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LNP023

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

Statistical Analysis Plan (SAP)

Author(s):	[redacted] Trial Statistician(s)
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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
27-June-2018	Prior to DB lock	Creation of initial version	N/A - First version	NA
20-Dec-2018	Prior to DB lock	Protocol Amendment v03	Assessment schedule updates	6.1.3, ,6.2.1
			Sensitivity analysis for primary endpoint was shifted under Secondary analysis	6.1.3.3
			Sensitivity analysis for UACR was added	6.2.3.1
			Clarifications throughout SAP document	
29-Oct-2019	Prior to DB lock	Protocol Amendment v04	Added one secondary objective for Part 2 of the study assessing the effects of LNP023 on renal function up to 180 days of treatment	1.3
			Updated FIR Section after finalizing FIR deck documents	2
			Details on further IA after the last patient has completed treatment in Part 2	3
			List of outputs added for IA2	
			General considerations section added	4
			Analysis sets definitions updated as per Protocol Amendment v04	5
			Updated analysis sets and removed T1/2 parameter from analysis	6, 6.1
			Dose proportionality/linearity assessment for PK parameters added	6.3
			Clarifications on analysis set and notation for primary MMRM model updated	7, 7.1.3.2, 7.1.3.2
			Replaced statistical analysis model for Hematuria with shift tables from baseline	7.2.2
			Updated outputs presentation, based on updated analysis sets definitions	7.2
			Physical examination section added	8.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Updated graphical presentation of safety data	8.3
			PK/PD	
			Pharmacometric modeling added for PK/PD relationship	9
			Analysis sets for biomarker data updated	10
			Specification on biomarkers normalized to urine creatinine levels added	
			Biomarkers Table 10 updated	
			Appendix to list the adverse events of special interest and rescue medication ATC codes added	13
20-Nov-2020	Prior to IA2 DB lock	Protocol Amendment v06	Renamed “rescue medication” to “use of corticosteroid or immunosuppressant therapy (CS/IS)”	Throughout document
			Added PD codes table	5
			General updates and clarifications based on Protocol Amendment v05	Throughout document
			Added formula to calculate the true 24h parameters	7.2.1
			Vaccination analysis added	8.2
			Clarification on vital signs and ECG evaluation ranges added	8.2
			AEoSI definitions in eCRS clarification	8.2
			Updated Biomarkers table	Table 10-1
			Added considerations of analyses section due to COVID-19	11
			Added ATC codes for Prohibited medication and for “use of corticosteroid or immunosuppressant therapy”	13
			Updated analysis to show 80%CI instead of 90% (except for PK analyses)	Throughout document
			Added information in regards adjusted exposure adverse events	8.2
02-Feb-2021	Prior to IA2 DBL lock	Updates requested	Update Baseline definition	Throughout document

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Included information of missing data for IA2	3
			Removed study futility assessment table as it is no longer applicable	2
			Added remapping rule	1.4.1
			Added output for heart rate and removed shift table for hematuria in FIR	2
			Changed the number of parametric bootstrap simulations and added specification on the percentages of times where ED90 could not be estimated	7.1.3
			Updated formulas in regards the CI of exposure adjusted rates	8.2
			Included information in regards the loess regression curve used for PK/PD and PK/biomarker plots	9
02-Aug-2021	Prior to DBL	Updates to align with IA2 changes	Added Day 30 for urine variables	6.1
			Clarify the graphical methods for endpoints	7.1.3, 7.1.3.2
			Added Day 135 for eGFR and Serum creatinine	7.2.1
			Added MMRM models for FAS2 only for all secondary endpoints	7.2.3
			Added MCP-Mod for UPR FMV as supportive analyses	
			Vaccination summary table updated	8.2
			Specifications on the clinical laboratory evaluations in regards the LL and UL	
			Added pregnancy data listing	
			Updated ATC codes for prohibited concomitant medication and corticosteroid or immunosuppressant therapy	13

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AE	Adverse Event
ANOVA	Analysis of Variance
AR	Autoregressive
AUC	Area Under the Curve
b.i.d	Twice Daily
BMI	Body Mass Index
CV	Coefficient of Variation
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLr	Renal Plasma Clearance
CSR	Clinical Study Report
DBL	Database Lock
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
[redacted]	[redacted]
FAS	Full Analysis Set
FAS1	Full Analysis Set 1
FAS2	Full Analysis Set 2
[redacted]	[redacted]
FIR	First Interpretable Results
FMV	First Morning Void
IA	Interim Analysis
IA1	Interim Analysis 1
IA2	Interim Analysis 2
LLOQ	Lower Limit of Quantification
MAR	Missing at Random
MCP-Mod	Multiple Comparison Procedure and Modelling
MMRM	Mixed Model of Repeated Measures
[redacted]	[redacted]
PD	Pharmacodynamic
PD	Protocol Deviation
PDT	Programming Deliverables Tracker
PK	Pharmacokinetic
PK	Pharmacokinetic Analysis Set
PK1	Pharmacokinetic Analysis Set 1
PK2	Pharmacokinetic Analysis Set 2

PT	Preferred Term
Q1	25% Quantile
Q3	75% Quantile
RAP	Report Analysis Plan
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAF1	Safety Analysis Set 1
SAF2	Safety Analysis Set 2
SAP	Statistical Analysis Plan
SCR	Screening Analysis Set
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TFL	Tables/Figures/Listings
UA	Urine Albumin
UACR	Urine Albumin to Creatinine Ratio
ULOQ	Upper Limit of Quantification
UP	Urine Protein
UPCR	Urine Protein to Creatinine Ratio

1 Introduction

1.1 Scope of document

The Report Analysis Plan (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"*CLNP023X2203"*** as well as for the Interim Analysis**.**

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol, where among them are the interim analyses at the end of Part 1 and Part 2, any additional interim analyses needed for safety during Part 2 and the full analysis after database lock.

1.2 Study reference documentation

Amendment study protocol (v06) is available at the time of finalization of the SAP.

1.3 Study objectives

1.3.1. Primary objective(s)

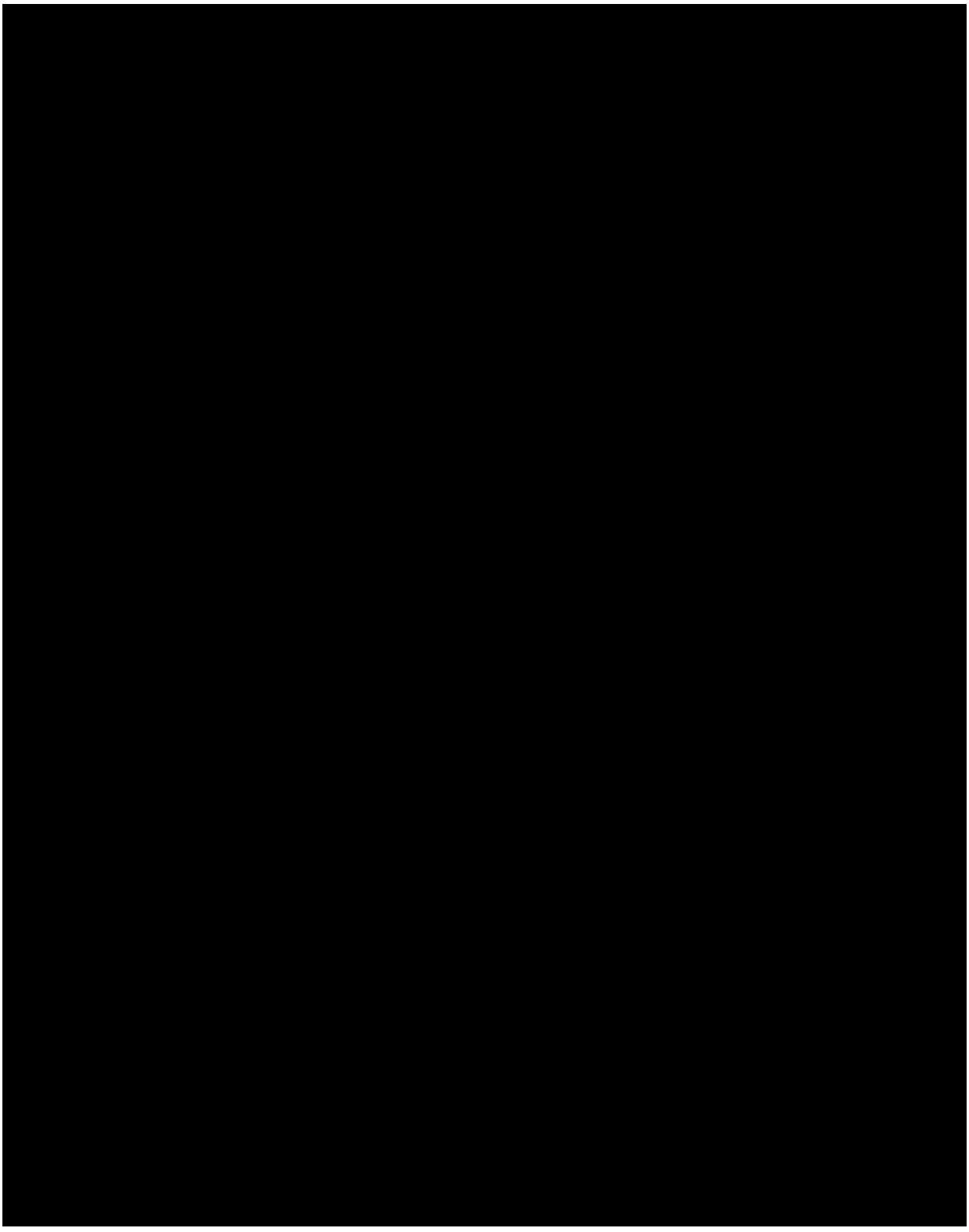
Primary objective(s)	Endpoints related to primary objectives
• To evaluate the dose response relationship of LNP023 on the reduction in proteinuria versus placebo after 90 days of treatment	• The primary variable for the statistical analysis is the ratio to baseline of urine protein to creatinine concentration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

1.3.2. Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objectives
• 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 Part 2 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
• 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 (CKP-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)

[redacted]



1.4 Study design and treatment

This is a multicenter, 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 (the run-in phase can be extended to minimize patient risk of visit sites during the COVID-19 pandemic), a 90 days treatment phase in Part 1; a 180 days treatment phase in Part 2 and a 90 days follow-up phase, for both Parts 1 and 2. All baseline safety evaluation results must be available prior to dosing. Drug administration and treatment period will start on Day 1.

Design of Part 1:

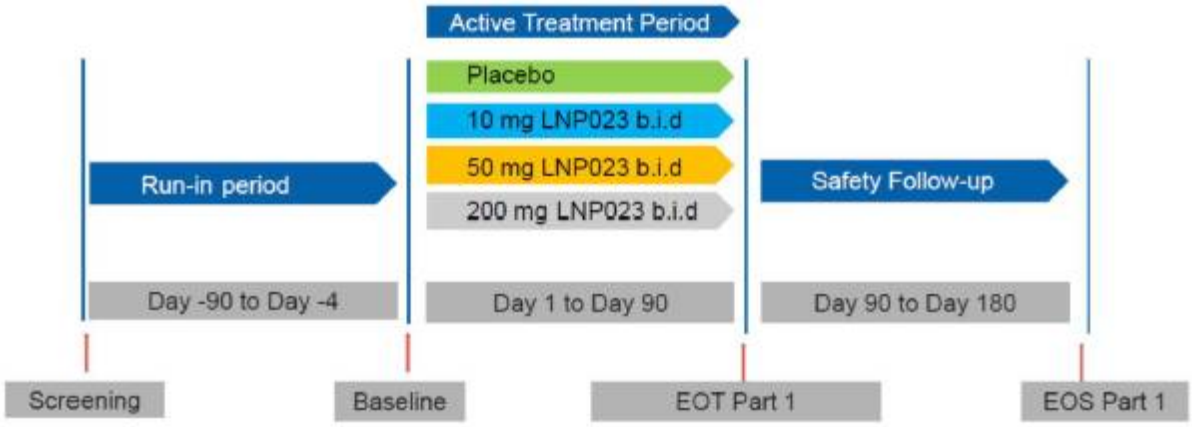
Approximately forty-eight (48) patients will be enrolled in Part 1 to allow for 40 patients to complete this part of the study. These patients will be randomized to one of four treatment groups as follows, with study treatment administered in all twice daily (b.i.d):

- 14 patients to placebo,
- 10 patients to LNP023 10 mg,
- 10 patients to LNP023 50 mg and,
- 14 patients to LNP023 200 mg

The patients who have been randomized to Part 1 will not be able to participate in Part 2 of the study.

Figure 1-1 depicts the study design for Part 1 and the study duration for patients will be maximum 270 days.

Figure 1-1: Study Design for Part 1



Design of Part 2:

An interim analysis (IA) 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 IA section (Section 3).

The design and doses tested for Part 2 will be determined according to pre-specified rules, defined in full in this SAP and Data Monitoring Committee (DMC) charter.

- a decision will be made on which dose (either 25 mg or 100 mg b.i.d.) is to be added in Part 2.

- a sample size re-estimation will be performed to determine the number of patients to be randomized in Part 2.

The sample size for Part 2 will be chosen to be in the range of 48 to 100 additional patients approximately (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 IA of 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 and a similar study design as for Part 1 will be also employed for Part 2 (Figure 1-2).
Two scenarios will be considered:

Scenario 1: placebo, 10mg, 50mg, 100mg and 200mg b.i.d.

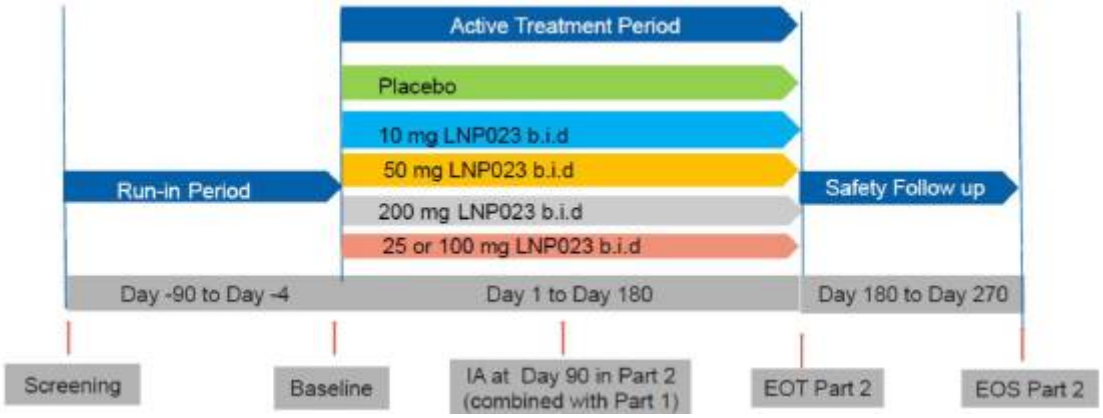
Scenario 2: placebo, 10mg, 25mg, 50mg and 200mg b.i.d.

- Scenario 1, using an additional 100mg dose, was chosen by the DMC after IA1.

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.

Patients in Part 2 will be allocated across the five treatment groups. The randomization ratio will be chosen to aim for an approximately equal allocation of patients to treatment groups across the whole study (Parts 1 and 2 combined).

Figure 1-2: Study Design for Part 2



1.4.1 Remapping rule

Subjects who received treatment as per protocol version 03 or earlier, but were assigned to an end of study day as per protocol version v04 and later (i.e., Day 270, Part 2), their end of study day will be remapped using the following rule: if the actual day of visit occurred is closer to the

planned day of end of study (i.e., Day 180, Part 1), then the planned day of end of study will be remapped to the end of study of Part 1, i.e. Day 180.

2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

Study outputs required to be created at the time of the FIR for interim and final analysis will be highlighted in Tables/Figures/Listings (TFL) shells document and marked as "Key" in the Programming Deliverables Tracker (PDT) output list.

FIR will focus on the following analyses for the final analysis:

- Subject disposition
- Demographics and baseline characteristics. Demographics and baseline characteristics include, but not limited to:
    - Age, Sex, Race, Weight, Height, BMI, Stratification factor (Asian/Non-Asian). The baseline characteristics table will include, among others, UPCR from 24hr urine collections (summary statistics as continuous variable and, by < 200 mg/mmol and ≥ 200 mg/mmol group) and eGFR (summary statistics as continuous variable and, by <60 mL/min/1.73m^2 and ≥ 60 mL/min/1.73m^2 group).
- Safety results
    - Number and percentage of subjects with adverse events (AEs)by body system organ class (SOC) and preferred term (PT) with a breakdown by treatment during the treatment period – Parts 1 and 2 to Day 90
    - Number and percentage of subjects with AEs by body system organ class (SOC) and preferred term (PT) with a breakdown by treatment during the treatment period – Part 2 patients on 180 days of treatment
    - Summary table of exposure adjusted treatment emergent AEs – Part 1 and Part 2
    - Number and percentage of subjects with treatment emergent serious AEs (SAEs), regardless of study drug relationship, by primary SOC and PT, with a breakdown by treatment – Parts 1 and 2 to Day 90
    - Number and percentage of subjects with treatment emergent SAEs, regardless of study drug relationship, by primary SOC and PT, with a breakdown by treatment – Part 2 patients on 180 days of treatment
    - Listing of SAEs and a listing of all AEs
    - Arithmetic mean (SD) profiles of hematology parameters over time by treatment group – Parts 1 and 2 to Day 90
    - Arithmetic mean (SD) profiles of hematology parameters over time by treatment group – Part 2 patients on 180 days of treatment

- Overlaying individual time profiles (spaghetti plots) of hematology parameters by time and treatment group - Parts 1 and 2 to Day 90
- Overlaying individual time profiles (spaghetti plots) of hematology parameters by time and treatment group – Part 2 patients on 180 days of treatment
- Arithmetic mean (SD) profiles of reproductive hormone levels over time, by gender and treatment group – Parts 1 and 2 to Day 90
- Arithmetic mean (SD) profiles of reproductive hormone levels over time, by gender and treatment group – Part 2 patients on 180 days of treatment
- Arithmetic mean (SD) profiles of thyroid hormones over time by treatment group – Parts 1 and 2 to Day 90
- Arithmetic mean (SD) profiles of thyroid hormones over time by treatment group – Part 2 patients on 180 days of treatment
- Arithmetic mean (SD) profiles of blood pressure over time by treatment group – Parts 1 and 2 to Day 90
- Arithmetic mean (SD) profiles of blood pressure over time by treatment group – Part 2 patients on 180 days of treatment
- Overlaying individual time profiles (spaghetti plots) of vital signs by time and treatment group - Parts 1 and 2 to Day 90
- Overlaying individual time profiles (spaghetti plots) of vital signs by time and treatment group – Part 2 patients on 180 days of treatment
- Arithmetic mean (SD) of QTcF interval over time by treatment group – Parts 1 2 to Day 90
- Arithmetic mean (SD) of QTcF interval over time– Part 2 patients on 180 days of treatment
- Arithmetic mean (SD) profiles of heart rate over time by treatment group – Parts 1 and 2 to Day 90
- Arithmetic mean (SD) profiles of heart rate over time by treatment group – Part 2 patients on 180 days of treatment
- Number and percentage of subjects with ECG abnormalities, by treatment group and time point – Parts 1 and 2 to Day 90
- Number and percentage of subjects with ECG abnormalities, by treatment group and time point – Part 2 patients on 180 days of treatment
- Number and percentage of subjects with newly occurring liver enzyme abnormalities, by treatment group and time point – Parts 1 and 2 to Day 90
- Number and percentage of subjects with newly occurring liver enzyme abnormalities, by treatment group and time point – Part 2 patients on 180 days of treatment

- Pharmacodynamic (PD) analyses include, but are not limited to:

- Table of model estimated geometric means and their ratios (MMRM) for the UPCR (24h urine collection) at Day 90 – Parts 1 and 2
- MCP-Mod analysis of the ratio to baseline in UPCR (g/mol) (from 24 hour urine collection) considering pooled data from Part 1 and Part 2 of the study (up to Day 90)
- Adjusted geometric mean (80% CI) of ratio to placebo (of ratio to baseline) for UPCR (24h urine collection) by LNP023 dose over time – Parts 1 and 2 to Day 90
- Table of model estimated geometric means and their ratios (MMRM) for the UPCR (24h urine collection) - Part 2 patients on 180 days of treatment
- Adjusted geometric mean (80% CI) of ratio to baseline for UPCR (24h urine collection) by LNP023 dose over time - Part 2 patients on 180 days of treatment
- Adjusted geometric mean (80% CI) of ratio to placebo (of ratio to baseline) for UPCR (24h urine collection) by LNP023 dose over time - Part 2 patients on 180 days of treatment

- Key secondary parameters (eGFR, UPCR (from first morning void [FMV]))
  - Table of model estimated geometric means and their ratios (MMRM) for UPCR (g/mol) (from first morning void) - Part 2 including patients on 180 days of treatment
  - Adjusted geometric mean (80% CI) of ratio to baseline for UPCR (g/mol) (from first morning void) by LNP023 dose over time – dose over time to safety follow-up period - Part 2 patients on 180 days of treatment
  - Table of model estimated arithmetic means and their differences (MMRM) for eGFR – Part 2 patients on 180 days of treatment
  - Plot of the model adjusted arithmetic mean (80% CI) change from baseline of eGFR – Part 2 patients on 180 days of treatment

[redacted]

- Biomarkers: [redacted] sC5b-9, Bb, [redacted]

3 Interim analyses

An IA 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 IA is to provide preliminary evidence of the 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 IA:

- Step 1. Futility Assessment
- Step 2: Dose selection to be studied in Part 2.
- Step 3. Sample size re-estimation for Part 2: The total sample size will be calculated which provides sufficient information for primary analysis.

At the time of final analysis all data from Part 1 and Part 2 up to day 90 of the study 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 IA results will become the final analysis results.

The IA will be undertaken based on the MCP-Mod procedure, described in Section 7.1.3. The MCP step, will test for the existence of a dose-response relationship via multiple contrast tests. The Mod step for the IA will use the Bayesian sigmoid Emax model to estimate the treatment effect.
During the IA, the following conditions will be considered:

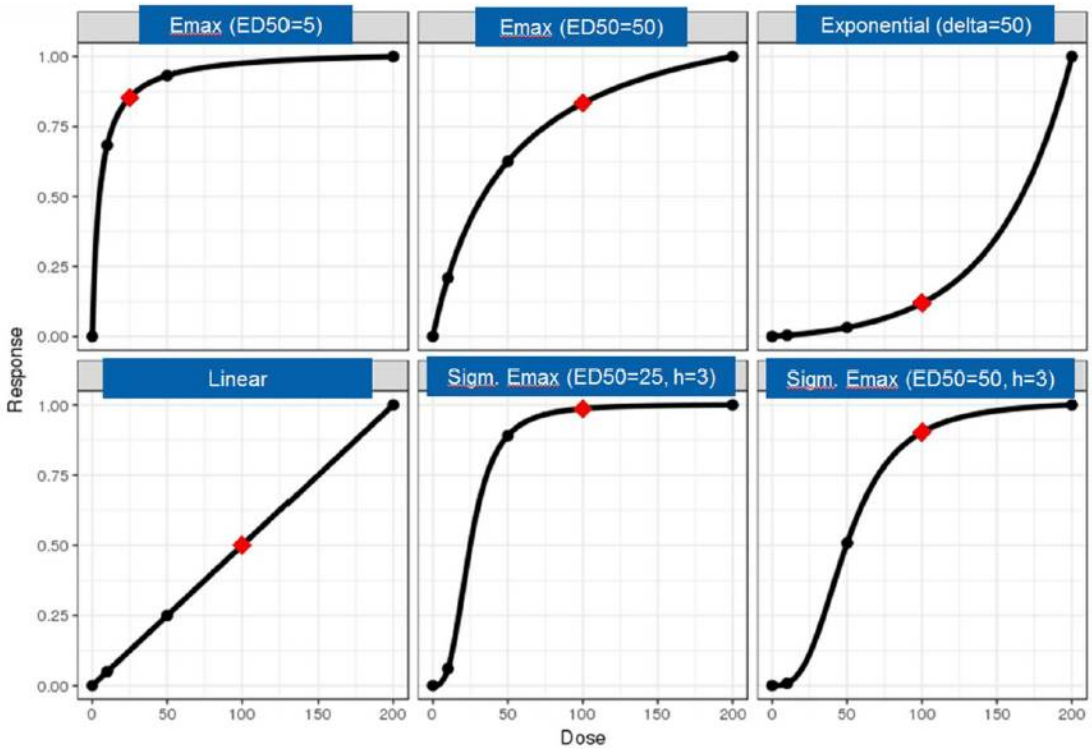
1. **Study futility:** if reduction in UPCR for LNP023 200 mg vs placebo is less than 20% or the one-sided p-value for the multiple contrast test is ≥ 0.1, then stop the study.

- The MCP-Mod procedure creates six contrast tests with weights derived from the pre-specified monotonic candidate models, as shown in Table 7-1. If the minimum of the multiplicity adjusted one-sided p-values is less than 0.1, the null hypothesis of no dose response relationship will be rejected.
- The maximum reduction (this will relate to the highest dose group [i.e. LNP023 200mg] since this is a model based estimate) in UPCR will be estimated based on the Bayesian sigmoid Emax model fit. The posterior median (on the log scale) for the difference between LNP023 200 mg and placebo will be calculated based on this model and then the results will be back-transformed to provide the percent (%) reduction on LNP023 200 mg vs placebo.

2. **Part 2 Dose groups:**

- In the absence of safety concerns, a recommendation will be made regarding which of the two possible additional dose groups (25 mg or 100 mg bid) should be included in Part 2. The chosen dose will be the most likely dose to increase the precision of the ED90 estimate of the proteinuria-dose response curve.
- The Mod step (from MCP-Mod) will determine which of the candidate models is likely to represent the best fit to the data. The ordering of the models from the multiple contrasts test will be used to choose the model based on which dose selection will be made. Based on this, Figure 3-1 provides a guidance for the decision rule for recommendation for dose selection for Part 2 of the trial. For example, if the contrast for the sigmoid Emax model with ED50=5 has the largest t-statistic, the 25 mg dose is introduced in Part 2 of the study. If any of the other contrasts has the maximum t-statistic, then the 100 mg dose is introduced.

Figure 3-1: Candidate model shapes and dose selection algorithm



3. **Sample size re-estimation for Part 2.**

- Using the estimated reduction of UPCR on LNP023 200 mg vs placebo from the Bayesian sigmoid Emax model, and the maximum of the estimate of the variability (SD) observed for log(UPCR) in Part 1 or 0.5, the total sample size will be calculated in order to provide at least 80% power assuming a 1-sided alpha of 5% for the final analysis (using MCP-Mod). The residual variance estimate at Day 90 will be used to obtain the estimate of variability observed for log(UPCR) in Part 1
- Conditional on non-futility at the IA, the sample size in Part 2 will be determined based on this calculation, and will be chosen to be in the range of 48-100 randomized patients (i.e. to aim for 40-85 patients completing 90 days of treatment in Part 2). The randomization allocation of patients to treatment group will be calculated to maintain approximate balance across treatment groups at the end of the trial.

The following efficacy information will be provided in an IA report to the DMC for their review at the time of first IA (further detail on the Safety-related information to be presented in the IA report in Part 1 such as for instance all AEs in double-blind period, AEs leading to study drug discontinuation, SAEs is provided in Section 8 of the DMC charter):

- Statistical analysis of UPCR using MCP-Mod, including figure of reductions in UPCR by dose (one figure with a 2-sided 80% CI and one with a 2-sided 90% CI)

- Summary of assessment of futility criteria (including six contrast tests and the estimate of the maximum reduction in UPCR between LNP023 and Placebo based on the Bayesian sigmoid Emax model).
- Proposal for sample size re-estimation for Part 2 – the assumptions used for the sample size calculation, proposed sample size for Part 2, total sample size, and the resulting power (conditional on non-futility) will be presented.
- Secondary variables to assess the effect of LNP023 on renal function (including but not limited to): change from baseline in eGFR, serum creatinine, hematuria, 24h-UP, and UPCR (from first morning void). These variables will be analyzed as defined in Section 7.2. Estimates of the differences between each dose of LNP023 and placebo will be provided, together with 80% confidence intervals (CI) for all endpoints apart from hematuria. Plots over time will be produced. Shift table of hematuria levels from baseline during treatment will be provided.

On top of the analyses defined above for the IA report to the DMC, the following key biomarkers will be analyzed at the time of IA to confirm and characterize target engagement:

- sC5b-9 and Bb levels in plasma, serum complement activity measured by Wieslab

[redacted]

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, using the analysis methods outlined in Section 7. 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 or higher. This second interim analysis will constitute the final analysis of the primary endpoint (which is based on all data from Part 1 and Part 2 up to and including the Day 90 visit); this will be considered final and will not be rerun at the time of the final database lock (DBL). A third interim analysis may be performed once the last patient has completed Day 180 in Part 2 to support future development.

At each IA, longitudinal PK/PD data may be modeled in order to assess the exposure-response relationship, as described in Section 9.

The following analyses for the IA2 analysis, will be performed:

- Safety results:

- Number and percentage of subjects with adverse events by body system organ class (SOC) with a breakdown by treatment during the treatment period.
- Number and percentage of subjects with adverse events by preferred term (PT) with a breakdown by treatment during the treatment period.
- Arithmetic mean (SD) profiles of reproductive hormone levels over time, by gender
- Arithmetic mean (SD) profiles of thyroid hormones over time
- Arithmetic mean (SD) of change from baseline over time in QTcF interval and vital signs by treatment group

- Pharmacokinetics (PK) results in plasma and urine:
  - Summary statistics for PK parameters in plasma (Cmax, AUC and [redacted]) and urine (Ae and CLr)

- Pharmacodynamic (PD) analyses include, but are not limited to:
  - Table of model estimated geometric means and their ratios (MMRM) for the UPCR (24h urine collection and FMV) from baseline at Day 90
  - Adjusted geometric mean (80% CI) of ratio to placebo (of ratio to baseline) for UPCR (24h urine collection and FMV) by LNP023 dose over time
  - MCP-Mod results for UPCR (24h urine collection and FMV):
    - MCP step: Multiple Contrasts Test table
    - Mod step:
      - Estimated geometric mean UPCR ratio to baseline and dose response relationship at Day 90.
      - Estimated geometric mean UPCR ratio to placebo (of ratio to baseline) and dose response relationship at Day 90

- Key secondary parameters (eGFR, UACR):
  - Table of model estimated arithmetic means and their differences (MMRM) for eGFR
  - Plots of model adjusted arithmetic mean (80% CI) change from baseline of eGFR
  - Table of model estimated geometric means and their ratios (MMRM) for UACR
  - Plots of model adjusted geometric mean ratio (80% CI) of UACR

[redacted]

[redacted]

- Biomarkers:
  - sC5b-9 and Bb levels in plasma, serum complement activity [redacted]

4 General Considerations

Throughout this SAP, the log transformation used refers to the natural log (base on e).

5 Statistical methods: Analysis sets

At the time of IA2, all data from Part 1 and Part 2 of the study will be pooled and analyzed.

The Screening set (SCR) will include all subjects screened during the study.

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 (i.e. allowing for 90 days of treatment) 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 or higher (i.e. allowing for 180 days of treatment).
Mis-randomized patients, that is, patients who were incorrectly randomized and did not receive the 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 randomized 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 (i.e. allowing for 90 days of treatment) 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 or higher (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 with relevant impact on PK data. For the PK analysis set, 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 (i.e. allowing for 90 days of treatment) or earlier.
The PK2 analysis set will be likewise derived for Part 2 that consented to receive randomized treatment as per protocol version 04 or higher (i.e. allowing for 180 days of treatment).

The analysis sets and protocol deviation codes are related as follows:

Table 5-1: Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK, PK1 and PK2 analysis set
OTH20	*Site has been closed down for GCP reasons*	Yes
Subjects are excluded from FAS analysis in case of these PDs:		Exclude subject from FAS, FAS1 and FAS2 analysis set
OTH20	*Site has been closed down for GCP reasons*	Yes
Subjects are excluded from SAF analysis in case of these PDs:		Exclude subject from SAF, SAF1 and SAF2 analysis set
OTH20	*Site has been closed down for GCP reasons*	Yes

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

6 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK set (up to Day 90) and PK2 only, will be included in the PK data analysis.

6.1 Variables

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, Tmax, AUClast, AUCtau and Cmin at Day 30.
  - Ctrough samples at Day 8, 15, 60, 90 (plus Day 135 and Day 180 for PK2 set))
  - Other pharmacokinetic parameters may be calculated as appropriate.
    [redacted]
- Urine
  - Non-compartmental parameters, including but not limited to total cumulative urinary excretion (Ae) and renal plasma clearance (CLr) at Day 30 and Day 90

(+/- 1 day) for PK (up to Day 90) and PK2 sets. Day 180 (for PK2 set only) may be also used.

6.2 Descriptive analyses

LNP023 plasma concentration data will be listed by treatment, subject and visit/sampling time point. Descriptive statistics will be provided by treatment and visit/sampling time point, for the PK set (up to Day 90) and for PK2 separately, including the frequency (n, %) of concentrations below the Lower Limit of Quantification (LLOQ) which will be reported as zero; these will be distinguished from values missing. Summary statistics will include mean (arithmetic and geometric), Standard Deviation (SD), Coefficient of Variation (CV) (arithmetic and geometric), median, minimum, and maximum. Since Tmax is generally evaluated by a nonparametric method, only median, minimum, and maximum will be reported. 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 as well as for Tmax.

Pharmacokinetic parameters will be listed by treatment, visit/sampling time point, and subject and summarized by treatment, for the PK set (up to Day 90) and for PK2 separately, with descriptive statistics as described above. Concentrations below the lower limit of quantification (LLOQ) or missing will be indicated in the data listings.

Graphical methods will be employed to show mean (SD) and individual concentration-time profiles (in linear and log-linear scale) for PK set (up to Day 90) and PK2 set separately.

6.3 Statistical model, assumptions and hypotheses

Dose proportionality/linearity

Dose proportionality assessment will be conducted for PK parameters such as Cmax and AUClast, for PK set (up to Day 90) and PK2 set separately.

PK parameters will be log transformed and analyzed using a power model:

$$\ln(\text{PK parameter}) = \mu + \beta \times \ln(\text{Dose})$$

The estimate of the slope β and the associated two-sided 90% confidence interval (CI) will be obtained based on the log-transformed observations, then "back-transformed" and presented on the original scale. Model goodness-of-fit will be explored by visually examining residuals. In case of evidence of lack-of-fit, alternative models will be explored, such as an ANOVA with dose as a classification factor.

PK dose proportionality will be concluded across the whole dose range if the 90% CI (β_L, β_U) for the slope β is completely contained within a pre-specified critical region (b_L, b_U), where the two limits b_L, b_U are derived as follows:

$$b_L = 1 + \ln(\theta_L)/\ln(r) \text{ and } b_U = 1 + \ln(\theta_U)/\ln(r),$$

with r=ratio of highest to lowest dose studied (highest dose/lowest dose), θ_L=0.8, θ_U=1.25 being the standard bioequivalence limits.

7 Statistical methods for Efficacy/Pharmacodynamic (PD) parameters

All subjects within the FAS (up to Day 90) will be included in all efficacy analysis as well as the following data analysis, unless otherwise stated. At the time of the IA2, all data from Part 1 and Part 2 of the study up to day 90 will be pooled and analyzed for the primary analysis.

Efficacy analyses performed at IA2 up to study Day 90 for the following primary and secondary endpoints: UPCR obtained from 24h urine (primary endpoint), Estimated glomerular filtration rate, Serum creatinine, 24h-UP, 24h-UA, UACR, UPCR from first morning void will be considered final. It is not planned to rerun them at the time of the final DBL. However, discrepancies in data between the IA2 and final DBL will be assessed, and if considered of impact, the respective efficacy analysis may be re-run on the final data representing a sensitivity analysis to that performed at the IA2. All discrepancies on these endpoints will be provided as listing.

7.1 Primary objective

The primary aim of this study is to evaluate the dose response relationship of LNP023 on the reduction in proteinuria versus placebo after 90 days of treatment.

7.1.1 Variables

The primary variable is the log ratio to baseline of urine protein to creatinine concentration ratio (UPCR), with the Day 90 (Visit 160) assessment being of primary interest.

For the primary analysis the UPCR measurements will be obtained from the 24h urine collection.

Baseline is defined to be the last measurement prior to the start of study drug administration.

7.1.2 Descriptive analyses

UPCR (raw and log ratio to baseline) will be listed by treatment group, patient and visit/time and descriptive statistics will be provided by treatment and visit/time. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), lower quartile (25% quantile) Q1, median, upper quartile (75% quantile) Q3, minimum and maximum as appropriate.

7.1.3 Statistical model, assumptions and hypotheses

The primary endpoint will be analyzed using a two-stage approach:

1. A change from baseline in log transformed UPCR at multiple timepoints will be analyzed using a Mixed Model of Repeated Measures (MMRM) model, as described below.
2. A global hypothesis will be tested for the day 90 timepoint, using the generalized Multiple Comparison Procedure and Modelling (MCP-Mod) approach described by Bretz et al 2005 and Pinheiro et al 2014. MCP-Mod will be applied on the dose estimates and variance-covariance matrix obtained from the MMRM model. MCP-Mod has two steps. In the MCP step, the existence of a dose-response trend is assessed based on

multiple contrasts test. In the Mod step the dose-response curve and the ED90 will be estimated based on model averaging techniques. Further details are provided below.

In general, the analysis will have the following steps:

a) Fit the MMRM model

b) Perform the MCP test based on the dose estimates and variance-covariance matrix from the MMRM. This step will give us information regarding the contrast values and contrast correlation matrix (per candidate model and dose) and t-tests with corresponding p-values for each candidate model.

c) Parametric bootstrap model averaging will be used to estimate the mean dose-response curve by dose and mean predicted difference between each LNP023 dose and placebo.

For all efficacy analyses, a one-sided type I error rate of 10% (equivalent to a two-sided type I error of 20%) will be employed. Correspondingly, two-sided 80% confidence intervals (CI) will be presented.

Mixed Model of Repeated Measures

Firstly, the log ratio to baseline in UPCR at multiple timepoints (day 30 and 90) will be analyzed using a Mixed Model of Repeated Measures (MMRM) model. This model will have treatment, timepoint (as study day to start of study treatment), study part (Part 1 or Part 2) and ancestry (Asian/non-Asian) as fixed effects, treatment*timepoint and timepoint*log(baseline UPCR) as interaction terms and baseline log UPCR as fixed covariate. The study part fixed effect will be only included at the final analysis and not during the planned IA at the end of treatment in Part 1. Timepoint will also be included as a repeated factor with an unstructured residual variance-covariance matrix to allow adjustment for correlations between timepoints within subject; if not possible, other appropriate covariance structures will be explored such as Autoregressive (AR(1)) and Compound symmetry.

The mathematical formula of this MMRM is given as follows:

$$\underline{y} = \beta_0 + \underline{\beta_1} treatment + \beta_2 timepoint + \beta_3 studypart + \beta_4 ancestry + \underline{\beta_5} treatment * timepoint + \beta_6 timepoint * \log(base\ UPCR) + \beta_7 \log(base\ UPCR) + \underline{\varepsilon}$$

where,

- $\underline{y}$ is vector of the log ratio to baseline in UPCR
- β_0 the fixed effect intercept
- $\underline{\beta_1}$ and $\underline{\beta_5}$ the vector coefficients of the corresponding parameters and β_2, β_3, β_4,β_6 and β_7 the coefficients of the corresponding parameters.
- $\underline{\varepsilon}$ the vector of residuals where $\underline{\varepsilon} \sim N(0, \boldsymbol{R})$ with **R** is a 2×2 diagonal covariance matrix.

Model estimated means and their difference versus placebo (and its 80% CI) will be calculated for each dose level. These will be back-transformed to the original scale to give a geometric mean ratio (and its 80% CI) between each dose and placebo.

Graphical methods will be used to present the model estimated means of ratio to baseline and ratio to placebo (of the ratio to baseline) along with CIs.

Multiple Comparison Procedure and Modelling

Secondly, the existence of a dose-response relationship will be assessed using the MCP-Mod approach via multiple contrast tests based on the log transformed model estimated means at Day 90 and covariance matrix obtained from the MMRM.

The following global hypothesis will be tested for the day 90 timepoint at the one-sided 10% significance level, to assess whether LNP023 is different from placebo (where H_o assumes no dose-response relationship and H_1 that a dose response relationship exists):

H_o: $c_m^T\mu = 0$ for all m in {1, …6} vs H_1 : $c_m^T\mu > 0$ for at least one m in {1, …6}

where c_m^T is the vector of optimal contrasts coefficients for the m[th] candidate dose response shape ($c_m^T\mathbf{1} = 0$) and μ is the vector of adjusted means (on the log transformed scale) for each treatment group from the analysis of primary endpoint at day 90, i.e. $\mu = \left(\mu_{placebo}, \mu_{LNP023d_1}, \dots, \mu_{LNP023d_n}\right)^T$. The H_o will be rejected if the maximum contrast test statistic is larger than the critical value (representing the multiplicity adjusted critical value for a one-sided significance level of 0.1).

The following candidate models will be used to derive contrasts:

- 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 (h) equal to 3
- Model 5: Sigmoidal emax with ED50 at 50mg and Hill parameter (h) equal to 3
- Model 6: Exponential with $\delta = 50$

Table 7-1 lists the mathematical formula corresponding to each of the above dose-response relationship models.

Table 7-1 Dose-Response Models

Model	$\boldsymbol{f(d,\theta)}$	**Guesstimates**
Linear	$E_0 + \delta d$	
Emax	$E_0 + E_{max}d/(ED_{50} + d)$	ED50
Sigmoidal Emax	$E_0 + E_{max}d^h/(ED_{50}^h + d^h)$	ED50, h
Exponential	$E_0 + E_1[\exp\left(\frac{d}{\delta}\right) - 1]$	δ

where d denotes the dose, E_0 is the placebo effect for d=0, δ denotes the scale parameter of the model and h denotes the Hill parameter.

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 the test statistics. The null hypothesis is to be rejected if the maximum of all t-statistics is larger than the derived critical value.

Parametric bootstrap model averaging from 10,000 simulations will be used to estimate the dose-response curve, the ED90 and 80% confidence intervals for each dose as follows:

1. The parametric bootstrap procedure will be performed to draw a sample of mean responses for each dose (including placebo) from the multivariate normal distribution of the estimated means from the different dose groups (including placebo) obtained from the MMRM model and associated variance-covariance matrix, described above.
2. All candidate dose-response models shown in Table 7-1 will be fitted to each simulated bootstrap resample using generalized least-squares (similar to Pinheiro et al. 2014), and the best fitting model will be selected for each resample using the gAIC criterion.
3. The estimates of the mean dose response over the dose range will be derived (all doses including placebo) for each resample using the best model for the respective resample, selected in Step 2. The difference in estimated dose response between each LNP023 dose and placebo will also be calculated and presented with the estimated ED90.
4. The above steps (1-3) will be repeated 10,000 times. The bootstrapped estimates and 80% confidence intervals will be derived based on the quantiles (median, 10^{th} and 90^{th} percentile) of the resampled distribution of the estimates generated. The percentage of times ED90 could not be estimated in the bootstrap samples will be stated. The CI for ED90 will be considered valid if the ED90 can be estimated in at least 60% of the bootstrap samples.

The MCP-Mod results for dose-response and dose estimates will be back-transformed from the log-scale after the analysis.

7.1.3.1 Handling of missing values/censoring/discontinuations

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

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). This implies that the primary analysis aims to estimate the treatment effect under the hypothetical scenario that all patients adhere to randomized treatment. Therefore, the MAR assumption implies that the UPCR measurements for patients who discontinue treatment would be similar to those from other similar patients if they had continued to take the treatment.

7.1.3.2 Supportive analysis

A supportive analysis may be performed considering the exclusion of subjects who have intercurrent events that may affect the primary analysis (for example, taking prohibited Concomitant Medications, listed in Table.), as well as under the cases with the following protocol deviations:

a. "Subject taking medication such as Gemfibrozil or Strong CYP2C8 inhibitors with 5 half-lives of the inhibitor prior to administration of LNP023" (PD code "COMD08")
b. "Subject taking P-gp substrates with narrow therapeutic index with 1 day prior to administration of LNP023" (PD code "COMD09")

As a separate supportive analysis, the following subgroup analyses will be performed for the FAS (up to Day 90):

- Baseline UPCR (24h sample) < 200mg/mmol and ≥ 200 mg/mmol

Graphical methods, such as forest plots, will be used to present the model estimated means of ratio to baseline and ratio to placebo (of the ratio to baseline), for each of the analyses.

At the final DBL, discrepancies between the primary efficacy outcome data at IA2 and at DBL will be investigated and a listing of any discrepancies by subject, timepoint, UPCR24h value at IA2 and UPCR 24h value at DBL, will be produced. Discrepancies in data between the IA2 and final DBL will be assessed and if considered of impact, the MMRM related to the primary efficacy analysis may be reproduced if required.

7.1.3.3 Sensitivity analysis

A sensitivity analysis of the ratio to baseline of UPCR (24-hour urine collection) for Part 1 and Part 2 at Day 90 will be performed, by excluding the linear model from the Mod step.

Graphical methods of the estimated geometric mean UPCR ratio to baseline and dose response relationship at Day 90 (Parts 1 and 2) and the estimated geometric mean UPCR ratio to placebo (of ratio to baseline) and dose response relationship at Day 90 (Parts 1 and 2) will be produced.

7.2 Secondary objectives

The secondary aim of the study is to assess the effect of LNP023 on renal function.

7.2.1 Variables

The secondary variables are the following:

- Log ratio to baseline in UPCR (from 24hr urine up to Day 180)
- Log ratio to baseline in UPCR (from first morning void)
- Change from baseline in eGFR
- Change from baseline in Serum Creatinine

- Hematuria
- Log ratio to baseline in 24h-UP.
- Log ratio to baseline in 24h-UA
- Log ratio to baseline in UACR

The 24h-UP and 24h-UA will be derived using the following formula:

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

Baseline is defined to be the last measurement prior to the start of study drug administration. Each secondary variable is derived from the 24h urine collections at baseline, day 30 and 90, except for the eGFR and Serum Creatinine which are derived from the blood measurements at baseline, day 1, 8, 15, 30 and 90 and UPCR and hematuria which are derived from FMV samples at baseline, day 1, 8, 15, 30, 60 and 90. For analyses on FAS2, measurements up to day 180 will be considered (additionally day 60 and 135 for eGFR and Serum Creatinine).

7.2.2 Descriptive analyses

Secondary variables (raw and change or ratio to baseline depending on the corresponding parameter) will be listed by treatment group, patient and visit/time, and descriptive statistics will be provided by treatment and visit/time, except from hematuria. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), Q1, median, Q3, minimum and maximum as appropriate. For parameters that will be analyzed as change from baseline, geometric means and CV will not be provided in the summaries.

A shift table of changes from baseline in hematuria levels will be provided, considering the following three levels: <9rbc/hpf, ≥ 9 rbc/hpf to ≤ 50 rbc/hpf and >50 rbc/hpf, for the FAS (up to Day 90) and FAS2 separately. In addition, a frequency table of hematuria levels will be also produced separately for FAS (up to Day 90) and FAS2.

7.2.3 Statistical model, assumptions and hypotheses

Secondary Variables - MMRM

For each secondary variable (apart from hematuria), a similar statistical model will be used as described for the primary variable, in Section 7.1.3. Each MMRM will have treatment, timepoint (as study day to start of study treatment), study part (Part 1 or Part 2) and ancestry (Asian/non-Asian) as fixed effects, treatment*timepoint and timepoint*baseline as interaction terms and baseline of the dependent variable as fixed covariate. Timepoint will be also included as a repeated factor with an unstructured residual covariance matrix to allow adjustment for correlations between timepoints within subject; if not possible, other appropriate covariance structures will be explored, such as Autoregressive (AR(1)) and Compound symmetry. Where log transformation is used for the dependent variables, log baseline will be used in lieu of baseline in the model covariates and the estimates will be back transformed from the log scale.

For all secondary variables (except hematuria), 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.

UPCR FMV – MMRM

As a supportive analysis, an MCP-Mod test will be also performed for the UPCR (based on FMV samples) for Parts 1 and 2 to Day 90, similar to the analysis described in Section 7.1.3.

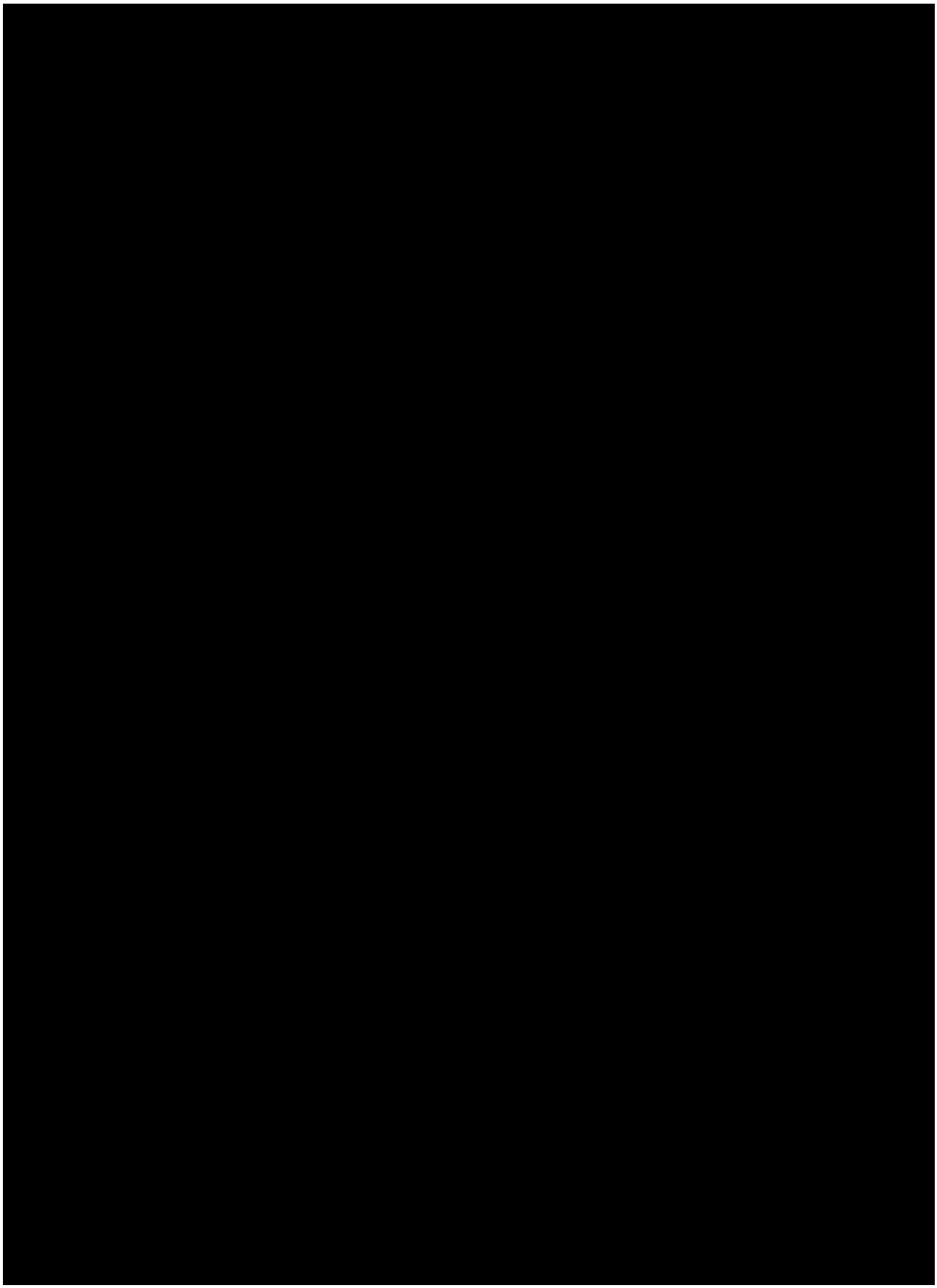
A further secondary analysis of UPCR (based on the FMV samples) after the end of treatment will be performed for FAS1 and FAS2 separately. This analysis would also follow the MMRM approach described for the primary variable but will include all UPCR measurements up to the EoS visit.

Model estimated means and their differences versus placebo (and its 80% CI) will be calculated for each dose level, for all secondary parameter MMRM analyses. These will be back transformed to the original scale to give a geometric mean ratio (and its 80% CI) between each dose and placebo. Graphical methods will be used to present the model estimated means by treatment group and time.

7.2.3.1 Sensitivity analysis

Sensitivity analyses include refitting the MMRM model used for the secondary analysis using the following data instead of the data defined in Section 7.2.1:

1. UACR obtained from the first morning void samples (baseline, day 1, 8, 15, 30, 60, 90).
2. In case a considerable number of cases with the protocol deviation “Spot urine collected not being First Morning Void” (PD code “Oth03”) are identified, a sensitivity analysis of UPCR and UACR from FMV excluding these will be considered.



[redacted]

8 Statistical methods for safety and tolerability data

Analyses of all safety data (Adverse events, vital signs, ECG intervals, laboratory measurements) produced at IA2 will be rerun after DBL as a part of the final analysis in order to account for data changes between IA2 and DBL in ongoing adverse events, laboratory abnormalities and safety laboratory evaluations.

8.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

Baseline for all variables, is defined to be the last measurement prior to the start of study drug administration.

8.2 Descriptive analyses

All subjects within the SAF (up to Day 90), SAF1 and SAF2 will be included in the safety data analysis separately, except background and demographic characteristics which will be included in the FAS data analysis.

Subject demographics

All data for demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group overall.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject, overall and for each study part separately.

The FAS will be used for these analyses.

Baseline characteristics

All data for background variables will be listed by treatment group and subject. Baseline characteristics include but are not limited to UPCR, eGFR, and Renal biopsy information (Oxford Classification). Summary statistics will be provided by treatment group overall.

Renal biopsies used to assess study inclusion will be scored according to the Oxford classification and will be summarized descriptively by providing the frequency (n, %) of patients in the following categories:

- Mesangial score: ≤0.5 (M0) or >0.5 (M1)
- Endocapillary hypercellularity: absent (E0) or present (E1)

- Segmental glomerulosclerosis: absent (S0) or present (S1)
- Tubular atrophy/interstitial fibrosis: ≤25% (T0), 26–50% (T1), or > 50% (T2)
- Cellular / fibrocellular crescents: none (C0), at least 1 (C1), in at least 25% of glomeruli (C2)

The total number of glomeruli will be also summarized separately.
UPCR and eGFR will be analyzed as continuous variables. In addition, the frequency (n, %) of patients with UPCR $<$ 200mg/mmol and $\geq$ 200 mg/mmol, and eGFR <60 mL/min/1.73m^2 and $\geq$ 60 mL/min/1.73m^2 will be provided.
The FAS will be used for these analyses.

Treatment

Treatment exposure (days) will be summarized as a continuous variable by descriptive statistics. The duration of treatment exposure (in days) is defined as the last known date the patient took the study drug – the first day the patient took the study drug + 1, regardless of any temporary treatment interruption. Treatment exposure 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.

Data for study drug administration, corticosteroid or immunosuppressant therapy (CS/IS) (as shown in Section 13) and concomitant medication and non-drug therapies will be listed by treatment group and subject.

Concomitant medications prior to randomization will be summarized by therapeutic class, PT and treatment group for the SAF. Concomitant medications after randomization will be likewise summarized for the SAF (to Day 90), SAF1 and SAF2 separately. Use of corticosteroid or immunosuppressant therapy (CS/IS) will be summarized. Significant non-drug therapies\procedures will also be summarized by ATC class and concomitant medication category and treatment group.

A summary of compliance of vaccination by vaccine type and treatment, will be tabulated.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged.

Vital signs should be within the following ranges:

- Body temperature between 35.0-37.5℃
- Systolic blood pressure between 90-160 mm Hg
- Diastolic blood pressure, 50-90 mm Hg
- Pulse rate, 40-90bpm

Summary statistics will be provided by treatment and visit/time for the SAF (up to Day 90) and for SAF1 and SAF2 separately. Summary statistics will include mean, SD, CV, Q1, median, Q3, minimum and maximum as appropriate.

To assess the effect of LNP023 on blood pressure after dosing with LNP023, blood pressure and heart rate at 1 and 2 hours post dose on Day 1, and 2 hours post dose on Day 30 expressed as change from baseline will be graphically presented by treatment, 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 evaluations

All ECG data (including but not limited to QTcF prolongation, QT interval and HR) will be listed by treatment, subject and visit/time and abnormalities will be flagged.

Summary statistics will be provided by treatment and visit/timepoint, for the SAF (up to Day 90) and for SAF1 and SAF2 separately, and the frequency of (n, %) patients with the following abnormalities will be displayed:

- QRS > 120 ms
- QRS increase from baseline > 25%
- QTcF > 500ms
- QTcF increase from baseline > 60 ms
- Resting heart rate sinus rhythm (HR) < 30 bpm
- HR decrease from baseline ≥ 25%
- HR > 130 bpm

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing will be provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time, for the SAF (up to Day 90) and for SAF1 and SAF2 separately. Summary statistics will include mean, SD, CV, Q1, median, Q3, minimum and maximum as appropriate. Values less than the Lower Limit (LL) will be imputed as $0.5 \times$LL and values greater than the Upper Limit (UL) will be imputed as $1.5 \times$UL. The number and percentage of values below the LL and above the UL will be presented. For the figures, imputed values will be displayed.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject. All information obtained on deaths will be likewise provided.

The overall incidence of treatment emergent AEs will be summarized by treatment group for the SAF (up to Day 90), SAF, SAF1 and SAF2 populations separately.

The number and percentage of subjects with adverse events will be tabulated by body 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 adverse events within a

body system is only counted once towards the total of this body system and treatment, for the event with highest severity. Summaries of SAEs will be provided in a similar manner.

A summary table of AEs leading to discontinuation of study treatment by preferred term will be produced for the SAF (up to Day 90), SAF1 and SAF2 separately.

Exposure-adjusted AE summaries will also be likewise considered for SAF.

For summary tables on exposure-adjusted AEs, the number of episodes per 100 patient months will be presented. The occurrence rate (number of episodes per 100 patient month) will be calculated as 100*(the total number of AE episodes from all patients in the population divided by the total number of patient-months). A patient may have multiple occurrences of the same event. All occurrences are counted. Total patient months will be computed as (sum of the duration of exposure over patients, in days)/30.4375. This method will account for the length of follow-up time under the assumption that events would occur with the same frequency at any point in time.
In addition, 95% confidence intervals will be presented for the occurrence rate. It will be assumed that for each of n subjects the time t_j (j=1,...,n) represents the duration of exposure to study treatment. The sequence of occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where $T = \sum_{j=1}^{n} t_j$ and D is the total number of events. Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% confidence interval for 100*D/T will be derived as follows (Sahai, 1993):

Lower confidence limit $L = \frac{0.5c_{\alpha/2,2D}}{T}$ *100 for D>0, 0 otherwise,

Upper confidence limit $U = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$ *100 for D>0, 0 otherwise,

where $c_{\alpha,k}$ is the αth quantile of the Chi-square distribution with k degrees of freedom.

Adverse events of special interest definitions are found in the compound electronic Case Retrieval Strategy (eCRS). The classification reflects the current version of the Development Safety Profiling Plan (DSPP) and might be updated based on review of accumulating data. A listing of the case retrieval strategy will be presented.

The frequency and percentage of patients with adverse events of special interest will be presented by MedDRA preferred term and treatment arm. These outputs will also be produced for the SAF (up to Day 90) and for SAF1 and SAF2 separately.

Further displays of AEs may be produced in order to appropriately describe the outcomes seen in this trial. For displays of Treatment Emergent events only, events will be considered as Treatment emergent if they started after the date of first administration of study treatment (or were present prior to start of study treatment but increased in severity based on preferred term) and up to 7 days after study treatment discontinuation. For post-treatment period, AEs and SAEs will be summarized separately for both SAF1 and SAF2 analysis sets.

For TEAE tables on SAF (Part 1 and Part 2 to Day 90) a cut-off of 90 + 7 days (post end of treatment) for Part 1 patients and Part 2 patients on 90 days of treatment will be used, whereas a cut-off of 90 days for Part 2 patients on 180 days of treatment will be used.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required Safety disclosure tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than a certain threshold based on the final database and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

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

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

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

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Physical Examination

Significant findings prior to informed consent will be recorded in the Medical history eCRF and any significant findings after informed consent will be recorded on the Adverse Events and thus will be summarized respectively.

Protocol deviations

Protocol deviations will be listed by treatment, subject and epoch period. A frequency summary table will be produced by treatment period for all protocol deviations (including Covid related).

Others

All pregnancy data will be listed by treatment, subject, and visit/time.

8.3 Graphical presentation

Overlaying individual time profiles (spaghetti plots) to visualize trends in longitudinal safety data (vitals, ECG, labs) by time and treatment group will be created. Arithmetic mean (SD) plots of the absolute values for safety data (vitals, ECG, labs) by time and treatment group will also be created.

9 Statistical methods for Pharmacokinetic/Pharmacodynamic interactions

Scatterplots will be considered to explore the relationship between systemic exposure to LNP023 and selected PD endpoints. PD endpoints that may be explored at Day 90, include but are not limited to:

- UACR and UPCR (from 24h-urine and FMV), 24h-UP, 24h-UA, serum creatinine, eGFR
- Plasma and urine levels of alternative pathway biomarkers including (but not limited to) Bb and sC5b-9

[redacted]

The relationship between PK and PD will be assessed using pharmacometric modeling approaches, for example using loess regression curve. 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), for example using loess regression curve. Inter-individual variability will be taken into account using mixed effects modeling.

Further details will be provided in a separate PK/PD analysis plan.

10 Statistical methods for biomarker data

The following biomarkers will be analyzed using the FAS (up to Day 90) and FAS2 analysis populations separately in this trial and fully reported in the CSR, if data are available at the dry run. [redacted]

Table 10-1: List of Biomarkers

* Biomarker name exactly as it will appear in the dataset
**1 iu corresponds to 1%
*** Only available in Part 1

Biomarker	Matrix	Unit	Description	Read out*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bb	Plasma	ng/ml	Circulating fragment Bb of Factor B	Bb
sC5b-9	Plasma	ng/ml	Soluble C5b-9	SC5b-9
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Biomarker	Matrix	Unit	Description	Read out*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Properdin***	Plasma	µg/mL	Properdin	Properdin
Bb***	Urine	ng/ml	Circulating fragment Bb of Factor B	Bb
sC5b-9	Urine	ng/ml	Soluble C5b-9	SC5b-9
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complement Factor H***	Urine	ng/mL	Complement Factor H	Complement Factor H
Properdin***	Urine	ng/mL	Properdin	Properdin
Creatinine	Urine	µmol/L	Creatinine	CREATININE

The biomarker data in Table 10 will be listed by treatment, patient, and visit/timepoint. Summary statistics will be provided by treatment and visit/timepoint. The effect of LNP023 treatment on biomarkers, will be explored graphically to show the percent change from baseline concentration plots based on geometric mean (i.e. calculated by back-transforming the mean of the log- transformed ratio to baseline values) and presented as a percentage (e.g. a geometric mean ratio to baseline value of 1.2 will be presented as 20% in the plot, whereas a geometric mean ratio to baseline value of 0.8 will be presented as -20%) over time/visit by treatment group. Additional plots may be used to further explore other relationships.

Biomarkers measured in urine will be analyzed both raw and normalized to urine creatinine levels. Normalization will be performed as the ratio of each biomarker to creatinine value.

Handling of LLOQ and ULOQ

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

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

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

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

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

11 Considerations due to COVID-19

Due to the COVID-19 pandemic it was not possible to perform some procedures as per protocol. All deviations due to COVID-19 will be listed along with other Protocol deviations and may also be tabulated.

Observations that were impacted due to COVID-19 may be excluded from the primary analyses and separately explored to identify if there is an impact of them on the analyses

12 Reference list

Bretz F, Pinheiro JC, Branson M (2005) Combining multiple comparisons and modelling techniques in dose-response studies, Biometrics, vol. 61, p. 738-748.

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Pinheiro J, Bornkamp B, Glimm E, et al (2014) Model-based dose finding under model uncertainty using general parametric models. Statistics in Medicine 33(10): 1646-661

Sahai H, Khurshid Anwer (1993). Confidence intervals for the mean of a poisson distribution: a review. Biom J, 35 (7); 857-867

13 Appendix

Table 13-1: ATC codes for Prohibited Concomitant medication

Prohibited concomitant medication group	Drugs	ATC code
Immunosuppressive agents		L04, L04A, L04AA
	Cyclophosphamide	L01AA01
	MMF or mycophenolate sodium	L04AA06
	Cyclosporine	L04AD01
	Tacrolimus	L04AD02
	Sirolimus	L04AA10
	Systemic Corticosteroids	H02, M01BA

Biologic agents		L04AA, L04AB, L04AC
	Rituximab	L01XC02
	Infliximab	L04AB02
	Canankinumab	L04AC08
	Gemfibrizol	C10AB04
Strong CYP2C8 inhibitors		
p-gp substrates		
	Digoxin	C01AA05
	Digitoxin	C01AA04
	Quinidine	C01BA01
	Paclitaxel	L01CD01
	Fentanyl	N02AB03
	Phenytoin	N03AB02

Table 13-2: ATC codes for Use of corticosteroid or immunosuppressant therapy (CS/IS)

Immunosuppressive group	**Drugs**	**ATC Code**
Glucocorticoids	Prednisone	S02BA03
	Dexamethasone	S02BA06
	Hydrocortisone	H02AB09
Cytostatics	Methotrexate	L01BA01
	Azathioprine and Mercaptopurine	L04AX01 and L01BB02
	Fluorouracil	L01BC02
Antibodies	Atgam, Thymoglobulin	L04AA03
	Muromonab-CD3	L04AA02
	Basiliximab (Simulect)	L04AC02
	Daclizumab (Zenapax)	L04AC01

Drugs acting on immunophilins	Ciclosporin	L04AD01
	Tacrolimus	L04AD02
	Sirolimus and Everolimus	L04AA10 and L01XE10
Other drugs	Interferon	L03AB
	Opioids	N02A
	Infliximab (Remicade)	L04AB02
	Etanercept (Enbrel) or Adalimumab (Humira)	L04AB01 and L04AB04
	Mycophenolic acid	L04AA06
	Fingolimod, Myriocin	L04AA27