NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LNP023

CLNP023D12201
ClinicalTrials.gov Identifier: NCT04154787

A randomized, open-label, two arm, parallel group, proof-of-concept clinical trial to investigate the efficacy and safety of LNP023 compared with rituximab in the treatment of subjects with idiopathic membranous nephropathy

Statistical Analysis Plan (SAP)

Author(s): Personal Protected Data

Document type: SAP Documentation – NIBR

Document status: Amendment 2/Final

Release date: 22-Feb-2023

Number of pages: 32

Property of Novartis
For business use only
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis

Commercially Confidential Information (CCI)

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Table of contents

Table of contents 7
List of tables 8
1 Introduction 9
1.1 Scope of document 9
1.2 Study reference documentation 9
1.3 Study objectives 9
1.4 Study design and treatment 10
2 First interpretable results (FIR) 13
3 Interim analyses 13
4 Statistical methods: Analysis sets 13
5 Statistical methods for Pharmacokinetic (PK) parameters 15
5.1 Variables 15
5.2 Descriptive analyses 15
5.2.1 Graphical presentation of results 15
6 Statistical methods for Pharmacodynamic (PD) parameters 16
6.1 Primary objective 16
6.1.1 Variable 16
6.1.2 Descriptive analyses 16
6.1.3 Statistical model, assumptions and hypotheses 16
6.2 Secondary objectives 17
6.2.1 Variables 17
6.2.2 Descriptive analyses 18
6.2.3 Statistical model, assumptions and hypotheses 18
6.3 Exploratory objectives 19
6.3.1 Variables 19
6.3.2 Descriptive analyses 22
6.3.3 Statistical model, assumptions and hypotheses 22
7 Statistical methods for safety and tolerability data 23
7.1 Variables 23
7.2 Descriptive analyses 23
7.3 Graphical presentation 26
8 Statistical methods for biomarker data 26
Commercially Confidential Information
10 Appendix 30
Commercially Confidential Information

List of tables

Table 4-1 Protocol deviation codes and analysis sets....14
Table 8-1 Biomarkers to be fully reported in CSR....26

1 Introduction

1.1 Scope of document

Commercially Confidential Information

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

The final study protocol (v01) dated 04 March 2021 and the final SOM (v02) dated 10 March 2021 are available at the time of the finalization of the Statistical Analysis Plan.

1.3 Study objectives

Objective(s)	Endpoint(s)
Primary objective(s)	Endpoint(s) for primary objective(s)
• To assess the efficacy of LNP023 compared with rituximab	• Ratio between baseline UPCR and UPCR at 24 weeks of treatment (from 24h urine collection)
Secondary objective(s)	Endpoint(s) for secondary objective(s)
• To assess the safety and tolerability of LNP023	• ECG parameters, vital signs, safety laboratory data, physical exam and collection of AEs assessed from baseline until the end of the study visit.
Commercially Confidential Information	• Plasma levels of Bb and sC5b-9 • UPCR measured in first morning void • Non-compartmental PK parameters related to drug exposure
• To assess the effect of LNP023 compared with rituximab on proteinuria remission and renal function	• Proportion of subjects with a complete remission, defined as proteinuria ≤0.3 g/day at 24 weeks of treatment, derived from 24h urine collection • Proportion of subjects with a partial remission, defined as reduction of proteinuria from baseline ≥50% plus final UP ≤ 3.5 g/24h but >0.3 g/24h at 24 weeks of treatment, derived from 24h urine collection. • Change in eGFR applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from baseline to 24 weeks of treatment

Objective(s)	Endpoint(s)
• To assess the pharmacokinetics of LNP023	• Plasma: non-compartmental PK parameters in plasma related to total parent drug, including, but not limited, to Tmax, Cmax, AUClast and AUCtau will be calculated for each dose level. • Urine: renal plasma clearance derived from 24h urine at week 16.
Exploratory objective(s)	Endpoint(s) for exploratory objective(s)

Commercially Confidential Information

1.4 Study design and treatment

This is a randomized, open-label, two arm, parallel group, proof-of-concept, non-confirmatory study evaluating the efficacy and safety of LNP023 compared with rituximab in subjects with MN at high risk of disease progression defined on the basis of anti-PLA2R antibody titer (≥ 60 RU/mL) and proteinuria (≥ 3.5 g/24h).

Approximately 52 subjects will be randomized into the study: approximately 24 on LNP023 200 mg, approximately 24 on rituximab Commercially Confidential Information

Treatment with LNP023 or rituximab is open label.

Commercially Confidential Information

Efficacy will be evaluated at the end of the 24-week period. The randomization ratio is 1:1 (LNP023:rituximab).

Commercially Confidential Information

Proteinuria will be assessed by collecting 24h urine samples and measuring the protein to creatinine ratio (UPCR). The 24h urine samples will be collected by the subject at home on the morning of the day prior to the indicated study visit and brought to the study site on the day of visit. Samples will be collected 1) at run-in, 2) for baseline, 3) between Day 112 and Day 113, and 4) between Day 168 and Day 169 (end of treatment).

First morning void samples for monitoring UPCR and other urine parameters will be collected 11 times by the subject at home: 1 time at run-in, 1 time for baseline, 7 times during the treatment period and 2 times during safety follow-up.

Total study duration from screening until end of study (EOS) is approximately 65 weeks.

The study includes Commercially Confidential Information

- a screening visit
- a run-in period of up to 12 weeks
- a baseline visit
- Day 1 (day of first study drug administration)
- a treatment period of 24 weeks
- a follow-up period without any treatment of 29 weeks, including the EOS visit

Commercially Confidential Information

Subjects will be randomized on Day 1 or up to 4 days before, only after eligibility is confirmed, to LNP023 or rituximab.

Treatment period (subjects randomized to the LNP023 treatment arm)

Treatment period lasts for 24 weeks from Day 1 to Day 169:

Commercially Confidential Information

Treatment period (subjects randomized to the rituximab treatment arm)

- Day 1 and Day 15: a dose of rituximab 1 g by intravenous infusion (i.v.), will be administered.

- Treatment period will continue until Day 169 without any further rituximab administration.

2 First interpretable results (FIR)

Commercially Confidential Information

3 Interim analyses

Commercially Confidential Information

4 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

The safety analysis set will include all subjects who received any study drug.

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 LNP023 and experienced no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects who received any study drug and experienced no protocol deviations with relevant impact on PD/efficacy data.

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

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from Safety analysis in case of these PDs:		Exclude subject Safety analysis sets
INCL01	Written informed consent not obtained before any study assessment is performed.	
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
INCL01	Written informed consent not obtained before any study assessment is performed.	
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL01	Written informed consent not obtained before any study assessment is performed.	

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

Commercially Confidential Information

Unless otherwise stated, throughout this document:

- *Treatment* and *treatment group* refer to the following treatment arms that will be used as labels for all outputs reported by treatment/treatment group:
  - Commercially Confidential Information
  - LNP023 200 mg b.i.d.*
  - Rituximab 1 g i.v.

Commercially Confidential Information

Commercially Confidential Information

5 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK analysis set will be included in the PK data analysis.

5.1 Variables

The following pharmacokinetic parameters of LNP023 will be determined, as feasible, using the actual recorded sampling times and non-compartmental analysis method(s):

- Plasma: C_{max}, T_{max}, AUC_{last}, $AUC_{tau,}$ C_{trough} (C_{min}) and, if applicable AUC_{inf} and T1/2, at day 29 and day 113
- Urine: Ue (amount of LNP023 excreted in the urine), renal clearance (Clr) of LNP023 calculated from the amount excreted over 24h and percent recovery of LNP023 at day 113

Other pharmacokinetic parameters may be calculated as appropriate.

5.2 Descriptive analyses

Descriptive summary statistics for LNP023 plasma and urine concentration data will be provided by dose and visit/sampling timepoint, Commercially Confidential Information

Summary statistics will include n, 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. Commercially Confidential Information

A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be listed by treatment, visit/sampling timepoint, and subject and summarized by dose with descriptive summary statistics as described above.

5.2.1 Graphical presentation of results

All individual plasma concentration-time profiles for LNP023 concentration with median will be displayed graphically by treatment on linear and/or semi-log view. In addition, the mean (+/- SD) and geometric mean plasma concentration-time profiles for LNP023 by dose over time will be displayed graphically on linear and/or semi-log view.

6 Statistical methods for Pharmacodynamic (PD) parameters

All subjects within the PD analysis set Commercially Confidential Information will be included in the PD data analysis.

Unless otherwise stated, summary statistics of continuous data will include n, mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum, as appropriate, while categorical data will be summarized as frequencies and percentages.

6.1 Primary objective

The primary objective of this study is to assess the efficacy of the LNP023 200 mg compared with rituximab.

The primary aim of the study is to assess the reduction in UPCR (measured in 24h urine) in LNP023 200 mg treated subjects compared with rituximab treated subjects after 24 weeks of treatment.

In the LNP023 treatment groups subjects are considered as under treatment whilst taking the treatment and until 30 days after the last administration. In the Rituximab arm, subjects are considered as under treatment 6 months from the second infusion. Subjects who received a single Rituximab infusion are considered under treatment until 3 months after this single infusion.

6.1.1 Variable

The primary endpoint of this study is the ratio of UPCR after 24 weeks of treatment (Day 169) to baseline UPCR measured in 24h urine ($UPCR_{24weeks}/UPCR_{baseline}$). Baseline is defined as the last non-missing measurement prior to randomization. This endpoint will be log-transformed prior to analysis, as it is assumed to follow a log-normal distribution.

6.1.2 Descriptive analyses

UPCR from 24h urine measurements will be listed by treatment, subject and visit/time and summary statistics for the raw UPCR and ratio of post-baseline UPCR to baseline UPCR will be provided by treatment and visit/time.

6.1.3 Statistical model, assumptions and hypotheses

To assess the primary objective, the log-transformed ratio to baseline in UPCR will be analyzed using a mixed model for repeated measures (MMRM). The results will be back transformed and presented on the original scale.

Commercially Confidential Information

Commercially Confidential Information

The following two criteria will be used to assess treatment efficacy (both criteria must be satisfied for success):

- Statistically significant decrease (no worse than 55% increase) in UPCR at week 24 visit in LNP023 200 mg-treated subjects vs. rituximab-treated subjects tested at one-sided 10% level from a lower-tailed test (i.e. H_0 : (24 week to baseline ratio in UPCR in LNP023 200 mg)/(24 week to baseline ratio in UPCR Rituximab) ≥ 1.55)
- Estimated mean reduction in UPCR in LNP023 200 mg-treated subjects better than 10% increase vs rituximab-treated subjects at week 24 visit (i.e. (24 week to baseline ratio in UPCR in LNP023 200 mg)/(24 week to baseline ratio in UPCR in Rituximab) < 1.1)

6.1.3.1 Model checking procedures

The adequacy of the model will be assessed by inspecting residual plots.

6.1.3.2 Graphical presentation of results

Model estimated geometric mean (95% CI) of ratio to baseline will be presented by time and treatment.

6.1.3.3 Handling of missing values/censoring/discontinuations

The primary analysis will include all available data up to the treatment discontinuation for all subjects with at least one post-baseline measurement of UPCR in 24h urine. The primary Mixed effect Model Repeat Measurement implicitly imputes missing data under a missing at random assumption.

6.1.3.4 Sensitivity analyses

As sensitivity analysis the same model as for the primary analysis will be fitted, however all collected efficacy data will be included in this analysis (irrespective of whether treatment was discontinued early or not, i.e. following the treatment policy approach).

6.2 Secondary objectives

6.2.1 Variables

The variables supporting the secondary objectives are:

- Ratio of post-baseline UPCR to baseline UPCR measured in first morning void
- Complete remission (defined as proteinuria ≤0.3 g/day at 24 weeks of treatment, derived from 24h urine collection)
- Partial remission (defined as reduction of proteinuria from baseline ≥50% plus final UP ≤ 3.5 g/24h but >0.3 g/24h at 24 weeks of treatment, derived from 24h urine collection)

- Change in eGFR applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from baseline to 24 weeks of treatment
- Plasma levels of Bb and sC5b-9 biomarkers

Analysis details for these biomarkers are given in Biomarker Section 8.

Baseline is defined to be the last non-missing measurement prior to randomization.

6.2.2 Descriptive analyses

The secondary PD variables will be listed by treatment, subject, and visit/sampling time. For the continuous variables change from baseline or ratio to baseline will be provided as deemed relevant. Summary statistics will be provided by treatment and visit/time for raw values and change from baseline or ratio to baseline as deemed relevant.

Graphical methods may be employed for the continuous variables to show group and individual summary plots over time by treatment.

Responder assessment

The number and proportion of responders in the rituximab and LNP023 200 mg will be determined and compared between treatment groups. A subject is a complete responder if he/she shows complete remission as defined in Section 6.2.1. A subject will be considered a partial responder if she/he shows a partial remission as defined in Section 6.2.1. Subjects who discontinue treatment early will be considered as non-responders in this analysis.

eGFR change from baseline

Summary statistics for the change from baseline to 24 weeks in eGFR (applying the Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI, equation) will be provided by treatment.

6.2.3 Statistical model, assumptions and hypotheses

Ratio of post-baseline UPCR to baseline UPCR measured in first morning void

The log-transformed ratio to baseline in UPCR measured in morning void will be analyzed using a MMRM. The results will be back transformed and presented on the original scale.

Commercially Confidential Information

6.2.3.1 Model checking procedures

The adequacy of the models will be assessed by inspecting residual plots.

6.2.3.2 Graphical presentation of results

Model estimated geometric means (95% CI) of ratio to baseline by time and treatment may be provided.

6.2.3.3 Handling of missing values/censoring/discontinuations

The analysis will include all available data up to the treatment discontinuation for all subjects with at least one post-baseline measurement of UPCR measured in first morning void. The Mixed effect Model Repeat Measurement implicitly imputes missing data under a missing at random assumption.

6.3 Exploratory objectives

Summary statistics will include n, mean, SD, median, minimum and maximum.

6.3.1 Variables

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

7 Statistical methods for safety and tolerability data

For all safety analyses, the safety analysis set will be used. All tables will be presented by treatment group. Baseline is defined as the last non-missing measurement prior to randomization.

Safety summaries (tables, figures) will include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries).

The on-treatment period in the LNP023 treatment groups lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment. The on-treatment period in the rituximab treatment group lasts from the first administration to 6 months after the date of the second administration. Subjects who received a single rituximab infusion are considered under treatment until 3 months after this single infusion.

Summary statistics of continuous data will include n, mean, SD, median, minimum and maximum, while categorical data will be summarized as frequencies and percentages.

7.1 Variables

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

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

Data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

The duration of exposure in weeks to LNP023 will be summarized separately by treatment group and by dose. For Rituximab, the number of doses administered will be summarized.

The duration of exposure in weeks to LNP023 will be calculated as:

(study day of last non-missing dose – study day of first dose + 1)/7.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment.

Protocol deviations

Protocol deviations will be listed by treatment group and subject. The number and percentage of subjects with pandemic-related and not pandemic-related protocol deviations will be summarized for each treatment by category and relationship.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. In addition, the number and percentage of subjects with notable ECG values will also be provided by treatment.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Abnormal laboratory values of potential clinical importance will be listed in a separate listing by treatment, subject, and visit/time. Pregnancy test results for women will also be listed in a separate listing by treatment group, subject, and visit/time. Shift tables using the low/normal/high/(low and high) classification will be used to compare baseline to the worst on-treatment value. Summary statistics will be provided by treatment and visit/time.

Adverse events

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

The number and percentage of subjects with treatment-emergent adverse events will be summarized in the following ways:

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

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

The number and proportion of subjects with adverse events of special interest related to identified and potential risks (i.e. systemic bacterial infection, Commercially Confidential Information will be summarized by treatment.

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

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset at or after the start of the treatment period that were absent pre-treatment, or which were present prior to the start of the treatment period but increased in severity, or changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period based on preferred term (PT).

Heatmaps will be provided by treatment group displaying the on- and off-set of the most severe AEs in a subject over time.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than **5%** 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.

Adverse events of special interest (AESIs)

All information obtained on AESIs will be displayed by treatment and subject.

The number and percentage of subjects with treatment-emergent AESIs will be summarized by treatment, risk name and preferred term (PT).

Case retrieval strategy

A listing for case retrieval strategy will be provided.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

8 Statistical methods for biomarker data

The PD analysis set will used for the biomarker analysis.

Only the LNP023 CCI 200 mg b.i.d.-treated and rituximab-treated subjects will be included in the biomarker analyses Commercially Confidential Information

Hence, the treatment groups will be reported as follows for the biomarker outputs:

- LNP023 CCI 200 mg b.i.d.
- Rituximab 1 g i.v.

Summary statistics will include n, mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum, as appropriate.

The following biomarkers will be analyzed in this trial and fully reported in the CSR, if data are available at the dry run.

Table 8-1 Biomarkers to be fully reported in CSR

Biomarker		Unit	Description	Read out*
Blood complement pathway markers (from biomarker group)				
Commercially Confidential Information				
Bb	Plasma	ng/mL	Circulating fragment Bb of Factor B	Bb
sC5b-9	Plasma	ng/mL	Soluble C5b-9	SC5b-9
Commercially Confidential Information				

Commercially Confidential Information

Commercially Confidential Information

Descriptive analyses and graphical presentation

Baseline is defined as the last non-missing measurement prior to randomization.

The Bb and sC5b-9 plasma biomarkers will be listed by treatment, subject, and visit/sampling time. Summary statistics and graphical summaries will be provided by treatment and visit/time for the raw values and the percent change from baseline or ratio to baseline values as deemed relevant. Commercially Confidential Information

Bland-Altman plots of UPCR from first morning void and 24h urine UPCR at each visit will be provided to assess UPCR from first morning void as a monitoring marker.

Scatterplots will be provided to assess the biomarkers of the complement pathway activity in urine (as ratio to creatinine) and serum/plasma as prognostic markers of the treatment effect on 24h UPCR after 24 weeks of treatment.

To assess the relationship of the disease severity with the anti-PLA2R at baseline, a scatterplot of urine protein level at baseline (based on 24h urine protein levels) and anti-PLA2R level at baseline will be provided.

Arithmetic mean (90% CI) plots of percent change from baseline in all biomarkers will be provided by visit and treatment.

Arithmetic mean (SE) dual y-axis plots of anti-PLA2R level vs proteinuria and plasma albumin vs proteinuria will be provided by visit and treatment.

In addition, the following plots will be provided for the blood B cell counts biomarker:

- Overlaying individual (spaghetti) plots overlaid with mean over time.
- A scatterplot of percent change from baseline in B cell counts vs 24h UPCR ratio to baseline at each post-baseline visit.

Statistical models

Plasma levels of Bb and sC5b-9

The effect on the treatment (LNP023 CCI 200 mg b.i.d. vs Rituximab) over time will be assessed using the same model as for the primary endpoint, with the only difference being that the baseline log biomarker will be used as a covariate instead of the baseline log UPCR. Plasma levels of Bb and cS5b-9 are assumed to be log-normal distributed and will therefore be log-transformed prior to statistical analysis.

Commercially Confidential Information

Commercially Confidential Information

10 Appendix

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information