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LNP023

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CLNP023X2204

A multi-center, randomized, open-label, efficacy, safety, pharmacokinetics and pharmacodynamics study, assessing multiple LNP023 doses in adult patients with paroxysmal nocturnal hemoglobinuria and active hemolysis

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"CLNP023X2204".**

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

1.2 Study reference documentation

This SAP has been developed using the Clinical Trial Protocol version v02 (amended protocol) dated 03-Aug-2021.

1.3 Study objectives

1.3.1 Primary objective(s)

Primary objective(s)	Endpoints related to primary objective(s)
• To assess the effect of LNP023 on the reduction of PNH associated hemolysis.	• Percentage of patients with 60% reduction in LDH or LDH below upper limit of normal (ULN) up to 12 weeks of treatment.

1.3.2 Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)
• To assess the dose-response effect of LNP023 on the reduction of PNH associated hemolysis	• LDH, and other relevant parameters such as but not restricted to hemoglobin and red blood cell count up to week 4 for each dose.

• To assess the effect of LNP023 on markers of intravascular and extravascular hemolysis.	• Potentially all of, but not restricted to,
	  • Total and free hemoglobin,
	  • carboxyhemoglobin,
	  • reticulocytes,
	  • C3 fragment deposition,
	  • haptoglobin,
	  • bilirubin,
	  • red blood cell count,
	  • platelet counts,
	  • ferritin,
	  • PNH type III red blood cells (RBC)
	  • PNH clone size.

• To assess the safety and tolerability of LNP023 in PNH patients.	• All safety parameters including: blood chemistry, hematology, urinalysis, ECG evaluation, vital signs, adverse events, transfusions, patient diary.
• To assess the plasma pharmacokinetics (PK) of LNP023	• Non-compartmental analysis of LNP023 PK parameters including, but not limited to Cmax, AUC, Ctrough and Tmax.
• To assess the effect of LNP023 on markers associated with risk of thrombosis.	• Assessments including, but not limited to, fibrinogen, prothrombin time, activated partial thromboplastin time, thrombin time, fibrin D-dimer and fibrinogen degradation products for fibrinolysis activity.

1.3.3 Exploratory objective(s)

Exploratory objective(s)	Endpoints related to exploratory objective(s)

1.4 Study design and treatment

This is a non-confirmatory, randomized, open-label, multicenter, efficacy, safety, pharmacokinetic and pharmacodynamic study assessing CCI LNP023 doses, in adult PNH patients with active hemolysis.

At least 10 patients will be included in the study, as replacement can occur if any patient withdraws for reasons unrelated to safety or lack of efficacy.

Total study duration from screening until EOS is approximately 2.5 years. This three-period study includes: a screening phase of up to 8 weeks, a baseline visit, Day 1 (first day that the investigational drug is given), a 4-week treatment period of LNP023 at the first dose in the assigned sequence (Period 1), an 8-week treatment period at the second dose in the assigned sequence (Period 2), an approximately 2 year extension Period 3, followed by a taper down period of 2 weeks, an end of study visit and a safety follow up call performed 30 days post end of treatment.

Patient will be randomized to sequence 1 or sequence 2 in ratio 1:1.

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Figure 1-1 Study design and dosing schema

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2 First interpretable results (FIR)

No FIR will be produced for the final analysis.

3 Interim analyses

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4 General considerations

The final study analysis will be conducted on all patients' data at the time the trial ends.

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5 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received. This implies that for subjects for whom the actual treatment received does not match the randomized treatment, the treatment actually received will be used for the analysis.

The Full Analysis Set (FAS) comprises all patients that received any study drug.

The Safety analysis set will also include all patients that received any study drug and hence is not referred to again.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

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

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 all *(safety and FAS)* analysis in case of these protocol deviations:		Exclude subject completely from all *(safety and FAS)* analysis sets
Subjects are excluded from PK analysis in case of these protocol deviations: INCL01		Exclude subject from PK analysis set
Subjects are excluded from PD analysis in case of these protocol deviations: INCL01		Exclude subject from PD analysis set
Subjects are excluded from PK and PD analysis in case of these protocol deviations: INCL01		Exclude subject from PK and PD analysis sets

6 Statistical methods for Pharmacokinetic (PK) parameters

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

6.1 Variables

The following PK parameters will be determined, if data permit, using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8.0 or higher), from the plasma concentration-time data:

AUCtau	The area under the plasma concentration-time curve calculated to the end of the dosing interval (tau) at steady-state (h*ng/ml)
AUClast	The area under the plasma concentration-time curve calculated to the last measurable concentration sampling time (tlast) (h*ng/ml)
Cmax	The observed maximum plasma concentration (ng/ml)
Ctrough (Cmin)	The concentration observed just prior to the beginning, or at the end, of a dosing interval (ng/mL)
Tmax	The time to reach maximum plasma concentration (h)
T1/2 (if feasible)	The elimination half-life associated with the terminal slope (lambda_z) of a semi-logarithmic concentration-time curve (h)

6.2 Descriptive analyses

LNP023 plasma concentrations will be listed by sequence, treatment dose group, patient, and visit/sampling time point. Summary tables will be presented as described in Section 4.

Pharmacokinetic parameters will be listed by patient and summarized by treatment with descriptive statistics as listed above. For Tmax, only median, minimum, and maximum will be reported. For T1/2 geometric means will not be calculated.

Graphical methods will be employed to show mean (SD) with time defined as the sampling time point by treatment dose group on linear and semi-log view based on nominal time.
Moreover, individual PK values trough levels up to Week 12 will be displayed. In addition, all individual concentration-time profiles will be displayed graphically by treatment dose and sequence (in separate plots), visit/sampling time point on linear and semi-log view based on nominal time.

6.3 Statistical model, assumptions and hypotheses

Modeling techniques will be applied on the PK parameters (AUCtau, AUClast and Cmax) at Period Week 4 (i.e. including data from both Period 1 Week 4 and Period 2 Week 4).

In the first instance a mixed model will be fitted with log transformed PK parameter as the dependent variable and dose as a categorical variable, and subject as a random term to give predicted estimates per each dose. The subject term will be considered as random so as to allow recovery of between subject information. The results of the treatment effects will be presented as geometric means by back-transforming estimates from the log scale and will be presented along with a 95% confidence interval.

6.3.1 Model checking procedures

6.3.2 Graphical presentation of results

The model predicted relationship curve between dose and PK parameter along with its corresponding 95% CI will be presented for the nonlinear model.

7 Statistical methods for Pharmacodynamic (PD) parameters

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

7.1 Primary objective

The primary objective is to assess the effect of LNP023 on the reduction of PNH associated hemolysis.

7.1.1 Variables

The primary variable is treatment response. A responder is defined as a patient with at least 60% reduction in LDH compared to baseline or LDH below upper limit of normal (ULN) at any time up to and including Week 12 for that patient, whether or not CCI , and a non-responder anyone who doesn't meet either of these criteria.

Baseline LDH will be calculated as the average of the last three screening values prior to randomization.

7.1.2 Descriptive analyses

Frequency tabulations reporting number and percentage of responders by week 12 by randomized sequence. Frequency tables will also be summarized by dose over time as described in Section 4.

There is no statistical model for the primary endpoint apart from observing and counting success or failure for each patient. For the purposes of this study a positive sign of efficacy is when the estimated response rate is at least 50%. For example, this criterion will be met when at least 5 out of 10 patients in the overall study, or 3 of 5 in one of the two Cohorts are considered responders.

7.1.2.1 Handling of missing values/censoring/discontinuations

For calculation of the success rate for the primary endpoint all patients enrolled in the study apart from those who were replaced for reasons other than safety or efficacy will be included in the denominator.

7.2 Secondary objectives

The secondary objectives of this study are:

- To assess the dose-response effect of LNP023 on the reduction of PNH associated hemolysis.
- To assess the effect of LNP023 on markers of intravascular and extravascular hemolysis.
- To assess the effect of LNP023 on markers associated with risk of thrombosis

7.2.1 Variables

The secondary variables of this study are:

- For dose response: LDH, and other relevant parameters including but not restricted to hemoglobin and red blood cell count
- Markers of intravascular and extravascular hemolysis CCI
  Including but not restricted to total and free hemoglobin, carboxyhemoglobin, reticulocytes, C3 fragment deposition, haptoglobin, bilirubin, red blood cell count, platelet counts, ferritin, PNH type III red blood cells (RBC) and PNH clone size
- Risk of thrombosis parameters: Including but not limited to, fibrinogen, prothrombin time, activated partial thromboplastin time, thrombin time, fibrin D-dimer and fibrinogen degradation products for fibrinolysis activity.

Baseline LDH will be calculated as the average of the last three screening values prior to randomization. For all parameters except LDH, baseline is the average of all pre-treatment values.

Partial exclusion of data

In case of an INCL05 deviation, all total and free hemoglobin records from the patient will be excluded from the PD analyses.

7.2.2 Descriptive analyses

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7.2.3 Statistical model, assumptions and hypotheses

Dose-response effect

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7.2.3.1 Model checking procedures

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7.2.3.2 Graphical presentation of results

The model predicted relationship curve between dose and PK parameter along with its corresponding 95% CI will be presented for any nonlinear models.

7.3 Exploratory objectives

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7.3.1 Variables

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7.3.2 Descriptive analyses

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7.3.3 Descriptive analyses

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8 Statistical methods for safety and tolerability data

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

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., when change from baseline is used). In addition, a separate summary for any deaths including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AE) will summarize only on-treatment events.

The on-treatment period lasts from the date of first administration of study treatment to 7 days after the date of the last actual administration of any study treatment.

8.1 Variables

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

8.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence. For baseline characteristics the values at the baseline visit will be listed/summarized.

Categorical data will be presented as frequencies by treatment sequence. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and subject.

Relevant medical history and current medical conditions will be summarized by reported term, system organ class (SOC) and preferred term (PT), by treatment sequence.

Treatment

Data for a) prior and concomitant medications, b) surgical/medical procedures and investigations and c) vaccinations and prophylactic antibiotics will be listed separately by treatment sequence and subject.

The duration of exposure in days (including half days) to each dose of LNP023 will be summarized by means of descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment sequence group. In addition, the incidence of on-study medical/surgical procedures and investigations by preferred term will be displayed. A subject with multiple medical/surgical procedures and investigations with the same preferred term is counted only once for that preferred term and treatment.

Number and percentage of subjects who received the vaccination during Screening period will be summarized.

Vital signs

All vital signs data will be listed by treatment sequence, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided as described in Section 4.

ECG evaluations

All ECG data will be listed by treatment sequence, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided as described in Section 4.

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 is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided as described in Section 4.

Adverse events

All information obtained on adverse events will be displayed as described in Section 4 taking into account the study design involving sequence.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by dose for each period separately.

An adverse event starting in one period and continuing into the next period is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to study and/or investigational drug discontinuation and any adverse events leading to dose adjustment.

Adverse event reporting for Clinical Trial Safety Disclosure (CTSD)

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables, 1) on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and 2) on treatment-emergent serious adverse events and SAE suspected to be related to study treatment, will be provided by SOC and PT on the full analysis set population. These tables will be produced by Novartis. The value of the cutoff value X will be decided with the team when disclosure tables are prepared.

The summary will be done by dose and Period as described in Section 4.

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 (AESI) definitions are found in the compound electronic Case Retrieval Strategy (eCRS). Treatment-emergent AESIs (based on the latest eCRS at the time of DBL) will be summarized by frequency and percentage of patients by risk name, MedDRA preferred term and by treatment sequence. A listing of the case retrieval strategy will be presented.

Exposure

Duration of exposure will be presented graphically, using a horizontal bar chart with subjects as the y-axis and the number of days exposed to LNP023 as the x-axis.

Other safety evaluations

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8.3 Graphical presentation

Individual overlaid profile plots over time will be used to visualize trends in longitudinal safety data (vitals, ECG, lab parameters) with current dose level per patient color-coded will be presented.

9 Pharmacokinetic / pharmacodynamic relationships

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