subjects enrolling must be vaccinated against *N. meningitidis*, *S. pneumoniae* and *H. influenzae*. To ensure full protection, the vaccines against *N. meningitidis* should cover the most common serotypes. This can be done with for example Menveo™ covering A, C, W135 and Y in combination with Bexsero™ against serotype B. In the US the serotypes C, B and Y accounts for 35, 32 and 26% respectively, while serotype B is responsible for 2/3 of the cases in Europe (Sridhar et al 2015). Vaccination against *S. pneumoniae* can be done using for example Pneumovax™ (against 23 serotypes). Against *H. influenza* vaccines such as Act-HIB™ could be used. For all vaccinations, local recommendations and guidelines must be followed. All vaccines should be administered at least 4 weeks prior to starting study treatment.

Continuous close monitoring of subjects for early symptoms and signs of meningococcal infection is required in order to evaluate subjects immediately if an infection is suspected.

Importantly, no live vaccines should be given to individuals on LNP023.

8.6.13 Blood hormone levels

Thyroid function is measured by analyses of T3, T4, TSH, and reversed T3. To monitor potential effects on testis, the hormone levels of testosterone, FSH, LH and DHT are also measured.

8.7 Pharmacokinetics

PK samples will be collected at the time points defined in the Assessment schedule.

The pre-dose PK samples will be obtained and evaluated in all patients at all dose levels.

The post-dose PK samples at Visit 140 (Day 30) will be obtained and evaluated as follows:

- All the patients randomized in Part 1
- At least 48 patients randomized in Part 2
- Fulfill the local regulatory guidelines or considerations

LNP023 in plasma (0-8 h) and in urine (from a 24h collection) will be determined by a validated LC-MS/MS method. The lower limit of quantification (LLOQ) will be approximately 1 ng/mL. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

[redacted]

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters of LNP023 will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher):

Plasma: Cmax,ss, Tmax,ss, AUCtau,ss and Cmin,ss at Day 30. Other pharmacokinetic parameters are measured as appropriate. To denote parameters determined at steady state "ss" will be used.

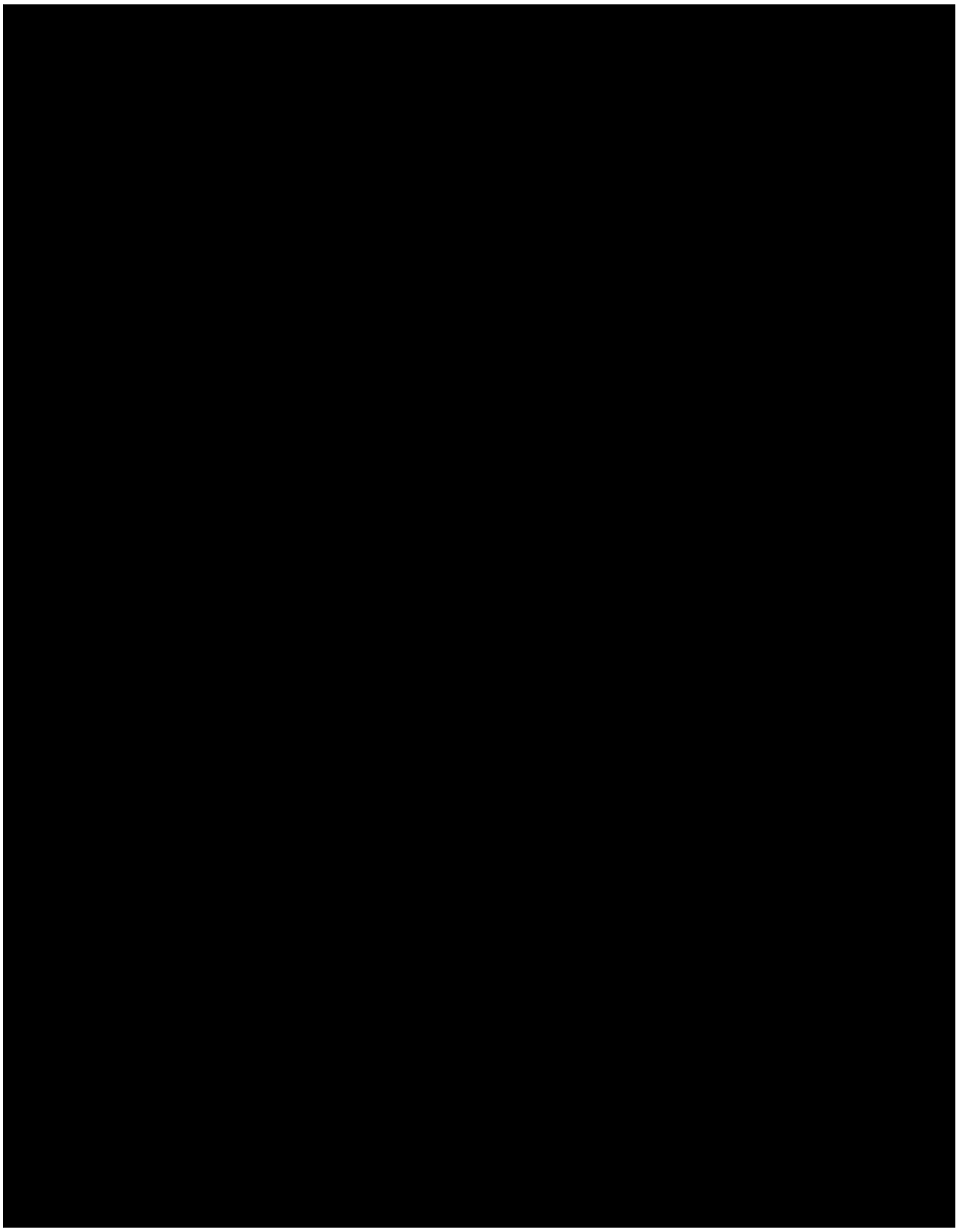
The linear trapezoidal rule will be used for AUC calculation. AUCtau will be calculated instead of AUCinf. Values below the lower limit of quantification will be treated as zero for calculation of PK parameters as well as for summary statistics.

Further details on sample collection, numbering, processing and shipment will be provided in the lab manual and/or SOM.

8.8 Other assessments

[redacted]

Further details on sample collection, numbering, processing and shipment will be provided in the lab manual and/or SOM.



[redacted]

8.9 Use of residual biological samples

Residual blood and urine samples may be used for another protocol specified endpoint.

[redacted]

9 Safety monitoring

9.1 Adverse events

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

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

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 should 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 patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver events are included in Appendix 1 .

Adverse events should be recorded on the appropriate CRF capturing AEs under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. The severity grade
   mild: usually transient in nature and generally not interfering with normal activities
   moderate: sufficiently discomforting to interfere with normal activities
   severe: prevents normal activities
2. its relationship to the study treatment
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 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.
   All adverse events must be treated appropriately. Treatment may include one or more of the following
   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved;, recovered/resolved with sequelae; fatal; or unknown

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of Investigator Notifications. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject'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.

Refer to the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any AE (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:

- is fatal or life-threatening
- 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 the start of study drug
  - 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
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the subject 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 ICH-E2D Guideline 2003).

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 subject or might require intervention to prevent one of the other outcomes listed above. 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 ICH-E2D Guideline 2003).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 9.2.2.

9.2.2 SAE reporting

Screen Failures

Note the following requirement for Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Randomized

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 90 days after the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence as described below.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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 within 24 hours of the investigator receiving the follow-up information. 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.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (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.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

To ensure subject 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 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 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 15-2-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject.

All follow-up information, and the procedures performed must be recorded on the appropriate CRFs. Refer to the Site Operations Manual for additional details.

9.4 Renal safety monitoring

Not applicable since this study is conducted in a population with renal disease.

9.5 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, patient/subject 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.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) Study Treatment CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO& PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in appropriate CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO& PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Guidance for capturing study treatment errors

Treatment error type	Document in CRF (Yes/No)	Document in AE CRF	Complete SAE form/CRF
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 Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

LNP023 was tested in an embryo-fetal development study in rats and rabbits. LNP023 is not considered teratogenic or embryo lethal. No LNP023-related adverse fetal findings were detected in any of the studies. The study excludes enrollment of women of child-bearing potential unless they are using effective methods of contraception, thus pregnancy is not an expected outcome for any female study participant. However, in the case that a pregnancy in a female study participant should occur, please follow the below reporting guidelines.

To ensure subject 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.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO& PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

9.7 Early phase safety monitoring

The Investigator will monitor AEs in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 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 monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis. Additionally, a central analytics organization may analyze data and 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 subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 the recording of data that will be used for all primary and safety 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 subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected by investigator staff, before transfer of the data to Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate and that entry and updates are performed in a timely manner. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Certain data may be captured via other source documentation (such as safety laboratory data report, imaging) and then transcribed, uploaded or transferred into the system. This, and any additional data treated in this manner, will be source data verified by the study monitor per the monitoring plan and the location of source data (i.e., Source, paper or a local electronic system) will be documented prior to study start in the Data Quality Plan. The system has the ability to illustrate when a document has been entered from another source. When using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application; rather, the electronic source record directly populates the study database.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the vendor working on behalf of Novartis.

Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

The investigator must certify that the data entered are complete and accurate and that entry and updates are performed in a timely manner. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedule (Section 8.1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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

10.3 Database management and quality control

Novartis staff review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database. The signed copy of the Resolved Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the 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.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes 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).

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.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, 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 management.

[redacted]

10.4 Data Monitoring Committee

An external DMC will be appointed to review and provide recommendations based on safety data study stopping rules (see Section 7.5) and based on the results from an interim analysis for efficacy conducted to assess design adaptations for Part 2 of the study and to assess the safety data at regular intervals throughout the study.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled the "Data Monitoring Committee Charter". The DMC Charter will include information about data flow, purpose and timing of DMC meetings, guidance in the decision making process, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

10.5 Adjudication Committee

Not applicable.

11 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

The full analysis set (FAS) will include all randomized patients. The full analysis set 1 (FAS1) will include all randomized patients in Part 1 and all randomized patients in Part 2 that consented to receive treatment as per protocol version 03 or earlier. The full analysis set 2 (FAS2) will include all randomized patients in Part 2 that consented to receive treatment as per protocol version 04 (i.e. allowing for 180 days of treatment). Mis-randomized patients, that is patients who were randomized incorrectly and did not receive any study drug will be excluded from all FAS sets. For the full analysis sets, patients will be analyzed according to the treatment they have been assigned to at randomization. The full analysis sets will be used for the assessment of efficacy.

The safety analysis set (SAF) will include all patients that received any study drug. The safety analysis set 1 (SAF1) will be likewise derived for patients in Part 1 and patients in Part 2 that consented to receive treatment as per protocol version 03 or earlier. The safety analysis set 2 (SAF2) will be likewise derived for Part 2 that consented to receive randomized treatment as per protocol version 04 (i.e. allowing for 180 days of treatment). For the safety analysis sets, patients will be analyzed according to the treatment they received.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data. Patients will be analyzed according to the treatment they received. The PK1 analysis set will be likewise derived for patients in Part 1 and patients in Part 2 that consented to receive treatment as per protocol version 03 or earlier. The PK2 analysis set will be likewise derived for Part 2 that consented to receive randomized treatment as per protocol version 04 (i.e. allowing for 180 days of treatment).

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and patient. Summary statistics will be provided by treatment group, overall and for each study part separately.

Relevant medical history, current medical conditions, outcome of renal biopsy at baseline and other relevant information will be listed by treatment group and patient, overall and for each study part separately.

The FAS will be used for these analyses.

11.3 Treatments

Data for study drug administration and concomitant therapies will be summarized by treatment group, for the SAF (up to Day 90) and for SAF1 and SAF2 separately.

Total duration of time on study drug and reasons for discontinuation of study drug will be summarized by treatment group, for the SAF (up to Day 90) and for SAF1 and SAF2 separately.

11.4 Analysis of the primary variable(s)

At the final analysis, a one-sided type I error rate of 10% (2-sided type I error rate of 20%) will be used for all efficacy analyses. Correspondingly, two-sided 80% confidence intervals (CIs) will be presented.

11.4.1 Primary Variable(s)

The primary variable is the change from baseline of log transformed UPCR derived from the 24h urine collections at baseline and day 90.

11.4.2 Statistical model, hypothesis, and method of analysis

At the time of final analysis all data from Part 1 and Part 2 of the study up to day 90 will be pooled and analyzed for the primary analysis; the FAS set (up to Day 90) will be used. If the study is stopped at the end of Part 1, then the results of the interim analysis will become the final analysis results.

The primary endpoint will be analyzed using Multiple Comparison Procedure (MCP) methodology as described as part of MCP-Modelling (MCP-Mod) by Bretz et al 2005 and Pinheiro et al 2014.

A two stage approach will be taken for this analysis: first, change from baseline in log transformed UPCR at multiple time points will be analyzed using a Mixed Model of Repeated Measures (MMRM) model. UPCR is derived from the 24h urine collections at baseline, day 30 and 90. The results will be back transformed and presented on the original scale.

The model will include treatment, time point (as study day relative to start of study treatment), study part (Part 1 or Part 2) and ancestry (Asian/non-Asian) as fixed effects and baseline log UPCR as fixed covariate. Baseline is defined to be the last measurement prior to randomization. Treatment by time point and time point by baseline log UPCR will be included as interaction terms. Timepoint will be included as a repeated factor with an unstructured covariance matrix to allow adjustment for correlations between time points within patients.

Secondly, the following global hypothesis will be tested for the day 90 time point using the generalized MCP-Mod approach (Pinheiro et al 2014) at the one-sided 10% significance level to assess whether LNP023 is different from placebo:

H_0: $c^T_m \mu = 0$ for all m in {1, …6}

H_1: $c^T_m \mu > 0$ for at least one m in {1, …6}

where μ is the vector of adjusted means (on the log transformed scale) for each treatment group from the analysis of the primary endpoint at day 90 i.e. $\mu = (\mu_{\text{Placebo}}, \mu_{\text{LNP023 dose 1}}, \ldots, \mu_{\text{LNP023 dose n}})^T$ and c^T_m is the vector of optimal contrasts coefficients for the m^{th} candidate dose response shape m, as described below.

- Model 1: Linear
- Model 2: Emax with ED50 at 5mg
- Model 3: Emax with ED50 at 50mg
- Model 4: Sigmoidal emax with ED50 at 25mg and Hill parameter=3
- Model 5: Sigmoidal emax with ED50 at 50mg and Hill parameter=3

- Model 6: Exponential with delta =50

The contrast test statistics will be calculated as standardized linear combinations of the estimated treatment effects using (i) the optimal contrast coefficients (ii) the adjusted means and variance-covariance matrix from the MMRM analysis.

The multiplicity adjusted critical value for the one-sided 10% significance level will then be determined from the joint multivariate t-distribution of the optimal contrasts using the correlation between test statistics. The hypothesis H_0 is to be rejected if the maximum of all t-statistics is larger than the derived critical value.

The dose response curve and the ED90 will be estimated together with 80% confidence intervals.

11.4.3 Handling of missing values/censoring/discontinuations

The primary analysis will include all available data up to the point of treatment discontinuation for patients who discontinue.

This method is valid and consistent under a missing at random (MAR) assumption, i.e. given the observed data (responses and covariates) the probability of drop-out does not depend on the unobserved responses.

Supportive analyses to assess the impact of any incomplete data on the results will be performed and will include all available data regardless of whether treatment was taken or not in an intention-to-treat manner. Further details will be provided in the Statistical Analysis Plan (SAP).

11.4.4 Sensitivity analyses

Sensitivity analyses aimed at assessing the sensitivity of the conclusions to the model specification will be described in the SAP.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

The secondary variables supporting the secondary objective to assess the effect of LNP023 on renal function are eGFR, serum creatinine, hematuria, 24h-UP, 24h-UA, UACR,, UPCR (from first morning void). These variables will each be analyzed with the same MMRM model used for the primary variable. Appropriate transformations for each variable will be detailed in the SAP. Estimates of the differences between each dose of LNP023 and placebo will be calculated.

For eGFR, UPCR (from 24 hour sample and first morning void), hematuria and UACR, the MMRM will be repeated considering measurements up to day 180 (i.e. for FAS2 only); the MMRM for this analysis will not include the study part fixed effect term.

A further secondary analysis of UPCR after the end of treatment will be performed, for FAS1 and FAS2 separately. This analysis would also follow the MMRM approach described for the primary variable but will include UPCR measured up to the EOS.

11.5.2 Safety

Vital signs

All vital signs data will be listed by treatment, patient, and time point and abnormalities will be flagged. Summary statistics will be provided by treatment and time point, for the SAF (up to Day 90), and for SAF1 and SAF2 separately.

To assess the effect of LNP023 on blood pressure after dosing with LNP023, blood pressure and heart rate at 1-2 hours post dose on Day 1 and Day 30 (see Assessment schedule) expressed as change from baseline will be summarized, for the SAF. This represents the blood pressure at the approximate time of Cmax after first dose and at steady state. The relationship between changes in blood pressure and heart rate and the Cmax concentrations will also be investigated graphically.

ECG

All ECG data will be listed by treatment, patient, and time point, and abnormalities will be flagged. Summary statistics will be provided by treatment and time point, for the SAF (up to Day 90) and for SAF1 and SAF2 separately; the number of patients with values above key threshold values will be displayed.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, patient and time point, and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and time point, for the SAF (up to day 90) and for SAF1 and SAF2 separately.

Adverse events

All information obtained on AEs will be displayed by treatment and patient.

The number and percentage of subjects with adverse events will be tabulated by System Organ Class (SOC) and Preferred Term (PT) with a breakdown by treatment, for the SAF (up to day 90) and for SAF1 and SAF2 separately. A subject with multiple AEs events within a SOC is only counted once towards the total of this SOC for the event of highest severity.

Exposure-adjusted AE summaries will also be likewise considered.

Summaries of SAEs will be provided in a similar manner.

Further displays of AEs may be produced in order to appropriately describe the outcomes seen in this trial.

11.5.3 Pharmacokinetics

LNP023 concentration data will be listed by treatment, patient and time point. Descriptive summary statistics will be provided by treatment and time point, for the PK set (up to Day 90) and for PK2 separately, including the frequency (n, %) of concentrations below the LLOQ and reported as zero; these will be distinguished from values missing.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below LLOQ or missing 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.

Pharmacokinetic parameters will be calculated as described in Section 8.7 and will be summarized by treatment, for the PK set (up to Day 90) and for PK2 separately.

11.5.4 Pharmacokinetic / pharmacodynamic interactions

The current study is not designed to investigate pharmacokinetic interactions which have been assessed previously *in vitro* (see IB section 5.1.5). Possible additive or synergistic PD interactions will also not be investigated. For safety aspects of PK or PD interactions please refer to inclusion/exclusion criteria (Section 4).

The relationship between PK and PD will be assessed using pharmacometric modeling approaches. Various pharmacodynamic variables will be considered and will be linked to serum exposure: biomarkers assessing complement activation and modulation (e.g. [redacted] and plasma and urine Bb, [redacted], sC5b9), and kidney impairment biomarkers (e.g. UPCR from 24h-urine, UPCR from first morning void). Different model structures will be explored (direct or indirect response models). Inter-individual variability will be taken into account using mixed effects modeling. Detail on these analyses will be provided in a separate Modeling Plan

[redacted]

11.7 Sample size calculation

The sample size calculation for Part 1 is based upon the number of patients required to demonstrate a statistically significant result (at the one-sided 10% alpha level) in the multiple comparison test (MCP step) of the MCP-Mod procedure in the interim analysis at the end of treatment in Part 1.

To allow for a drop-out rate of up to 20%, 48 patients will be enrolled with the aim of having at least 40 patients complete Part 1 of the study. With a sample size of 40 patients in total (8 randomized to 10mg, 8 to 50mg, 12 to 200mg LNP023 and 12 to placebo), if the true effect of LNP023 is to reduce UPCR by 50% then Part 1 has at least 85% of demonstrating a statistically significant difference from placebo.

The calculations are based on log UPCR and assume a standard deviation in log UPCR of 0.7 (estimated from Fellström et al 2017). Calculations were performed in ADDPLAN-DF using the candidate models as described in the statistical analysis section.

The definitive sample size for Part 2 will be calculated at the interim analysis if non-futility is declared at the end of treatment in Part 1, and will be chosen to be in the range of 48 to 100 randomized patients (i.e. to aim for 40 – 85 patients completing 90 days of treatment in Part 2 of the study). Conditional on non-futility at the interim analysis in Part 1, the sample size for Part 2 will be based upon the number of patients required to provide sufficient information for primary analysis combining data from Part 1 and Part 2. Detailed information on the sample size calculation is provided in the DMC charter.

11.8 Power for analysis of key secondary variables

Not assessed.

11.9 Interim analyses

In the interim analysis at the end of Part 1 (see Section 3.5) the focus will be on the results of the MCP step together with the estimate of the treatment effect at 90 days derived from the MMRM model. This procedure creates six contrast tests with weights derived from the pre-specified candidate models. The null hypothesis of no dose response relationship will be rejected if the maximum contrast test statistic is greater than the critical value (representing the multiplicity adjusted critical value for a one-sided significance level of 0.1).

The Mod step will be implemented to determine which of the candidate models is likely to represent the best fit to the data. Using the estimated reduction of UPCR on LNP023 200mg vs placebo from the sigmoid Emax model and the maximum of the estimate of the standard deviation (on the log scale) observed for UPCR in Part 1 or 0.5, the sample size and allocation of patients to dose groups in Part 2 will be determined.

A further interim analysis will be performed with timing defined according to Section 3.5 and using the analysis methods outlined in Section 11. This IA2 will consider the pooled data from Part 1 and Part 2 of the study (up to Day 90), the safety follow-up data from Part 1 and Part 2 patients that consented to receive treatment as per protocol version 03 or earlier (up to Day 180), and any additional data of patients in Part 2 that consented to receive randomized treatment as per protocol version 04. Selected efficacy and safety analyses may be done in an interim analysis once the last patient has completed treatment (Day 180) in Part 2 to support future development.

At each interim analysis, longitudinal PK/PD data may be modeled in order to assess the exposure-response relationship, as described in Section 11.5.4.

See Section 3.5 for more information on the interim analysis and further details will be included in the DMC charter.

12 Ethical considerations

12.1 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 Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 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, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. 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.

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group 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.

13 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 subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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.

13.1 Protocol Amendments

Any change 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.

Amendments that are intended to eliminate an apparent immediate hazard to subjects 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

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[redacted]

15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	ALT or AST > 8 × ULN 5 x ULN < ALT/AST ≤ 8 x ULN 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	ALP > 2 × ULN (in the absence of known bone pathology)
Others	Any clinical event of jaundice (or equivalent term) Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN*	If confirmed, consider interruption or discontinuation of study drug If elevation persists for more than 2 weeks, discontinue the study drug Establish causality Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation*	Repeat liver chemistry tests within 48-72 hours If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality Complete CRFs per liver event guidance*
Any AE potentially indicative of liver toxicity*	Consider study treatment interruption or discontinuation Hospitalize if clinically appropriate Complete CRFs per liver event guidance*

*Liver event guidance for CRF completion is available in the Site Operations Manual

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease	Ceruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin