NOVARTIS

Clinical Development

LNP023/Iptacopan

CLNP023C12302

A randomized, multicenter, active-comparator controlled, open-label trial to evaluate efficacy and safety of oral, twice daily LNP023 in adult patients with PNH and residual anemia, despite treatment with an intravenous anti-C5 antibody

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation Amendment 3
Document status:	Final
Release date:	12-Oct-2022
Number of pages:	63

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
CRF	Case Report Form
CSR	Clinical Study Report
DMS	Document Management System
EOS	End of Study
FAS	Full Analysis Set
IA	Interim Analyses
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient-reported Outcomes
MAP	Master Analysis Plan
RAP	Reporting & Analysis Process
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of the document is to describe the statistical analyses to be included in the clinical study report (CSR) to be produced for submission at the time the last patient has completed the randomized treatment period in study CLNP023C12302. Hence the document covers the efficacy analysis on the randomized treatment period and the safety analysis on the data in the randomized treatment period, as well as the safety data in the treatment extension period collected till the data cut off for the submission of the CSR mentioned before.

An additional CSR will be produced when the last participant has completed the last visit in the treatment extension period, when the final study database has been locked. The statistical analyses for that CSR will be mentioned in a separate document.

1.1 Study design

This study is a multi-center, randomized, open-label, active comparator-controlled, parallel group study, which is comprised of three periods (see Figure 1-1):

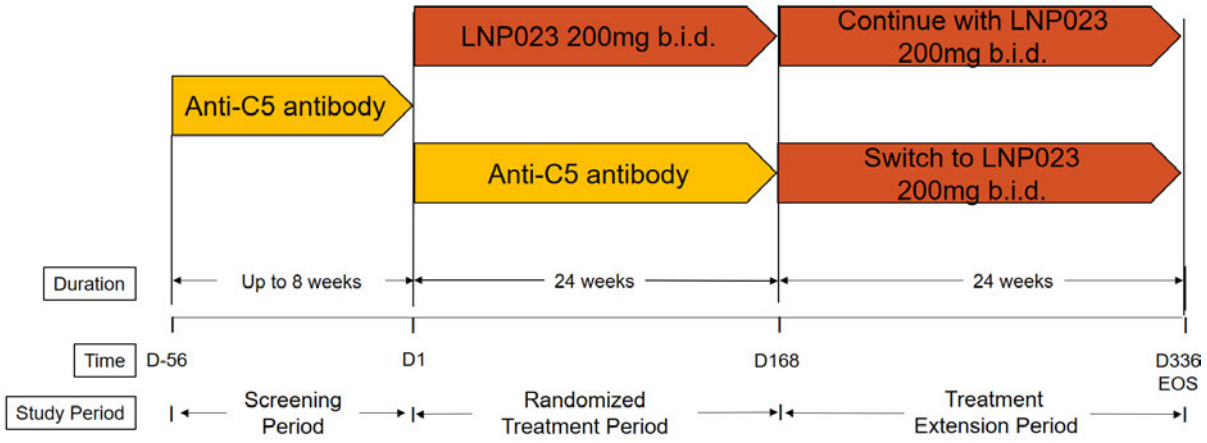
- A screening period lasting up to 8 weeks (unless there is a need to extend it for vaccinations required for inclusion, vaccinations should be started at the earliest possible time to avoid extension of the screening period)
- A 24-week randomized, open-label, active controlled, parallel group treatment period for the primary efficacy and safety analyses
- A 24-week open-label, LNP023 treatment extension period

The study will enroll PNH patients with residual anemia, defined as hemoglobin < 10 g/dL, despite stable regimen of anti-C5 antibody treatment (eculizumab or ravulizumab) in the last 6 months before randomization, with approximately 40% of participants having received at least 1 packed-RBC transfusion in the 6 months prior to randomization.

A total of approximately 91 participants will be randomized in the trial. All participants must provide written informed consent prior to start of any study-related activities.

The study design is shown in the schematic below.

Figure 1-1 Study design



The database of the study will be locked for the randomized treatment period when the last participant has completed the Day 168 visit in the study or End of Study (EOS) for participants who discontinue from the study prior to the treatment extension period. The final database lock will take place when the last participant has completed the last visit (Day 336 or EOS) in the treatment extension period.

Screening

Screening period starts at the time of ICF signing and lasts until the day preceding Day 1 of the randomized treatment period.

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

By signing the ICF, the participants will provide access to the following records: hemoglobin levels reported during the last 4 months; the number of transfusions and unit numbers of packed-RBC received in the last 12 months prior to Screening; Major Adverse Vascular Events (MAVEs) reported during the screening (History of MAVE); and the anti-C5 antibody regimen they have followed for the last 6 months up to randomization (History of anti-C5 antibody treatment).

Vaccinations should be completed as per Inclusion criteria (Section 5.1 in the study protocol). To fulfill the hemoglobin eligibility criterion, participants will have two different samples collected during the screening period and tested by the central laboratory with the mean <10 g/dL, prior to Randomization. In case the participant has received a RBC transfusion following the initial sample collection, the patient is eligible based on the initial central hemoglobin value if < 10 g/dL.

In the event that the absolute reticulocytes count as assessed by the central laboratory during the Screening period is below the protocol defined threshold (absolute reticulocytes $<100x10^9/L$) and only in this scenario, the results from the local lab testing can be used to determine participant's eligibility. The results of the local laboratory values (including reference ranges) will be included in the eCRF to document eligibility.

If eligibility criteria are not met due to any measurement falling outside the inclusion criteria, the participant should be considered as having failed the screening and does not proceed to randomization. The participant can be re-screened once as described in detail in Section 8.1 in the study protocol.

Randomization

The randomization will be stratified into four strata (defined by the combination of the stratification factors). Participants who meet the eligibility criteria at screening will be stratified based on the type of prior anti-C5 antibody treatment (eculizumab or ravulizumab) and based on the transfusion history as reported during the last 6 months prior to randomization (i.e. transfusion received/not received). It is assumed that approximately 40% of randomized participants will have received at least one packed red blood cell (pRBC) transfusion in the 6

months prior to randomization. For all analysis, the stratification factors as used for randomization will be used.

Participants will be randomized to one of the two treatment arms in an 8:5 ratio to either LNP023 monotherapy at a dose of 200 mg orally b.i.d. (approximately 56 participants), or i.v. anti-C5 antibody treatment (approximately 35 participants continuing with the same regimen during the randomized treatment period as they were on prior to randomization), respectively.

Randomized Treatment period

Treatment will start on the first day of dosing (Day 1) and continue for 24 weeks with study visits.

Participants assigned to the comparator arm will continue receiving the same type, and regimen of anti-C5 antibody treatment as received prior to randomization, while those randomized to the LNP023 treatment arm will start taking LNP023 at a dose of 200 mg b.i.d. Please refer to Section 6 in the study protocol for details on study medication and timing for starting LNP023 treatment in relation to the prior anti-C5 antibody treatment ensuring a seamless switch with an overlap of at least one (eculizumab) or two (ravulizumab) weeks of prior anti-C5 and LNP023 treatment.

The randomized treatment period will end with completion of the Week 24 visit assessments and, on that visit, participants in the active comparator arm will receive the last dose of anti-C5 infusion as part of the study treatment.

For participants who permanently discontinue LNP023 administration during the randomized treatment period, close monitoring and treatment proposals are indicated in Section 9.1.1 in the study protocol. Participants should complete all visits and assessments up to the Week 24 visit.

Upon completion of the Week 24 visit, participants may enter the treatment extension period, as described below.

Treatment Extension period

The participants randomized to the active comparator arm will be offered to switch to LNP023 on Day 168 (Week 24 visit) and enter the treatment extension period, after receiving a last dose of anti-C5 (eculizumab or ravulizumab) antibody treatment. For participants in the comparator arm not agreeing to switch treatment, Week 24 will be the EOS visit for the trial and there will be no participation in the treatment extension period. For participants agreeing to switch to oral LNP023, the Extension treatment will start on the day after completion of the Week 24 visit.

After switching to LNP023, the participants in the comparator arm will follow study visits and assessments according to the schedule described in Table 8-2 in the study protocol.

The participants in the LNP023 arm, who benefit from treatment and are taking LNP023 at the Week 24 visit (i.e. did not permanently discontinue study medication), will be offered to continue the oral treatment during the treatment extension period. For participants not agreeing to continue in the treatment extension period after completing the Day 168 visit, EOS will be after completing the recommended procedures defined in Section 9.1.1 in the study protocol.

The treatment extension period will last 24 weeks. After completion of the treatment extension period, the participant will be able to join the Roll-over extension study, which will provide access to LNP023 and enable long-term safety monitoring. For participants not agreeing to continue in the Roll-over extension study after completing the Day 336 visit, EOS will be after completing the recommended procedures defined in Section 9.1.1 in the study protocol.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints for the Randomized Treatment period

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate superiority of LNP023 compared to anti-C5 antibody treatment in the proportion of participants achieving a sustained increase in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of red blood cell transfusions	• Response defined as having an increase from baseline in Hb ≥ 2 g/dL assessed between Day 126 and Day 168, in the absence of packed red blood cell transfusions between Day 14 and Day 168
• To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in the proportion of participants achieving sustained hemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions	• Response defined as having Hb ≥ 12 g/dL between Day 126 and Day 168 in the absence of packed-red blood cell transfusions between Day 14 and Day 168
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment in transfusion avoidance as the proportion of participants who remain free from transfusions	• Absence of administration of packed-red blood cell transfusions between Day 14 and Day 168
• To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in average change in hemoglobin	• Change from baseline in hemoglobin (g/dL) as mean of visits between Day 126 and Day 168
• To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in improving fatigue, using the FACIT-Fatigue questionnaire	• Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168
• To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in average change in reticulocyte counts	• Change from baseline in reticulocyte count (10^9/L) as mean of visits between Day 126 and Day 168
• To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in average percent change in LDH	• Percent change from baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168
• To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in the rate of breakthrough hemolysis (BTH)	• Occurrences of breakthrough hemolysis reported between Day 1 and Day 168
• To assess the rates of Major Adverse Vascular Events (MAVEs incl. thrombosis)	• Occurrences of MAVEs occurring between Day 1 and Day 168

Objective(s)	Endpoint(s)
of LNP023, compared to anti-C5 antibody treatment	
• To assess safety and tolerability of LNP023 compared to anti-C5 antibody treatment*	• Safety evaluations (including adverse events/serious adverse events, safety laboratory parameters, vital signs etc.)
*The assessment of safety and tolerability is not included among the secondary estimands nor in the multiple testing strategy.	
[redacted]	[redacted]

Table 1-2 Objectives and related endpoints for the Treatment Extension period

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To assess long term safety, tolerability and efficacy of LNP023 in PNH participants	• Safety evaluations including adverse events/serious adverse events, safety laboratory parameters, vital signs etc. through End of Study visit. • Efficacy endpoints including hematological response parameters, transfusion avoidance, BTH, FACIT-fatigue score, MAVEs through End of Study visit.

1.2.1 Primary estimands

The primary clinical questions of interest are:

- What is the treatment effect of LNP023 at a dose of 200 mg b.i.d. versus anti-C5 antibody treatment in PNH patients with residual anemia, regardless of discontinuation of study medication and occurrence of breakthrough hemolysis or MAVEs, on the odds of being a responder, with the endpoint defined as a composite of an increase in Hb levels ≥ 2 g/dL from baseline assessed between Day 126 and Day 168 without requiring RBC transfusions between Day 14 and Day 168?

  The justification of this first primary estimand is that it will capture both the hematological benefit of the study drug as a clinically relevant increase in hemoglobin levels and the absence of RBC transfusions (which are regarded as treatment failure).
- What is the treatment effect of LNP023 at a dose of 200 mg b.i.d. versus anti-C5 antibody treatment in PNH patients with residual anemia, regardless of discontinuation of study medication and occurrence of breakthrough hemolysis or MAVEs, on the odds of being a responder, with the endpoint defined as a composite of Hb levels ≥ 12 g/dL assessed between Day 126 and Day 168 without requiring RBC transfusions between Day 14 and Day 168?

  The justification of this second primary estimand is that it will capture the hematological benefit of the study drug as a normalization of hemoglobin levels that is achieved free from RBC transfusions (which are regarded as treatment failure).

The two primary estimands share the following attributes:

1) Population: Patients with PNH who are on a stable regimen of SoC (anti-C5 antibody treatment) and have residual anemia (Hb < 10 g/dL).
2) Treatment of interest: the randomized treatment (the investigational treatment LNP023 200 mg b.i.d. or anti- C5 therapy (SoC)) regardless of whether patient discontinues treatment (treatment policy).
3) Intercurrent events: Transfusions after day 14 will be considered treatment failures whereas discontinuations of study medication for any reason, breakthrough hemolysis events, and MAVEs will be handled with a treatment policy strategy.
4) The summary measure: the probability of being a responder on each treatment in the studied patient population tested as an odds ratio.

However, the estimands differ in the definition of the associated endpoints as the proportion of responders where the responder definitions are as follows:

- Responder defined as a participant having Hb ≥ 2 g/dL increase from baseline between Day 126 and Day 168 and who has not received a RBC transfusion between Day 14 and Day 168 of the randomized treatment period.
- Responder defined as a participant having Hb ≥ 12 g/dL between Day 126 and Day 168 and who has not received a RBC transfusion between Day 14 and Day 168 of the randomized treatment period.

In addition to odds ratios, estimates of the proportions of responders in each treatment and their differences as well as the ratio of proportions between treatments will be derived as a supportive

estimand to quantify the magnitude of the effect of treatment with LNP023 compared to anti-C5 antibody treatment.

Table 1-3 Justification of handling of intercurrent events

Intercurrent event	Handling strategy	Justification
Discontinuation of study medication	Treatment policy	The effect of randomized treatment will be assessed even when participants discontinue study medication. Data collection will be maintained and available measurements post-treatment discontinuation used maintaining the treatment label as assigned at randomization.
Breakthrough hemolysis events	Treatment policy	The effect of randomized treatment will be assessed. Breakthrough hemolysis may affect the endpoints considered in the study, hence data collection will be maintained and available measurements collected after breakthrough hemolysis event keeping the treatment labels as assigned at randomization.
MAVEs	Treatment policy	The effect of randomized treatment will be assessed, in particular in the presence or after the occurrence of MAVEs. Data collection will be maintained and available measurements collected after MAVEs used under the treatment assigned at randomization.

1.2.2 Secondary estimands

The population associated with the secondary estimands is the same as for the primary estimands. For these secondary estimands we consider the same intercurrent events as for the primary estimands. The proposed approach in the case of transfusion handling will be described in the estimand definition, while discontinuations of study medication, breakthrough hemolysis events, and MAVEs will be handled with a treatment policy strategy.

The secondary estimands are defined by the evaluation of treatment effect on the following endpoints and summary measures:

- Proportions of participants not receiving any transfusions between Day 14 and Day 168 (Transfusion Avoidance). The summary measure is the same as for the two primary endpoints.

- Difference in achieved hemoglobin changes from baseline between Day 126 and Day 168 where transfusions occurring between Day 14 and Day 168 are treated within a hypothetical strategy (as if the participants had not received any transfusions). The summary measure is the comparison of the mean changes from baseline in hemoglobin levels assessed between Day 126 and Day 168.
- Difference in change from baseline in scores of fatigue using the FACIT Fatigue questionnaire between Day 126 and Day 168, where the strategy applied to transfusions is treatment policy. The summary measure is the comparison of mean changes from baseline in FACIT fatigue scores assessed between Day 126 and Day 168.
- Difference in change from baseline in reticulocytes counts between Day 126 and Day 168 where the strategy applied to transfusions is treatment policy. The summary measure is the comparison of the mean changes from baseline in reticulocyte counts assessed between Day 126 and Day 168.
- Difference in percent change from baseline in LDH between Day 126 and Day 168 where the strategy applied to transfusions is treatment policy. The summary measure is the comparison of the log transformed LDH ratio to baseline assessed between Day 126 and Day 168.
- Rates of breakthrough hemolysis occurring between Day 1 and Day 168. The summary measure is a rate difference.
- Rates of MAVE between Day 1 and Day 168. The summary measure is a rate difference.

An overview of estimands and associated estimation methods are presented in Section 5.2.1

Estimand considerations in case of COVID-19 pandemic impact

The overarching principle for primary and secondary estimands, is answering questions of treatment effect of LNP023 that are valid in conditions when the COVID-19 pandemic is no longer present.

Data capture and clinical evaluation activities include possible adaptations to restrictions for patient access to investigational sites in case of a new infection wave. The planned analyses could be supplemented by supportive analyses as well as sensitivity analyses if required by the presence of deviations from the normal methods of patient follow up and data capture.

Potential impact of a new wave of COVID-19 infections affecting measurements has been minimized through the measures proposed in the study protocol. However other impact that at this stage cannot be excluded, such as withdrawal from study follow up due to infection, which would require dealing with such events as additional intercurrent events. This would define additional estimands, possibly primary and secondary estimands all of which would deal with the COVID-19 related intercurrent events so that inference would still concern treatment effects in a world that is not in the midst of an extraordinary pandemic situation. The methodology for these estimands and additional sensitivity analyses for cases of missing data due to the impact of COVID-19 infections will be specified in detail in an amendment to the document developed in the event of renewed COVID-19 infection waves. Decisions on handling of possible increases

in background risks impacting study endpoints will also take into consideration relevant epidemiological information on local incidence of COVID-19 infections.

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by the sponsor. Data will be analyzed according to Section 12 of the CLNP023C12302 clinical study protocol. The most recent version of SAS and R softwares available in the statistical programming environment will be used for the analysis. All analyses of data using randomization codes to be provided to the DMC will be carried out by an independent statistical group (CRO) as described in the DMC charter; the statistical analyses for the DMC will be drafted in a separate document.

2.1.1 General definitions

2.1.1.1 Study day

Study day is defined as the number of days since the date of first dose of study treatment. The date of first dose of study treatment is defined as Day 1 and the day before the first dose of study treatment is defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the first date of study treatment,

  Study day = Assessment date – Date of first dose of study treatment + 1;

- for dates prior to the first date of study treatment,

  Study day = Assessment date – Date of first dose of study treatment.

If a patient never took study treatment, the randomization date will be used instead of the date of first dose of study treatment. In that case, the randomization date is defined as Day 1 and the day before the randomization is defined as Day -1.

2.1.1.2 Baseline definition

For the analysis on efficacy and safety data in the randomized treatment period (on the analysis sets FAS and SAF as defined in Section 2.2), the baseline value is defined to be the last result obtained at or prior to start of study treatment (Day 1) for baseline demographics, medical history, lab values, vital signs and ECGs. Most variables will have their baseline at Day 1, unless otherwise specified. For assessments not performed at Day 1, the assessment at the screening visit or most recent assessment prior to start of study treatment will be used as baseline. For baseline derivation of laboratory parameters, central lab measurements will be used. If there are no central lab data available, then local lab measurements will be used for baseline computations only.

- The baseline hemoglobin will be the mean of the two confirmatory measurements (planned) taken during screening that confirm the hemoglobin entry criterion in patients who do not receive a transfusion between the first and second confirmatory

measurements. In patients who receive a transfusion after the first confirmatory measurement, the baseline will be the first measurement.

If there is only one confirmatory measurement but additional unplanned measurements taken during screening, for patients who do not receive transfusion in the screening period, then the mean of the first measurement and the second measurement taken within 2 to 8 weeks after the first measurement will be considered to be the baseline. In patients who receive a transfusion after the first measurement, the baseline will be the first measurement. For patients with transfusion on same day, but hemoglobin measurement taken before transfusion, the baseline hemoglobin should be the average of the measurements considering the hemoglobin measurement before transfusion.

- The baseline score of fatigue using the FACIT-Fatigue questionnaire will be defined as the mean of first assessment prior to Day 1 and the Day 1 value. Baseline derivation for EORTC QLQ-C30 will be similar to the baseline derivation of FACIT-Fatigue questionnaire. Baseline derivations for all other patient reported outcomes (PGIS, and EQ-5D-5L) will be at Day 1 or the last value before start of study treatment.

For the analysis on long term safety data on patients receiving LNP023 200 mg b.id. in the randomized treatment period or the treatment extension period (on the analysis set Comb. SAF as defined in Section 2.2), the baseline value for patients who received anti-C5 antibody in the randomized period will be defined as the last result obtained prior to the start of LNP023 200 mg b.i.d. in the treatment extension period.

2.1.1.3 Post baseline measurement

Post baseline measurements are defined as those assessments after the start of study treatment.

2.1.1.4 Change from baseline

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value; and

If baseline or post-baseline values are missing, then the change from baseline will be missing.

2.1.1.5 Completion and last contact

A patient will complete the randomized treatment period when the patient has completed the Day 168 visit in the study or EOS for participants who discontinue from the study prior to the treatment extension period. The maximum of the date of last visit in the randomized treatment period, date of withdrawal of consent (in case of withdrawal from study), would be the date of last contact for the patient in the randomized treatment period.

2.2 Analysis sets

The **Screening set** (SCR) consists of all patients who have been screened. If a patient has been screened multiple times then the patient should be included for his/her last screening.

The purpose of the screening set is to describe the number of patients in screen failures. Screen failures are the patients included in the screening set but not in the randomized set.

The **Randomized Analysis Set** (RAS) consists of all randomized participants. This data set will not be used for any analyses, and is solely for providing complete information on how patients were randomized.

The **Full Analysis Set** (FAS) comprises all participants to whom study treatment has been assigned by randomization, and will exclude participants to whom a randomization number has been assigned in error (mis-randomized participants). According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to, taking into account the strata in which they were included during the randomization procedure. This will be the data set used for analysis of all efficacy endpoints. For efficacy analysis, the data on the randomized treatment period will be analyzed.

It is expected that the Randomized Set and Full Analysis Set will be identical. For that reason, the Randomized set will be described only once and all the analyses (disposition in particular) will be produced on the Full Analysis Set, with the following exceptions: Randomized set will be used for the description of protocol deviations and the description of patients randomized by country.

The **Safety Set** (SAF) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment they received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The **LNP023 combined Safety Set** (comb. SAF) includes all participants who received at least one dose of LNP023 200 mg b.i.d either in the randomized treatment period or in the treatment extension period. The analysis set will be used for analyzing long term safety data on LNP023 and will consider analysis of the data collected after the first administration of LNP023. Note that for this specific safety set a specific baseline will be defined (see Section 2.1.1.2).

2.2.1 [redacted]

[redacted]

- [redacted]

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for the FAS. In addition, summaries of relevant past or current medical conditions will be presented.

Categorical data will be presented as frequencies and percentages. The summary statistics shown for continuous data will be mean, standard deviation, median, minimum, and maximum.

2.3.1 Patient disposition

Randomized treatment period

The number of patients screened, screened but not randomized, randomized, completed and discontinued from the study in the randomized treatment period will be summarized. The reasons for screen failure will be provided. Participants who discontinued from the study in the randomized treatment period will also be summarized with reasons for discontinuation. In addition, number of participants who discontinued study treatment, reason for discontinuation of study treatment and number of participants who discontinued study treatment but stayed in the randomized treatment period will be summarized. Participants who discontinued study treatment but stayed in the study during the randomized treatment period are defined as participants with the date of study discontinuation or Day 168 visit - the end date of study treatment > 0.

Treatment extension period

The number of participants who completed and discontinued from the study in the Treatment extension period will be summarized. The reasons for discontinuation will be provided.

For each treatment group, the number of participants with protocol deviations will be tabulated by deviation category and deviation for the RAS.

Based on the RAS, the number of participants randomized by country will be presented.

2.3.2 Relevant Medical History and current medical conditions

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology using the most recent version at the time when the last participant has completed the randomized treatment period. Medical history terms will be summarized by primary system organ class and preferred term. Hemoglobin history prior to screening (defined as mean result for hemoglobin obtained over a minimum of 4 months prior to screening), disease duration (as derived from the start date of PNH in Medical History page up to the date of screening), and duration of anti-C5 treatment will be summarized separately.

History of MAVE (MAVEs prior to screening) will be summarized by medical history term. Anti-C5 antibody medication history 6 months prior to randomization will be summarized by medication (eculizumab, ravulizumab) and dose administered. Transfusion history (the numbers of transfusions and unit numbers of packed-RBC received in the last 12 months prior to screening), transfusions up to 6 months prior to randomization (yes, no) will be presented. Additionally, type of transfusions and number of units of packed RBC transfused will be summarized. Vaccination history will be presented by serogroup/polyvalent.

Alcohol history will be reported based on usage (never, current, former). Smoking and vaping history will be presented based on type of substance (e-liquids, tobacco) and usage (never, current, former).

PNH related signs and symptoms at baseline will be tabulated. Percentage of C3d positive PNH-type RBCs (Type I, Type II and Type III RBC), PNH Type I, Type II and III RBC, total PNH clone size in RBC, PNH clone size in WBCs (granulocyte, monocyte), total C3 positive PNH-type RBCs (C3d positive PNH Type II and Type III RBC) at baseline will also be reported. The total PNH clone size in RBC will be calculated as the sum of PNH Type II RBC and Type III RBC.

All the summaries will be presented on FAS and for both treatment groups.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatments

Treatment of interest

The randomized treatment (the investigational treatment LNP023 200 mg b.i.d. or stable regimen of anti- C5 antibody therapy (SoC)) regardless of whether the participant discontinues treatment (treatment policy).

Duration of treatment in the randomized treatment period

The duration of randomized treatment in the randomized treatment period is defined as the duration from the date of first administration of study treatment in the randomized treatment period to the maximum of the following:

- Date of last administration in the randomized treatment period
- Minimum between:
  - Date before the planned next administration after the last administration
  - Date before any treatment administration in the treatment extension period
  - Date of death

In the case of LNP023, the end of the randomized treatment period is the date of last administration (any dose) which is also the day before the next planned administration.

In the case of anti-C5 administered at fixed time intervals, the end of the randomized treatment period is until one day before the next planned dose, except if the participant has received open-

label LNP023 earlier (for instance the day after the last dose) in which case the participant is not considered in the randomized treatment period anymore.

Duration of treatment in the treatment extension period

The duration of LNP023 treatment in the treatment extension period will be defined as the duration from the first date of administration of LNP023 200 mg b.i.d in the treatment extension period to the date of last administration of LNP023 (any dose) in the treatment extension period.

Overall iptacopan duration of treatment

An overall duration of iptacopan (LNP023) treatment would include both randomized treatment period and treatment extension periods, with a start date and a stop date as described above for randomized treatment period and treatment extension periods respectively.

Exposure and Dose Intensity for LNP023

The Safety sets will be used for the analyses of exposure to LNP023 (based on SAF and Comb. SAF separately) described below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure (in days) to LNP023 as well as the dose intensity and the relative dose intensity of LNP023 and anti-C5 treatments will be summarized by means of descriptive statistics using SAF during the randomized treatment period and for overall (for LNP023 in the Comb. SAF).

Duration of exposure to study treatment will be calculated as the number of days between the first dose date and the last dose date exposed to that treatment over the specified period but excluding temporary treatment interruptions (expressed as: Duration of exposure = Date of last known dose of study drug – Date of first dose of study drug + 1 excluding interruptions).

The duration of exposure to study treatment will be computed and summarized as the duration of treatment, but excluding temporary treatment interruptions. To establish the start of an interruption, the same rules should apply as for end of the duration of treatment described above.

For instance a patient receiving eculizumab 3 weeks apart while the administration scheme is every 2 weeks will have an interruption of 7 days starting 2 weeks after the first dose and lasting until the last day before the next dose.

For patient on LNP023, an interruption will be defined as at least one full day without any dose.

Cumulative exposure for the randomized treatment period based on SAF will be summarized as a categorical variable classified into ≤4, ≤8, ≤12, ≤16, ≤20, ≤24 weeks. Cumulative exposure on LNP023 based on Comb. SAF will be summarized as a categorical variable classified into ≤4, ≤8, ≤12, ≤16, ≤20, ≤24, ≤28, ≤32, ≤36, ≤40, ≤44, ≤48 weeks.

The duration of exposure will be the basis for the computation of the dose intensity and the relative dose intensity. The dose intensity for patients on LNP023 will be computed as the ratio of actual cumulative dose received and actual duration of exposure. Relative dose intensity for patients on LNP023 will be computed as the ratio of dose intensity and planned dose intensity.

The planned dose intensity for patients on LNP023 will be 400 mg/day. The dose intensity for patients on LNP023 will be summarized as a categorical variable classified into the categories stated in Table 2-1. Relative dose intensity will also be summarized on a continuous scale as well as considering categories (%): ≤ 75 , > 75-90, > 90-100 and summaries on dose intensities will be presented on SAF and Comb. SAF separately.

The information on LNP023+transfusions will be summarized as a categorical variable considering the dose intensity and tranfusions in the randomized treatment period. Summaries on the categories stated in Table 2-1 will be considered. Such summaries will be presented on SAF and Comb. SAF separately.

For participants on LNP023 the calculation of duration of treatment, exposure, dose intensity and relative dose intensity will include the investigational treatment LNP023 200 mg bid as well as the LNP023 tapering doses (if applicable).

Table 2-1 Summary on dose intensity and transfusions for patients on LNP023

Dose intensity	Dose intensity and transfusions
<400 mg/day	<400 mg/day + no transfusion
400 mg/day	<400 mg/day + 1 transfusion
	<400 mg/day + ≥2 transfusions
	400 mg/day + no transfusion
	400 mg/day + 1 transfusion
	400 mg/day + ≥2 transfusions

For participants on LNP023, an interruption will be defined as at least one full day without any dose. The number of participants on LNP023 with interruptions, number of interruptions and durations of interruptions will be summarized separately on SAF and comb. SAF. The information on study medication intake for the LNP023 participants having at least one interruption will be listed. The number of participants with missed doses and number of missed doses will be summarized on SAF.

Dose Intensity for anti-C5 treatment

Relative dose intensity for each participant on anti-C5 treatment in the randomized treatment period will be defined as the ratio of actual cumulative dose received and planned cumulative dose. The actual cumulative dose received by a participant is defined as the stable dose of anti-C5 medication*number of infusions received by the participant in the study. The planned cumulative dose is defined as the stable dose of anti-C5 medication*number of infusions the participant should have received as per protocol considering the duration of treatment in the study.

Based on SAF, for participants receiving the anti-C5 antibody treatment in the randomized treatment period, the information will be summarized according to the number of participants

receiving specific doses and regimens of anti-C5 antibody treatment (eculizumab or ravulizumab). Based on SAF, the information on anti-C5 antibody+transfusions will be summarized as a categorical variable considering the number of participants receiving specific doses and regimens of anti-C5 antibody treatment (eculizumab or ravulizumab) and transfusions in the randomized treatment period. The following categories for transfusions will be considered: no transfusion, 1 transfusion, ≥2 transfusions.

2.4.2 Prior, concomitant and post therapies

Medications and significant non-drug therapies started and stopped prior to study treatment, and those taken concomitantly, will be summarized by treatment group separately based on SAF and Comb. SAF. Among the concomitant medications, rescue medications will be summarized separately by treatment group based on SAF and Comb. SAF. The medications and significant non-drug therapies will be classified into "prior", "concomitant", or "post-treatment" based on the start/end dates. The rescue therapy will be used for analysis as it is reported by the investigator under the subcategory of Rescue Medications/Therapy on the Concomitant Medication, Surgical and Medical Procedures CRF page

Prior: Any medication and significant non-drug therapy with a start date and end date before Day 1.

Concomitant: Any medication or significant non-drug therapy administered at least once during the duration of the treatment (as defined in Section 2.4.1). It does not include 7 days after the last dose of LNP023 as in the definition of the on-treatment period for treatment emergent adverse event (TEAE). Medications started prior to first day of study drug intake and continuing after study drug start will be counted as concomitant.

Post-treatment medication will be defined as any medication with start date after the end of treatment (any dose).

A therapy started within 7 days after the last dose of LNP023 is not considered as concomitant although some TEAEs leading to concomitant medications may be reported in that period. The objective of this convention is to avoid reporting as concomitant medication some post treatment therapies targeting the study indication.

Prior, concomitant, post-treatment medications will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group. More than one ATC class per medication is possible and the medication will be reported under all applicable classes.

Prior, concomitant, and post-treatment therapies will be recorded and summarized separately for surgical and medical procedures.

Booster vaccinations received by participants any time during the study (including randomized treatment period, treatment extension period) will be tabulated by serogroup/polyvalent and for each period. All vaccinations will also be recorded as prior and/or concomitant medication, as appropriate

2.5 Analysis of the primary objective

For all efficacy analyses based on laboratory data (e.g. hemoglobin, reticulocytes etc.) addressing primary and secondary objectives, the information obtained from the central lab will be used.

2.5.1 Primary endpoint(s)/Primary estimand(s)

The two primary endpoints corresponding to the primary estimands are defined. The first primary endpoint defines the response as sustained increase in hemoglobin and a participant as a responder if:

- The change from baseline in hemoglobin is ≥ 2 g/dL on three out of four measurements taken at the visits occurring in the last six weeks (from Day 126 to Day 168) of the randomized treatment period, and
- The participant has not met the criteria for administration of RBC transfusions nor received a transfusion between Day 14 and Day 168.
- The baseline hemoglobin will be the mean of the two measurements taken during screening that confirm the hemoglobin entry criterion in patients who do not receive a transfusion between the first and second confirmatory measurement. In patients who receive a transfusion after the first confirmatory measurement, the baseline will be the first measurement.

The second primary endpoint defines response as the achievement of sustained hemoglobin levels and a participant as a responder if:

- The hemoglobin levels are ≥ 12 g/dL on three out of four measurements taken at the visits occurring in the last six weeks (from Day 126 to Day 168) of the randomized treatment period, and
- The participant has not met the criteria for administration of RBC transfusions nor received a transfusion between Day 14 and Day 168 .

Handling of intercurrent events of primary estimand

Reaching the protocol established criteria for RBC transfusions will be handled using a composite strategy for both primary endpoints.

Intercurrent events stemming from discontinuation of treatment, breakthrough hemolysis events and MAVEs, expected to be reflected in the endpoint, are handled with a treatment policy strategy.

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.2.1 Primary null hypotheses

Superiority of LNP023 in achieving a larger proportion of participants who reach a sustained hemoglobin response compared to anti-C5 antibody treatment will be tested by the null hypothesis comparing the probability of response in LNP023 (π_{LNP023}) to the probability of response on anti-C5 antibody treatment ($\pi_{\text{anti-C5}}$) for both endpoints as:

$$H_0 : \frac{\pi_{LNP023}/(1-\pi_{LNP023})}{\pi_{anti\text{-}C5}/(1-\pi_{anti\text{-}C5})} = 1$$

versus

$$H_A : \frac{\pi_{LNP023}/(1-\pi_{LNP023})}{\pi_{anti\text{-}C5}/(1-\pi_{anti\text{-}C5})} > 1$$

2.5.2.2 Familywise type I error rate control

The overall study Type I error is one-sided 0.025. The multiplicity adjustment to be applied for the test of two primary endpoints as well as to the secondary endpoints for which the study wise Type I error is controlled, is described graphically in Figure 2-1.

The secondary endpoint hypotheses are described in Section 2.6. Figure 2-1 describes an abbreviated version of the alpha propagation rules following principles described in Bretz et al. (2009, 2011) which can be summarized as follows:

1: Hypotheses H1 and H2 are tested using the permutation test. The available ½ study alpha may be distributed between the two as shown in the figure by shifting 10% from a successfully rejected hypothesis.

2: Secondary endpoints H3 and hypotheses H41, H42, and H43 denoted by the node H4i if a primary endpoint hypothesis is rejected, are tested by a weighted Simes procedure with 50% of weight available for secondary endpoints (45%) given to H3 and the other 50% of the corresponding weight (45%) given equally to hypotheses in H4i (see Figure 2-2).

3: Secondary endpoints in H5i: H51, H52, and H53 are tested after successful rejection of hypotheses in H1, H2, H3, and all H4i.

The alpha weights as shown in the graph are only schematic and should not be interpreted as compatible with the principles of the intended graphical procedure. Full details including complete alpha propagation rules are provided in Figure 2-2.

H1: Increase in hemoglobin ≥ 2 g/dL from baseline

H2: Reaching a fixed threshold ≥ 12 g/dL

H3: Transfusion avoidance

H41: Change from baseline in hemoglobin levels

H42: Change from baseline in FACIT-fatigue scores

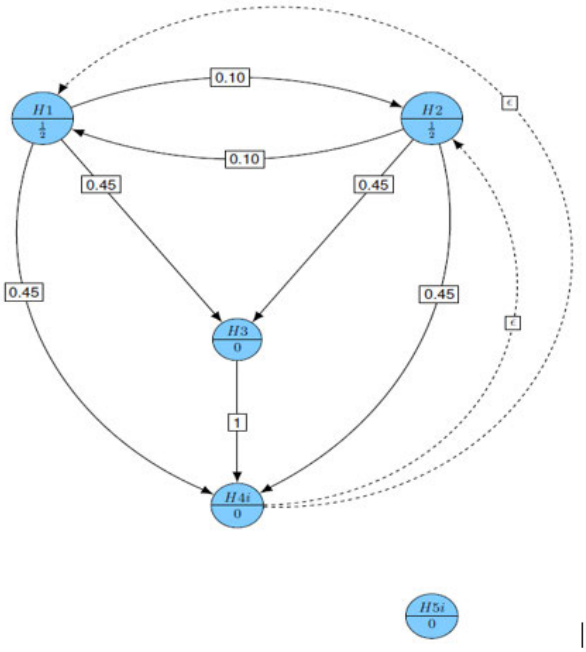
H43: Change from baseline in reticulocyte counts

H51: Percent change from baseline in LDH

H52: Rates of breakthrough hemolysis

H53: Rates of Major Adverse Vascular Events

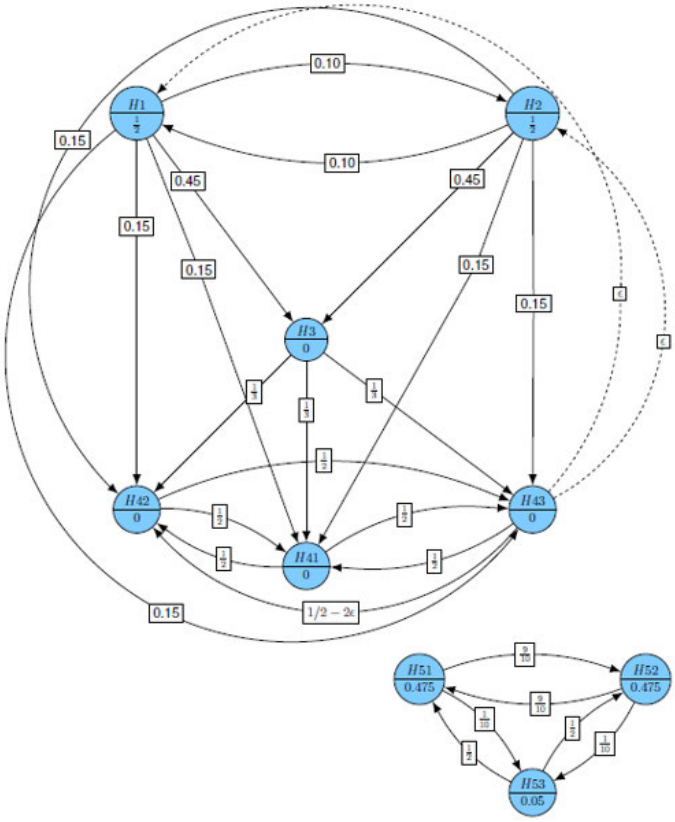
Figure 2-1 Graphical display of multiple testing procedure



H1:Increase ≥ 2 g/dL
H2: Threshold ≥ 12 g/dL
H3: Transfusion Avoidance
H4i contains:
H41: Change in Hb
H42: FACIT-Fatigue
H43: Reticulocytes counts
H5i contains:
H51: LDH
H52: Breakthrough Hemolysis
H53: MAVE

Figure 2-2 Detailed description of graphical procedure used for testing of primary and secondary endpoints

Hypotheses H51, H52 and H53 are tested only after successful rejection of H1, H2, H3, H41, H42, and H43



1. The primary endpoint hypotheses are both tested at ½ alpha (0.025/2=0.0125) each, with the p-value level corresponding to rejection derived using the permutation method described below (Section 2.5.2.4). If only one of the 2 hypotheses, H1 (increase in hemoglobin ≥ 2 g/dL from baseline) and H2 (reaching a fixed threshold ≥ 12 g/dL) is rejected using the 1.25% percentile of the permuted p-values, the rejected hypothesis may pass 10% of the local alpha to the other hypothesis. The increased alpha fraction available is equivalent to using the 1.375% percentile of the permuted p-values to be compared with the observed p-value for the hypothesis that failed to be rejected using the 1.25% percentile.

2. If a primary endpoint hypothesis is rejected, its local alpha is the passed on to the set of four secondary endpoint hypotheses H3, H41, H42, and H43. The test of these hypotheses is a weighted Simes closed testing procedure, and the alpha propagation rules reflect the weights given: ½ of the local alpha available for the secondary endpoint hypotheses (45%) is passed on to H3, while the other 45% is propagated using equal weights to the 3 hypotheses denoted as H41, H42, and H43. If rejected H3 passes the available local alpha equally to all 3 hypotheses H41, H42, and H43. The alpha propagation between the 3 hypotheses denoted H41, H42, and

H43 gives them equal weights. When all of H41, H42, and H43 have been rejected, their local alpha will be propagated back to the primary endpoint hypotheses (represented by the 2 epsilon edges from H43 to H1 and to H2).

3. If all hypotheses (H1, H2, H3, H4i) are rejected, the three hypotheses in H5i will be tested using a weighted Simes' closed testing procedure at full study alpha, where weights of 0.475 are given to each of H51 and H52, and 0.05 to H53. If one of H51 or H52 is rejected, its local alpha up to 90% will be passed to the other hypothesis at the same weight level, and 10% to H53. The weights for alpha propagation from H53 are described in the graph.

Unadjusted p-values and unadjusted 95% CI for all the endpoints stated in Figure 2-2 will be presented. The unadjusted p-values and CI will not be reflective of the pre-specified multiplicity scheme and hence should not be interpreted as a basis for claiming significance.

2.5.2.3 Summary statistics for the primary variable

All descriptive statistics supportive of the the primary variable will be based on non-imputed and observed data. For patients who did not require any RBC transfusion (i.e. not met the criteria for administration of RBC transfusions nor received a transfusion) between Day 14 and Day 168 separate summaries will be presented by treatment group on the following information:

Number of participants having no missing hemoglobin data in the last six weeks (from Day 126 to Day 168), number of participants having an increase in hemoglobin ≥ 2 g/dL from baseline on three out of four measurements taken at the visits occurring in the last six weeks (from Day 126 to Day 168), Number of participants reaching a fixed threshold ≥ 12 g/dL on three out of four measurements taken at the visits occurring in the last six weeks (from Day 126 to Day 168), Number of participants having both an increase in hemoglobin ≥ 2 g/dL from baseline and reaching a fixed threshold ≥ 12 g/dL on three out of four measurements taken at the visits occurring in the last six weeks (from Day 126 to Day 168).

2.5.2.4 Statistical model for primary variable

The test of hypothesis will be implemented by fitting a conditional logistic regression model, which conditions on the stratum within which participants were randomized, and includes as covariates treatment, sex, age (indicator of age ≥ 45 years), and an indicator variable of baseline hemoglobin ≥ 9 g/dL, the same for each of the two endpoints.

In case of non-convergence in any of the multiple imputed datasets arising from sparsity or no response in one of the treatment arms in at least one imputed dataset, the logistic regression model based on Firth's penalized maximum likelihood method (Heinze and Schemper 2002; Firth 1993) as stated in Section 2.5.6 will be implemented. The documentation of the covergence issues will be provided in an appendix of the clinical study report. The same analysis model will be used for all steps of the primary analysis including the permutation test procedure with multiply imputed data (Section 2.5.3) and for evaluation of the distribution of the permutation of the test statistics. In such a situation, the test of hypothesis will be implemented by fitting a logistic regression model, based on Firth's penalized maximum likelihood method, which includes as covariates stratum, treatment, sex, age (indicator of age ≥ 45 years), and an indicator variable of baseline hemoglobin ≥ 9 g/dL, the same for each of the two endpoints.

Odds ratio

The summary measure provided will be the log odds ratio derived as the coefficient for treatment effect from the logistic regression. The estimated odds ratios and their confidence intervals will be provided for each of the two endpoints as well as the corresponding p-values. Log odds ratios obtained from multiple imputations will be combined using Rubin's rule.

Hypothesis testing

To test for the two primary endpoints, we will apply a permutation test to each of the two endpoints. The reference distribution of the p-values will be derived using 50,000 permuted realizations of the treatment labels within each randomization stratum and obtaining the p-values of each of the two endpoints for each realization of permuted treatment labels. The observed p-values with the actual treatment labels will be compared with the 1.25^{th} percentiles (or 1.375^{th} percentile as appropriate – See testing strategy in Section 2.5.2.2) of the 50,000 resulting p-values from fits with permuted treatment labels for each of the two endpoints (Westfall and Troendle 2008, Westfall and Wolfinger 1997, Westfall et al 1993).

2.5.3 Handling of missing values not related to intercurrent event.

For the primary response definitions, RBC transfusion will qualify the patient as a non-responder, hence missing hemoglobin data after meeting the criteria for transfusion or after receiving a transfusion during Day 14 to Day 168 does not impact the primary analyses.

Missing hemoglobin data due to withdrawal from the study in the randomized treatment period in the event that a patient did not have a prior RBC transfusion, will be imputed in a multiple imputation framework based on pattern mixture models. This aims to be consistent with the inclusion of hemoglobin data under the treatment policy strategy following all other intercurrent events. The need for transfusion will then be derived from this imputation with imputed values $\leq$ 9g/dL considered sufficient to warrant a transfusion. Furthermore, the impact on hemoglobin levels will also take into account the treatment participants were on at the time of withdrawal from study:

The details of missing data handling as well as additional details for implementing the analyses are as follows:

- For participants withdrawing from the study after discontinuation of LNP023, the model implemented will recover a return to pre-treatment levels of Hb. This will be implemented by borrowing from the control group (anti-C5 antibody treatment) whose on-treatment response will be considered similar to the pre-treatment levels in participants in the LNP023 arm.
  In practice, imputation using the "copy-reference" will be used: this is achieved by imputing post-intercurrent event (I/C) values assuming the joint distribution of an LNP023 participant's outcome data pre- and post-I/C is Multivariate Normal with mean vector and covariance matrix corresponding to that of the reference arm, regardless of when the I/C occurred [Carpenter et al 2013] [Cro et al 2020].
  If an LNP023 group participant is above the reference group mean, then this positive residual will be reflected in subsequent draws from the conditional distribution of post-I/C data, to a degree dependent by the correlation. As a result, this LNP023

participant's profile slowly reverts backs to the reference group for later visits [Carpenter et al 2013].

- For anti-C5 randomized participants withdrawing from the study, missing data will be imputed by borrowing from participants in the anti-C5 antibody treatment arm (missing at random (MAR) assumption).
- For participants with intermittent missing data during randomized treatment period, where reasons for missingness are assumed to be unrelated to response or compliance status, their missing data will be handled with a MAR approach and imputed consequently.
- For LNP023 randomized participants having missing data at the end of the follow-up (irrespective of whether they were immediately preceding treatment discontinuation or after treatment discontinuation will be imputed using "copy-reference" approach.

The model for imputation will be mixed model for repeated measures (MMRM) considering an unstructured covariance matrix and include main effect of prior anti-C5 treatment, transfusion history, age (indicator of age ≥ 45 years), sex, treatment, visit, baseline hemoglobin.

Implementing the permutation test procedure with multiply imputed data

The process for implementing multiple imputation alongside the permutation test is as follows:

1) Multiple imputation will be performed 100 times based on the randomized treatment labels, and following the imputation rules outlined in Section 2.5.3, resulting in 100 imputed datasets. The responder status of each participant will be derived within each imputed dataset. The conditional logistic regression model described in Section 2.5.2.4 will be fitted to each imputed dataset and a single p-value derived by combining the results (estimated log odds ratio and corresponding standard error) using Rubin's rule.

   If in one or several of the imputations, it happens that no responses are observed in one of the treatment arms, the suggested multiple imputation method by Rubin's rule cannot be applied due to the non-existence of treatment effect estimates in the approach. In case of sparse responder in one treatment arm, even if a treatment effect can be computed, the assumptions of asymptotically normal treatment effect estimates underlying the application of Rubin's rule breaks down. The use of Firth's penalized likelihood method (as stated in Section 2.5.2.4) to estimate the treatment effects and their standard deviation allows to overcome this limitation.

2) A set of 50,000 permutations of the randomized treatment labels will be created for each randomization stratum in each imputed dataset The same set of permutations of the randomized treatment labels will be used for all imputed datasets.

3) The logistic regression model described in Section 2.5.2.4 will be fitted to each imputed dataset using each permutation of the treatment labels, i.e. 100 analyses will be performed for each permutation.

4) For each permutation, the 100 results will be combined using Rubin's rule to obtain a single p-value for each permutation. The resulting 50,000 p-values will form the basis of the permutation test described in Section 2.5.2.4.

5) The observed p-value calculated in Step 1) will be compared to the 1.25th percentile (or 1.375th percentile as appropriate – See testing strategy in Section 2.5.2.2) of the 50,000 p-values derived in Step 4).

The same procedure will be applied to both primary endpoints simultaneously: imputation will be done on hemoglobin data from which the two primary endpoints will be derived.

2.5.4 Sensitivity analyses for primary endpoint/estimand

The sensitivity of the primary estimands with respect to the treatment of missing data described above will be evaluated using a tipping point analysis.

In this method, missing values in each treatment group will be imputed separately as mentioned in Section 2.5.3 and an adjustment 'delta' for the LNP023 group will be applied to the imputed values. The delta values will lead to hemoglobin values being lower than those imputed in the LNP023 group. The primary analysis, as stated in Section 2.5.2.4 , will be repeated applying each of the delta values in the LNP023 group. The results will be displayed in a forest plot displaying the odds ratio and 95% confidence intervals as for the primary analysis (See Section 2.5.2.4).

Additional sensitivity analyses on the two primary endpoints will be performed where missing central lab hemoglobin data will be replaced by available local lab data collected at the same visit. The regression model which is used for primary efficacy analysis will be performed for the two primary endpoints. In addition, the marginal proportions, their difference and ratio will be computed using logistic regression model (see Section 2.5.6.1).

2.5.5 Supplementary analyses

A supplementary estimand considering the use of rescue therapy (as defined in the study protocol) under intercurrent event as treatment failure, for the purpose of efficacy assessment, will be performed. The supplementary estimand will have the same population, treatment of interest, and summary measure as the primary estimand. In addition, the marginal proportions, their difference and ratio will be computed using logistic regression model (see Section 2.5.6.1). The regression model which is used for primary efficacy analysis will be performed for the supplementary analyses on the two primary endpoints. For the analysis the following will be considered:

- Participant meeting the criteria for administration of RBC transfusions or having received a transfusion between Day 14 and Day 168 will be considered treatment failures
- Use of rescue medication and rescue therapy during the randomized treatment period between Day 1 and Day 168 will be considered treatment failures. The rescue therapy will be used for analysis as it is reported by the investigator under the subcategory of Rescue Medications/Therapy on the Concomitant Medication, Surgical and Medical Procedures CRF page.
- Discontinuations of study medication for any reason will be handled with treatment policy strategy.

2.5.6 Supportive analyses

A key supportive estimand reflecting the proportions of responders for each of the two primary endpoints will be derived from fitting a logistic regression model with a common intercept, where the stratum indicator (prior anti-C5 antibody treatment, transfusion history) will be covariates in the model, together with the covariates sex, age (indicator of age ≥ 45 years), and an indicator variable of baseline hemoglobin ≥ 9 g/dL. The estimated probabilities will be derived as a standardized estimator, to reflect the marginal probability of response for all participants in the study if they had received LNP023 or anti-C5 antibody treatment. The confidence intervals for the difference as well as for the ratio of proportions will be derived by use of bootstrap. Cases of non-convergence due to sparsity or if there are no responders in one treatment arm in at least one imputed dataset will be handled within a penalized likelihood (Firth) approach.

If there are convergence issues or quasi-complete separation in fitting a logistic regression model with covariates to any of the imputed datasets, then a logistic regression model with only treatment will be fitted. If the logistic regression model with only treatment also leads to convergence or quasi-complete separation for any of the imputed datasets, then logistic regression with Firth approach including only treatment as a covariate will be implemented.

The final model which is used for estimating the marginal treatment effect based on imputed datasets, will be used for bootstrap for derivation of the confidence intervals (Section 2.5.6.1).

2.5.6.1 Marginal proportion of responders

In order to quantify the magnitude of the effect of treatment with LNP023 compared to anti-C5 antibody treatment, estimates of the proportion of responders in each treatment group, as well as the difference and ratio between groups will be derived using the marginal standardization method (Section 5.2.2.2).

This method uses the same fitted logistic model as described in Section 2.5.6, but involves using the model to predict, for each participant in the study, their outcome assuming assignment to each of the two treatment groups in turn, using observed values for the other covariates. Confidence intervals will be derived using bootstrap methods.

In case of multiple imputation, the marginal proportions, their difference and ratio, and the associated two-sided 95% confidence intervals will be obtained by combining multiple imputations with bootstrapping as follows:

1) Point estimates for each parameter of interest will be obtained by averaging across the estimates obtained from each multiple imputed dataset
2) The 95% confidence interval will be obtained by bootstrapping each imputed dataset 100 times and selecting the 2.5^{th} and 97.5^{th} percentiles of the pooled distribution of 10,000 bootstrapped parameter estimates (obtained from 100 imputed datasets and 100 bootstrap samples from each imputed dataset) as the confidence interval boundaries

2.5.6.2 [redacted]

[redacted]

2.5.6.3 Additional supportive analyses

A supportive analysis in order to address the primary estimand will be done by fitting a stratified Cochran Mantel Haenzel (CMH) test to each of the two primary endpoints separately. Handling of missing data will be similar to that stated in Section 2.5.3 but the results from the CMH test applied on each imputed dataset will be combined using Rubin's rules (Lu, 2020).

2.6 Analysis of secondary endpoints/estimands

2.6.1 Secondary endpoints/secondary estimands

Descriptive statistics and summaries on the secondary endpoints based on FAS will be provided.

2.6.1.1 Transfusion avoidance

The number and percentage of patients in each treatment group not receiving and not meeting the criteria for administration of packed RBC tranfusions in the randomized treatment period will be summarized overall and by transfusion during the last 6 months prior to randomization (i.e. transfusion received/not received). The number and percentage of patients in each treatment group not receiving and not meeting the criteria for administration of RBC transfusion between Day 14 and Day 168 will be summarized overall and by transfusion during the last 6 months prior to randomization (i.e. transfusion received/not received). Time to first packed RBC transfusion from start of study treatment (Day 1) will be plotted using Kaplan Meier curves for overall and by transfusion during the last 6 months prior to randomization (i.e. transfusion received/not received).

For RBC transfusions during the study, the hemoglobin level criterion deemed appropriate by the investigator for requiring the transfusion and signs and symptoms reported prior to receiving the transfusion will be summarized by treatment. The information will be summarized based on the 'Transfusion- during the study' CRF page.

Transfusion avoidance will be evaluated comparing the proportion of participants not receiving and not meeting the criteria of administration of RBC transfusion between Day 14 and Day 168, similarly to the comparison applied to the primary estimand by means of the odds ratio (as in Section 2.5.2.4) with standardized marginal proportions (as in Section 2.5.6.1) derived similarly (including in both cases the randomization strata and covariates). The logistic regression model will include the following covariates: prior anti-C5 treatment, transfusion history , sex, age (indicator of age ≥ 45 years), and an indicator variable of baseline hemoglobin ≥ 9 g/dL.

In case of non-convergence arising from sparsity or no response in one of the treatment arms, the logistic regression model based on Firth's penalized maximum likelihood method (Heinze and Schemper 2002; Firth 1993) as stated in Section 2.5.6 will be implemented.

The p-value obtained from the model will be included in the multiple testing procedure mentioned in Figure 2-1 and Figure 2-2.

2.6.1.2 Change from baseline in hemoglobin levels

Comparison of change from baseline in hemoglobin levels under the hypothetical situation in which participants would not have received RBC transfusions on any of the treatments. For this analysis, if a participant had a transfusion during the randomized treatment period then the hemoglobin values 30 days following the transfusion will be considered missing and hemoglobin data will be imputed. In practice, this would be implemented considering participants on LNP023 and on anti-C5 to have data imputed assuming missing at random (Section 2.5.3).

The model for the comparison between treatments is a mixed model for repeated measures (MMRM) considering an unstructured covariance structure. The model will include main effect of prior anti-C5 treatment, transfusion history, age (indicator of age ≥ 45 years), sex, treatment, visit, baseline hemoglobin and the interactions between visits and treatment and visits and baseline levels. The treatment contrasts will be computed as the comparison of treatments corresponding to the average measured in the last 6 weeks of randomized treatment (that is the visits occurring between Day 126 and Day 168). The p-value obtained from the model will be included in the multiple testing procedure mentioned in Figure 2-1 and Figure 2-2.

The estimated least square mean estimate of the treatment effect and the associated 95% will be plotted over time.

2.6.1.3 Change from baseline in FACIT-Fatigue scores

The endpoint consists of changes from baseline in scores of fatigue using the FACIT-Fatigue questionnaire where baseline is defined as in Section 2.1.1.2 . As for the other endpoints, the longitudinal model will be a repeated measures model including test scores collected at all visits.

The model for the comparison between treatments is a MMRM considering an unstructured covariance structure. The model will include main effect of prior anti-C5 treatment, transfusion history, age (indicator of age ≥ 45 years), sex, treatment, visit and baseline in scores of fatigue, and the interactions between visits and treatment and visits and baseline levels. The comparison between treatments will be an average of treatment estimates derived for visits occurring between Day 126 and Day 168. The p-value obtained from the analysis will be included in the

multiple testing procedure mentioned in Figure 2-1 and Figure 2-2. The estimated least square mean estimate of the treatment effect and the associated 95% will be presented over time.

2.6.1.4 Change from baseline in reticulocyte counts

The comparison of the change from baseline in absolute reticulocyte counts will be derived from a MMRM including data collected throughout the study and where baseline is defined as the value on Day 1. The model for the comparison between treatments is a MMRM considering an unstructured covariance structure. The model will include main effect of prior anti-C5 treatment, transfusion history, age (indicator of age ≥ 45 years), sex, treatment, visit, baseline reticulocyte count and the interactions between visits and treatment and visits and baseline levels. The comparison between treatments will use the average of model derived estimates for each treatment obtained at visits occurring between Day 126 and Day 168. The p-value obtained from the analysis will be included in the multiple testing procedure mentioned in Figure 2-1 and Figure 2-2. The estimated least square mean estimate of the treatment effect and the associated 95% will be presented over time.

2.6.1.5 Percent change from baseline in LDH

The treatment effect on percent change from baseline in LDH will be assessed using a MMRM of log transformed ratio to baseline based on all observations collected during randomized. The model for the comparison between treatments is a MMRM considering an unstructured covariance structure. The model will include main effect of prior anti-C5 treatment, transfusion history, age (indicator of age ≥ 45 years), sex, treatment, visit, log-transformed baseline LDH and the interactions between visits and treatment and visits and log-transformed baseline levels. Treatment comparisons will be derived based on the average of the log transformed ratio from baseline in each treatment estimated between Day 126 and Day 168. The p-value obtained from the analysis will be included in the multiple testing procedure mentioned in Figure 2-1 and Figure 2-2. Geometric means and associated 95% confidence intervals will be presented for treatment effect over time.

2.6.1.6 Rates of clinical breakthrough hemolysis

Information of clinical breakthrough events as collected on the 'Breakthrough Hemolysis' CRF page will be used for analysis and the information will also be reported as a part of the adverse event summaries. The following analyses will be done on safety set. The number and percentage of patients experiencing treatment emergent clinical breakthrough hemolysis events in the randomized treatment and on the combined SAF will be summarized.. The information on whether the patient received packed-RBC transfusions and the quantity of packed-RBC transfusions due to clinical breakthrough hemolysis will be summarized by treatment group. Clinical breakthrough hemolysis events (including those in the screening period) will be listed and the treatment emergent events will be flagged.

Based on FAS, the comparison of rates of clinical breakthrough hemolysis will be carried out using a negative binomial model. The model will include the following covariates: treatment, randomization strata (prior anti-C5 antibody treatment, transfusion history), sex, age (indicator of age ≥ 45 years), indicator variable of baseline hemoglobin ≥ 9 g/dL. Following the treatment policy strategy for handling treatment discontinuations, the offset variable will be defined as

the time from Day 1 till minimum (end of study, end of randomized treatment period). The p-value obtained from the analysis will be included in the multiple testing procedure mentioned in Figure 2-1 and Figure 2-2.

If the above model fails to converge or to give valid estimates (if all events are in one level of at least one of the covariates) due to low frequency of occurrences, then the model will be run considering only treatment as a factor in the negative binomial model. If the model fails to converge or to give valid estimates then a Poisson model with treatment as a factor will be fitted. If there is one treatment with no observed events and rate ratio cannot be computed, then rate difference and corresponding p-value will be presented.

2.6.1.7 Rates of Major Adverse Vascular Events (MAVE)

Information of MAVEs as collected on the 'MAVE' CRF page will be used for analysis and the information will also be reported as a part of the adverse event summaries. The number and percentage of participants with treatment-emergent major adverse vascular events (MAVE) in the randomized treatment (based on SAF) and on the combined SAF will be summarized by reported term. The information on MAVEs (including those in the screening period) will be listed and the treatment emergent events will be flagged.

Based on FAS, the comparison of rates of Major Adverse Vascular Events (MAVEs) will be carried out using a negative binomial model. Due to the expected low frequency of occurrences, no covariates are planned to be included. Only treatment will be added as a factor in the negative binomial model. Following the treatment policy strategy for handling treatment discontinuations, the offset variable will be defined as the time from Day 1 till minimum (end of study, end of randomized treatment period). The p-value obtained from the analysis will be included in the multiple testing procedure mentioned in Figure 2-1 and Figure 2-2.

If the model fails to converge or to give valid estimates then a Poisson model with treatment as a factor will be fitted. If there is one treatment having no events and rate ratio cannot be computed, then rate difference and corresponding p-value will be presented.

2.6.2 Statistical hypothesis, model, and method of analysis

The secondary estimands described in Section 2.6.1 will be tested after successful rejection of the null hypothesis associated with the primary estimands following the pre-defined weighting scheme applied to the tests of secondary endpoints and the alpha propagation rules synthesized in the graphical scheme.

For all estimands defined in Section 2.6.1, we consider the same intercurrent events as for the primary estimands, except in the case when the intercurrent event itself is considered an endpoint. In the case of discontinuation of study medication, clinical breakthrough hemolysis events, and MAVEs expected to be reflected in the endpoint the analysis will apply treatment policy, for all endpoints.

2.6.3 Handling of missing values for secondary endpoints

Missing data during study follow up will be imputed following the same principles as for the primary estimands/endpoints: intermittent missing data will be imputed according to the MAR principle in both the arms. Missing data due to withdrawal from the study will be imputed using

a "copy-reference" in the LNP023/iptacopan arm and according to MAR in the control arm (see Section 2.5.3). In general as in Section 2.5.3, the model for imputation will be mixed model for repeated measures (MMRM) considering an unstructu.red covariance structure and include main effect of prior anti-C5 treatment, transfusion history, age (indicator of age ≥ 45 years), sex, treatment, visit, baseline value. For endpoints, eg. FACIT-fatigue which are constrained to be in a finite range of values, if some imputed values are lower than the limit, then theywill be truncated to the lower limit and if some imputed values exceed the upper limit then they will be truncated to the upper limit.

For the transfusion avoidance endpoint the handling of missing data will be very similar to the handling of missing data for the primary endpoints and the same multiple imputed datasets can be used. Logistic regression model (as specified in Section 2.6.1.1) need to be run on each of the multiple imputed datasets and the results will be combined using Rubin's rules.

For the specific case of missing hemoglobin due to withdrawal, the imputation will reflect whether or not data were missing following a transfusion.

In the case of definitive withdrawal of study follow up following a transfusion only hemoglobin levels at visits during 30 days following the transfusion and until treatment discontinuation would be imputed under the MAR assumption. The missing hemoglobin after treatment discontinuation will be imputed using a "copy-reference" in the LNP023/iptacopan arm and according to MAR in the control arm (see Section 2.5.3). More specifically a patient in the iptacopan arm should be first imputed in the hypothetical scenario for hemoglobin until end of treatment The imputed hemoglobin value at end of treatment will be the starting point for the "copy-reference". In case of definite withdrawal of study follow up without transfusion missing data will be imputed as stated in Section 2.5.3.

In all comparisons based on a longitudinal model, missing data will be imputed multiple times. The imputed datasets will be used in the estimation of the longitudinal model. Where both intercurrent events (as for the hypothetical estimand comparing hemoglobin levels) and missing data are imputed or where only missing data are imputed, the model comparisons will be derived using Rubin's combination rules.

2.6.4 Supportive analyses

To complement the secondary estimand analysis of average changes in hemoglobin under a hypothetical strategy, the analysis comparing average changes in hemoglobin will be repeated using a treatment policy approach, to obtain the comparison of the combination of LNP + transfusions as needed to anti-C5 antibody treatment + transfusions as needed.

The comparison of changes from baseline in hemoglobin will also be carried out using all collected values even following transfusions, to differentiate the effect on hemoglobin changes by either LNP023 or anti-C5 from the effect that is mediated by the use of RBC transfusions. The model for the comparison between treatments is an MMRM considering an unstructured covariance structure. The model will include the main effects of prior anti-C5 treatment, transfusion history, age (indicator of age ≥ 45 years), sex, treatment, visit, baseline hemoglobin and the interactions between visits and treatment and visits and baseline levels. The treatment contrasts will be computed as the comparison of treatments corresponding to the average measured in the last 6 weeks of randomized treatment (i.e. the visits occurring between Day

126 and Day 168). Missing hemoglobin data will be imputed following the same principles as in Section 2.6.3. However, hemoglobin data recorded in the 30 days following transfusion will be considered for analysis and will not be imputed.

Supportive analyses on the secondary endpoints: change from baseline in LDH, FACIT, reticulocytes will be performed under a hypothetical strategy. For these analyses, the values on these 3 endpoints in the 30 days following transfusion will be considered missing and the values will be imputed. The imputation methods will be similar to those outlined in Section 2.6.3.

2.6.5 Sensitivity analyses

Sensitivity analyses will be performed where missing central lab data will be replaced by available local lab data collected at the same visit. MMRM for analysis of change from baseline in hemoglobin under a hypothetical strategy, change from baseline in reticulocytes, and change from baseline in LDH levels stated in Sections 2.6.1.1, 2.6.1.2, 2.6.1.4, 2.6.1.5, respectively, will be performed.

2.7 Safety analyses

Unless otherwise specified all safety summaries will be presented by SAF and Comb. SAF. All tables will be presented by treatment group.

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). In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period of LNP023 lasts from the date of first administration of study treatment to 7 days after the date of the last actual administration of LNP023 (including randomized treatment period, treatment extension period and tapering procedures after permanent treatment discontinuation) which covers slightly more than 5 times the estimated half-life of LNP023.

The on-treatment period of anti-C5 antibody lasts from the date of first administration of anti-C5 study treatment in the randomized treatment period to the date of the last actual administration of anti-C5 antibody in the randomized treatment period.

2.7.1 Adverse events (AEs)

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

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

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

Separate summaries will be provided for study treatment related adverse events, deaths, serious adverse events and adverse events leading to discontinuation of study treatment, and for

LNP023 tapering if this is followed prior to complete LNP023 discontinuation. For patients receiving LNP023, treatment emergent SAEs and AEs with PTs in the AESI 'PNH haemolysis and thrombosis' occurring after discontinuation of LNP023 200 mg b.i.d will be reported separately.

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

Most frequent AEs, most frequent SAEs, AEs leading to treatment discontinuation will be presented by preferred term.

Summaries presenting exposure adjusted incidence rates and associated 95% CI based on treatment emergent adverse events and treatment emergent serious adverse events will be provided. Adverse events (including pre-treatment, on-treatment, post-treatment events) will be listed.

In order to address the issue of variable follow-up duration within study, the exposure adjusted incidence rate of TEAE will be presented by primary System Organ Class (SOC) and Preferred Term (PT).

For the most common adverse events the 95%CI of the exposure adjusted incidence rate of TEAE can be presented as well as the Incidence Rate Ratio between treatment arms.

TEAE risk difference by SOC will be presented by a forest plot. The risk difference for most common TEAEs by PT will be also presented by a forest plot. The confidence intevals will be calculated using the Exact method.

Risk difference and 95% confidence interval

For an investigational drug group with n_1 subjects at risk, independent from the control group (e.g. placebo or comparator) with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event, the risk difference is estimated as p_1-p_0 with $p_1 = x_1/n_1$ and $p_0 = x_0/n_0$.

Risk differences will be estimated for LNP023 200 mg b.i.d versus anti-C5 antibody, with 95% CIs constructed by the method of [Agresti and Caffo (2000)].

Exposure adjusted occurrence rate and 95% confidence interval

For summary tables on exposure-adjusted AEs, the number of episodes per 100 patient years will be presented. The occurrence rate (number of episodes per 100 patient years) will be calculated as 100*(the total number of AE episodes from all patients in the population divided by the total number of patient-years). A patient may have multiple occurrences of the same event. All occurrences are counted. Total patient years will be computed as (sum of the duration of on-treatment periods over patients, in days)/365.25. The Approximate 95% CIs for the occurrence rate will be calculated with correction for overdispersion using the asymptotically robust method ([Scosyrev 2016], [Scosyrev and Pethe 2022]).
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. Although this analysis is referred to

as “Exposure adjusted” it actually uses by default the on-treatment period (Section 2.7) which includes periods of interruption during which there is no exposure.

2.7.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) are defined in the latest version of the compound electronic Case Retrieval Strategy (eCRS) that is stored in the Global Programing System (GPS). This classification reflects the safety topics of interest identified in the current version of the LNP023 Development Safety Profiling Plan, and may be updated based on review of accumulating data. At the time of analyses, the latest version of the eCRS will be used to identify the AESIs. Safety topics of interest to be reported are identified by the flag “SP”.

The number (and percentage) of participants with treatment-emergent adverse events of special interest/related to identified and potential risks will be summarized by treatment. The frequency and percentage of participants with treatment emergent adverse events of special interest (TEAESI) and serious TEAESI will be summarized by treatment group and preferred term.. The exposure adjusted incidence rates and associated 95% CI (as stated in Section 2.7.1) will be presented for each safety topic of interest AEs/SAEs. TEAE risk difference by SOC will be presented by a forest plot. The risk difference for treatment emergent adverse events of special interest by PT will be also presented by a forest plot. The confidence intervals will be calculated using the Exact method (as stated in Section 2.7.1).

A listing of participants experiencing AESIs will also be provided by treatment group. The eCRS safety topic definitions to identify AESIs will be provided as a listing.

For patients receiving LNP023, treatment-emergent and all AEs of special interest within the search ‘PNH haemolysis and thrombosis’ occurring after discontinuation of LNP023 200 mg b.i.d will be reported separately. All such AEs occuring after LNP023 200 mg b.i.d will be listed and the treatment emergent AEs will be flagged.

2.7.1.2 Adverse events reporting for safety disclosure

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 a certain threshold 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.

2.7.2 Deaths

The number of deaths resulting from treatment-emergent AEs will be summarized by SOC and PT. Death refers to treatment-emergent adverse events with fatal outcome. In addition, a separate summary of death events including on treatment and post treatment deaths will be provided if appropriate.

All the deaths in the clinical database will be listed.

2.7.3 Laboratory data

For all safety analysis based on laboratory data, the information obtained from the central as well as local labs will be used. For summaries by visits, local lab data will be used when the corresponding central lab data are missing. For summaries on overall post-baseline data, all available data (including central and local lab data) from scheduled and unscheduled visits will be used.

Laboratory evaluations' summaries will be presented for groups of laboratory data (clinical chemistry, clinical hematology, urinalysis, UACR, coagulation/markers of thrombosis and reproductive and thyroid hormone panel).

For all continuous laboratory parameters, the absolute on-treatment laboratory values will be summarized with standard descriptive statistics (mean, median, standard deviation, minimum, maximum) by parameter, scheduled visit/ time-point, and treatment. The on-treatment laboratory values will be defined as in Section 2.7.
For categorical laboratory parameters and categorical urinalysis parameters, a frequency table of results will be produced by laboratory parameter, scheduled visit and time-point, and treatment.
It is to be noted that for analysis on SAF and Comb. SAF analysis sets, different baseline values need to be considered as mentioned in Section 2.1.1.2.
For summary tables on laboratory parameters considering values which are lower or greater than the limit of quantification:

- The values less than the Lower Limit of Quantification LLoQ will be imputed to 0.5×LLoQ and the values greater than the Upper Limit of Quantification ULoQ will be imputed to 1.5×ULoQ.

- The number and percentage of values below the LLoQ and above the ULoQ will be presented.

For the figures, imputed values will be displayed.

Shift tables using the low/normal/high (low and high) classification may be provided as appropriate to compare participant's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the standard low/normal/high (low and high) classifications

based on upper and lower limits of normal range will be used.. If a participant presents with both low and high values during the on-treatment period, then these participants will be counted for the shift table in a category "low and high". These summaries will be presented by laboratory parameter, visit and treatment group.

The version 4.03 of the CTCAE grading will be used at the time of reporting and the following reports could be used:

- New or worsening abnormalities based on CTCAE grade (hematology, chemistry)
- Shift tables based on CTCAE grade (hematology, chemistry).

For selected laboratory parameters, abnormalities occurring at any time-point from scheduled, unscheduled and premature discontinuation visits considering all post-baseline on-treatment data will be summarized. Where normal ranges are available, abnormalities in laboratory data will be listed by treatment group, participant, and visit/time.

Arithmetic mean (SD) of selected safety parameters (e.g. thyroid and reproductive hormone levels) over time will be provided by treatment group for each of the parameters listed in Table 2-2.

Table 2-2 Selected thyroid and reproductive hormone level parameters

Thyroid hormone level	Reproductive hormone level
• T3	• Testosterone
• T4	• DHT
• Reverse T3	• LH
• TSH	• FSH

Note that displays of reproductive hormone level parameters will be further split by sex.

Liver toxicities

A criterion-based table for selected liver function tests and AEs will be presented including the number and percentage of the events described in Table 2-3. In the PNH indication, aspartate aminotransferase (AST) can increase for reasons not related to liver toxicity and therefore should not be considered in the derivation of liver toxicities. Moreover INR is routinely monitored and can be used for the definition of liver function events. Events for the PNH indication are described in Table 2-3.

Liver toxicity finding based on laboratory values and accounting for presence of bone pathology, symptoms, Gilbert syndrome will be presented. AEs collected in the analysis dataset and related to liver toxicities (Jaundice, AE potentially indicative of a liver toxicity) will either be reported separately in a specific table or will simply be displayed as part of the general AE tables.

Table 2-3 Liver Toxicities

Definition	Label for output display
Potential Hy's Law case	
(ALT or AST > 3 × ULN) and TBL > 2 × ULN and ALP to ≤ 2 × ULN in the absence of bone pathology[a]	Potential Hy's Law case

(ALT or AST > 3 × ULN) and TBL > 2 × ULN and ALP to ≤ 3 × ULN in the presence of bone pathology[a]	
ALT elevations	
If ALT ≤ ULN at baseline: (ALT > 3 × ULN) and INR > 1.5 If ALT > ULN at baseline then criteria for ALT are defined as ALT > 2 x baseline or > 300 U/L and INR > 1.5	(ALT > 3 × ULN) and INR > 1.5
ALT > 8 × ULN	ALT > 8 × ULN
If ALT ≤ ULN at baseline: ALT > 5 to ≤ 8 × ULN If ALT > ULN at baseline then criteria for ALT are defined as ALT > 3 x baseline or > 300 U/L	ALT > 5 to ≤ 8 × ULN
If ALT ≤ ULN at baseline: ALT > 3 to ≤ 5 × ULN (accompanied by symptoms)[a] If ALT > ULN at baseline then criteria for ALT are defined as ALT > 2 x baseline or > 300 U/L (accompanied by symptoms)[a]	ALT > 3 to ≤ 5 × ULN with symptoms
If ALT ≤ ULN at baseline: ALT > 3 to ≤ 5 × ULN (patient is asymptomatic)[a] If ALT > ULN at baseline then criteria for ALT are defined as ALT > 2 x baseline or > 300 U/L (patient is asymptomatic)[a]	ALT > 3 to ≤ 5 × ULN no symptoms
ALP (isolated)	
ALP > 2 × ULN (in the absence of known bone pathology)[a] ALP >3 x ULN (if bone pathology[a] is present)	ALP > 2 × ULN (>3 x ULN if bone pathology is present)
AEs indicative of liver toxicity	
Jaundice[b]	Jaundice
Any AE potentially indicative of a liver toxicity[b]	AE potentially indicative of a liver toxicity
ALT: alanine aminotransferase [a] concomitance between abnormal laboratory values and symptoms or disease (bone disease, Gilbert syndrome) will be established based on reported AEs or medical history with a start date prior to laboratory measurement and stop date posterior to laboratory measurement. Selection of AEs and medical History will be based on eCRS and is described in Table 2-4 for MedDRA version 23.1 [b] Selection of AEs described in Table 2-4	

When a criterion contains multiple laboratory parameters (e.g. ALT or AST > 3 × ULN), the criterion should considered as met only if the elevation in parameters occurs on the same sample day (as evidenced by the same date that the lab samples were taken).

Table 2-4 Definition of symptoms and AEs for liver toxicities

Term in table	MedDRA term(s)

Bone pathology	HLGT = Bone disorders (excl congenital and fractures)
Symptoms:	
Severe Fatigue (1)	PT = Fatigue
Abdominal pain right upper quadrant	PT = Abdominal pain upper
Nausea	PT = Nausea
Vomiting	PT = Vomiting
General malaise	*PT = Malaise*
Rash with eosinophilia	*PT = Drug reaction with eosinophilia and systemic symptoms*
Gilbert syndrome	PT = Gilbert's syndrome
Jaundice	PT = Jaundice PT = Jaundice cholestatic
AEs indicative of liver toxicity	
Hepatic failure	HLT = Hepatic failure and associated disorders
Hepatic fibrosis and cirrhosis	HLT = Hepatic fibrosis and cirrhosis PT = Hepatic cirrhosis
Non-infectious hepatitis	PT = Hepatitis PT = Hepatitis acute PT = Hepatitis toxic PT = Hepatitis fulminant PT = Hepatitis chronic active PT = Hepatitis chronic persistent
Liver neoplasm	HLGT = Hepatobiliary neoplasms

HLT: High Level Term
HLGT: High Level Group Term
MedDRA codes listed above are based on version 23.1 The list will be updated for each MedDRA version change and will be included in the eCRS with flag "OS". eCRS will be the reference for analyses.
(1) presence of Fatigue term with severity ≥ "Severe"

Renal alert values will be summarized by treatment where renal alert values are identified as:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- New onset dipstick proteinuria ≥ 3+

2.7.3.1 Electrocardiogram (ECG)

The following ECG parameters will be obtained during the study and summarized descriptively: ECG mean heart rate, RR interval, PR interval, QRS duration, QT interval and corrected QT interval by the Fridericia criteria (QTcF). Summary statistics (absolute values and change from baseline) for all ECG parameters will be provided by treatment and time point; the number of participants with values outside the normal range will be displayed. Where normal ranges are

available, participants with abnormalities in ECG data will be listed by treatment group and visit/time.

Categorical summary statistics for ECG values will also be provided based on the number and proportion of participants meeting or exceeding the following predefined limits any time post baseline:

- 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

In addition, a listing of these participants will be produced by treatment group. A listing of all newly occurring or worsening abnormalities will be provided.

Noticeable ECG abnormalities such as ventricular tachychardia, new complete heart block (Grade III AV block) and Mobitz II AV block are reported as adverse events and will be described as part of AEs.

2.7.3.2 Vital signs

Vital signs measurements include systolic blood pressure (SBP) and diastolic blood pressure (DBP), pulse rate, body temperature, height and body weight. Summary statistics (absolute on-treatment values and change from baseline) will be provided for all vital signs data (weight, temperature, pulse rate, SBP, DBP) by treatment and visit/time. On-treatment values will be defined as in Section 2.7.

Where ranges are available, abnormalities will be summarized and listed by treatment group, participant, and visit/time. Arithmetic mean (sd) of absolute values over time for SBP and DBP and pulse rate will also be plotted by treatment group.

Frequency tables displaying the number of patients with abnormal blood pressure or heart rate values (by visit or worst post baseline) can be displayed.

Boundaries are the following:

- Blood pressure (BP):
  1. Systolic BP: 100 – 140 mmHg
  2. Diastolic BP: 65 – 95 mmHg

- Heart rate :
  - <= 50 bpm
  - >=120 bpm

2.8 [redacted]

[redacted]

2.9 [redacted]

[redacted]

2.10 Patient-reported outcomes

In this study, the question addressed by the analysis of PRO measurements is whether treatment with LNP023 improves patient-reported fatigue symptoms as measured by the FACIT-Fatigue.

[redacted]

Changes in scores of fatigue using the FACIT-Fatigue questionnaire are a secondary endpoint and the analysis is described in Section 2.6.

To further calibrate the performance of the FACIT-Fatigue in the context of treatment with LNP023 and determine within-patient, anchor-based minimally important change in FACIT-Fatigue scores, analyses of changes in FACIT-Fatigue scores will be examined by change in PGIS severity level by patient or based on patient exit interviews..

All supportive analyses of the performance of the FACIT-F questionnaire (including responder analyses derived from a priori definition of a meaningful change) and of the behavior of meaningful change over time as well as of the impact of clinical endpoints as reflected in the FACIT-F will be detailed in a separate analysis plan for PROs.

[redacted]

2.11 [redacted]

[redacted]

[redacted]

2.13 Interim analysis

No formal interim analyses of efficacy are planned in this study. A data cut-off will be applied and a clinical study report (CSR) will be produced for submission at the time the last patient has completed the randomized treatment period. An additional CSR will be produced when the last participant has completed the last visit in the treatment extension period, when the final study database has been locked.

Safety data will be monitored by an independent DMC, and analyses to the effect of this evaluation will be performed during the course of the study with the frequency as definedin the DMC Charter. Access to a limited number of efficacy measurements by the DMC will be provided solely for the purpose of evaluating benefit of treatment with LNP023 against any risk. Such safety evaluations do not inflate the type I error for the primary efficacy hypothesis testing and thus no adjustment for multiplicity is considered necessary. All analyses of data using randomization codes to be provided to the DMC will be carried out by an independent statistical group (CRO) and communications concerning any findings between the DMC and the independent statistical group will be handled following the same process as for studies in which the treatment given is blinded. The DMC will function under the DMC Charter which has been finalized. The Charter includes guidelines for communication concerning safety of participants between the DMC and the sponsor representative to ensure that these are in keeping with the sensitive nature of the open label trial and do not introduce bias.

3 Sample size calculation

3.1 Primary endpoint(s)

Power of the two primary endpoints is determined based on the summary measure used for testing: the odds ratio corresponding to the proportions of participants achieving the status of responder in the two treatment groups being compared. Due to the small sample size and possible sparseness of observations in the randomization strata, the test will be computed using exact methods, hence the probability of rejection at the study wise significance level is obtained from the distribution of Fisher's exact test. The distribution of the test statistic is asymmetric with respect to a two tailed rejection region, hence the sample size has been calculated based on a one-sided rejection region for a Fisher's exact test corresponding to a significance level of 0.025.

Participants will be randomized to one of the two treatment arms in an 8:5 ratio to LNP023 monotherapy at a dose of 200 mg b.i.d. (approximately 56 participants), or anti-C5 antibody treatment (approximately 35 participants continuing with the same stable regimen as that prior to randomization), respectively.

Under an assumption that participants on LNP023 treatment would achieve a proportion of 50% of responders who achieve and increase of ≥ 2 g/dL from baseline to be compared to a proportion of 16% of responders on anti-C5 antibody treatment the sample size of 56 participants on LNP023 and 35 participants on anti-C5 antibody treatment will provide 83.2 % power for this endpoint at a significance level of 0.0125. Power for the endpoint corresponding to the achievement of sustained levels of hemoglobin ≥ 12 g/dL is calculated under the assumption that the proportions are 35% on LNP023 treatment and 5% on anti-C5 antibody treatment and it is 89.1% for a significance level of 0.0125. The sample size/power calculations were carried out using the package exact2x2 by Fay, Hunsberger, Nason, and Gabriel and R version 3.4.3. Power for the simultaneous test cannot be exactly derived but a minimum power corresponding to assuming a Bonferroni adjustment is approximately 95% for the above described marginal power assumptions.

3.2 Secondary endpoint(s)

Nominal power for prioritized secondary endpoints corresponding to hypotheses H3, H41, H42, and H43 is estimated to be between 85% and 90% at full study alpha (one-sided 0.025), without considering the adjustment for multiple testing derived from the procedure used. The three hypotheses tested as H51, H52 and H53 are estimated to have lower power, hence the alpha allocated is very small, leading to a test at full study alpha only after rejection of all primary endpoint hypotheses and secondary endpoint hypotheses H3 and H4i.

4 Change to protocol specified analyses

In case of sparse data or if no responses are observed in one of the treatment arms the conditional logistic regression cannot be implemented for primary analysis. If such situation occurs, the statistical model based on logistic regression with Firth penalized method, as specified as a supportive analysis in protocol, will be implemented as the statistical model for primary analysis.

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

5.1.1.1 AE end date imputation

Rules for imputing AE end dates are stated below. Date of last contact in the study has been defined as in Section 2.1.1.5 .

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (date of last contact, 31DECYYYY, date of death).

2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (date of last contact, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

5.1.1.2 AE start date imputation

Rules for imputing the AE start date:

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the imputed AE end date is complete and the imputed AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete imputed AE end date is available and the imputed AE start date is greater than the imputed AE end date, then imputed AE start date should be set to the imputed AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant medication end date imputation

Rules for imputing the CM end date are stated below. Date of last contact in the study has been defined as in Section 2.1.1.5. Concomitant medication end dates will not be imputed for ongoing records.

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of date of last contact and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of date of last contact and the end of the year (31DECYYYY).
3. If CM day/month/year is missing then use the date of last contact + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

5.1.2.2 Concomitant medication start date imputation

Rules for imputing the CM start date:

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain
YYYY < TRTY	**(2.a)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start
YYYY = TRTY	**(4.a)** Uncertain	**(4.b)** Before Treatment Start	**(4.a)** Uncertain	**(4.c)** After Treatment Start
YYYY > TRTY	**(3.a)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete imputed CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.2 Statistical models

5.2.1 Tabular view of estimands and associated estimation methods

Table 5-1 Overview of estimands and estimation methods

Estimand	**Endpoint**	**Handling strategy of intercurrent events**				**Summary measure**
		Discontinuation of study medication	Breakthrough hemolysis events	MAVEs	RBC transfusions	
Primary estimands						
Primary estimand 1	composite of: increase in Hb levels ≥ 2 g/dL from baseline* without requiring RBC transfusions[#]	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference	Treatment policy	Treatment policy	Not an intercurrent event-included in the composite estimand	Odds ratio
Sensitivity analysis 1.1	Same	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference Tipping point analysis for imputation of missing data	Same	Same	Same	Odds ratio
Sensitivity analysis 1.2	Same	Treatment policy Missing hemoglobin central lab data replaced by local lab data at same visit. Missing data on LNP023 after study discontinuation imputed using copy reference	Same	Same	Same	Odds ratio

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
Sensitivity analysis 1.3	Same	Same	Same	Same	Same	Difference and ratio of marginal proportions from a Logistic model with common intercept
Primary estimand 2	composite of: having Hb levels ≥ 12 g/dL* without requiring RBC transfusions [#]	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference	Treatment policy	Treatment policy	Not an intercurrent event-included in the composite estimand	Odds ratio
Sensitivity analysis 2.1	Same	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference Tipping point analysis for imputation of missing data	Same	Same	Same	Odds ratio
Sensitivity analysis 2.2	Same	Treatment policy Missing hemoglobin central lab data replaced by local lab data at same visit. Missing data on LNP023 after study discontinuation imputed using copy reference	Same	Same	Same	Odds ratio
Sensitivity analysis 2.3	Same	Same	Same	Same	Same	Difference and ratio of marginal proportions from a Logistic model with common intercept
Supplementary estimands						

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
Supplementary estimand 1.1	composite of an increase in Hb levels ≥ 2 g/dL from baseline* without requiring RBC transfusions[#] and not receiving rescue medication[$]	Treatment policy	Treatment policy	Treatment policy	Not an intercurrent event-included in the composite estimand	Odds ratio
Supplementary estimand 1.2	Same	Same	Same	Same	Same	Difference and ratio of marginal proportions from a Logistic model with common intercept
Supplementary estimand 2.1	composite of Hb levels ≥ 12 g/dL* without requiring RBC transfusions[#] and not receiving rescue medication[$]	Treatment policy	Treatment policy	Treatment policy	Not an intercurrent event-included in the composite estimand	Odds ratio
Supplementary estimand 2.2	Same	Same	Same	Same	Same	Difference and ratio of marginal proportions Logistic model with common intercept
Supportive analysis						
Supportive analysis 1.1	composite of an increase in Hb levels ≥ 2 g/dL from baseline* without requiring RBC transfusions[#]	Treatment policy	Treatment policy	Treatment policy	Not an intercurrent event-included in the composite estimand	Difference and ratio of marginal proportions Logistic model with common intercept
Supportive analysis 2.1	composite of Hb levels ≥ 12 g/dL* without requiring RBC transfusions[#]	Treatment policy	Treatment policy	Treatment policy	Not an intercurrent event-included in the composite estimand	Difference and ratio of marginal proportions Logistic model with common intercept

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
Supportive analysis 1.2	composite of an increase in Hb levels ≥ 2 g/dL from baseline* without requiring RBC transfusions[#]	Treatment policy	Treatment policy	Treatment policy	Not an intercurrent event-included in the composite estimand	Odds ratio estimated using CMH test
Supportive analysis 2.2	composite of Hb levels ≥ 12 g/dL* without requiring RBC transfusions[#]	Treatment policy	Treatment policy	Treatment policy	Not an intercurrent event-included in the composite estimand	Odds ratio estimated using CMH test
Secondary estimands						
Secondary estimand 1	Proportions of participants not receiving any transfusions [#]	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference	Treatment policy	Treatment policy	Not an intercurrent event since this is the endpoint of interest	Odds ratio
Supportive analysis (secondary) 1.1	Same	Same	Same	Same	Same	Difference and ratio of marginal proportions from a Logistic model with common intercept
Secondary estimand 2	Difference in achieved hemoglobin change from baseline**	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference	Treatment policy	Treatment policy	Transfusions[#] are treated within a hypothetical strategy (as if patients had not received any transfusions)	comparison of mean change from baseline in hemoglobin levels
Sensitivity analysis (secondary) 2.1	Same	Treatment policy Missing hemoglobin central lab data replaced by local lab data at same visit. Missing data on LNP023 after study discontinuation imputed using copy reference	Same	Same	Same	Same

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
Supportive analysis (secondary) 2.1	Same	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference	Same	Same	Treatment policy	Same
Secondary estimand 3	Difference in change from baseline in scores of fatigue using the FACIT Fatigue questionnaire**	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference	Treatment policy	Treatment policy	Treatment policy	comparison of mean change from baseline in FACIT fatigue scores
Supportive analysis (secondary) 3.1	Same	Same	Same	Same	Transfusions[#] are treated within a hypothetical strategy (as if patients had not received any transfusions)	Same
Secondary estimand 4	Difference in change from baseline in reticulocyte counts**	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference	Treatment policy	Treatment policy	Treatment policy	comparison of the mean change from baseline in reticulocyte counts
Sensitivity analysis (secondary) 4.1	Same	Treatment policy Missing reticulocyte central lab data replaced by local lab data at same visit. Missing data on LNP023 after study discontinuation imputed using copy reference	Same	Same	Same	Same
Supportive analysis (secondary) 4.1	Same	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference	Same	Same	Transfusions[#] are treated within a hypothetical strategy (as if patients had not received any transfusions)	Same

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
Secondary estimand 5	Difference in percent change from baseline in LDH**	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference	Treatment policy	Treatment policy	Treatment policy	comparison of the log transformed LDH ratio to baseline
Sensitivity analysis (secondary) 5.1	Same	Treatment policy Missing LDH central lab data replaced by local lab data at same visit. Missing data on LNP023 after study discontinuation imputed using copy reference	Same	Same	Same	Same
Supportive analysis (secondary) 5.1	Same	Treatment policy Missing data on LNP023 after study discontinuation imputed using copy reference	Same	Same	Transfusions[#] are treated within a hypothetical strategy (as if patients had not received any transfusions)	Same
Secondary estimand 6	Rates of breakthrough hemolysis occurring	Treatment policy	Not an intercurrent event since this is the endpoint of interest	Treatment policy	Treatment policy	Rate difference between treatments
Secondary estimand 7	Rates of MAVE s	Treatment policy	Treatment policy	Not an intercurrent event since this is the endpoint of interest	Treatment policy	Rate difference between treatments

* between Day 126 and 168 (at least 3 out of 4 scheduled measurements)

** between Day 126 and 168

[#] between Day 14 and Day 168

[$]between Day 1 and Day 168

5.2.2 Analysis considerations

For all inferential efficacy analysis, the analysis model will use the strata variables based on the assigned strata at randomization. However the imputation model for imputing missing data (Section 2.5.3 and Section 2.6.3) will use the strata variables based on the eCRF data.

5.2.2.1 MMRM convergence issues

For MMRM, by default, the correlations between visits (aka. timepoints) within subjects will be modeled using an unstructured covariance matrix.

In case of non-convergence issues the following steps should be taken:

- Simplify covariance structure (possibly AR(1) then CS)
- Simplify the model by removing some covariates (baseline value should always be kept in the model and visit x baseline value interaction can for instance be first removed)

5.2.2.2 Method for calculation of marginal proportions

Binary outcomes will be analyzed using a logistic regression model with treatment and randomization strata as fixed effect factors. Additional covariates can be included when relevant, including continuous baseline values.

The marginal proportions, difference in marginal proportions and associated two-sided 95% confidence interval will also be provided.

The marginal standardization method will be used to calculate the mean response rate in each treatment group as well as their difference. The logistic regression model to estimate the response probability is written as:

$$\log \frac{P(Y=1)}{1-P(Y=1)} = \beta_0 + \beta_1 X + \beta_2 T$$

Where $\mathrm{P}(\mathrm{Y}=1)$ refers to the probability to be responder, X refers to the vector of covariates, T refers to treatment and N refers to number of participants.

The maximum likelihood estimator for $\hat{\beta}_0, \hat{\beta}_1, \hat{\beta}_2$ will be plugged in to obtain the probability to be a responder for each participant i had he/she received treatment T

$$\hat{\theta}_{\mathrm{iT}} = \hat{P}(Y_i = 1) = \frac{\exp[\widehat{\beta}_0 + \hat{\beta}_1 X_i + \hat{\beta}_2 T]}{1 + \exp[\widehat{\beta}_0 + \hat{\beta}_1 X_i + \hat{\beta}_2 T]}$$

The proportion of responders will be derived for each treatment arm from the estimated marginal probabilities derived from the model fit as the mean of the individual logistic regression model predictions,

$$\hat{\theta}_T = \frac{\sum_{i=1}^{N} \hat{\theta}_{iT}}{N}$$

The 95% confidence intervals will be derived by the bootstrap method. For the bootstrap method, multiple sets of patients will be bootstrapped from the initial population. For each set the steps (model fitting, predicting, averaging) will be repeated to obtain bootstrapped $\hat{\theta}_T$. The 2.5% quantile and 97.5% quantile of the distribution of bootstrapped $\hat{\theta}_T$ will be used as 95% CI boundaries.

5.2.3 Rule of exclusion criteria of analysis sets

Considering the relatively low sample size in the study there are no protocol deviations which will lead to exclusion of patients from any analysis set. Data records containing confirmed cases of biological sample analysis after WoC, or when not allowed per ICF or local regulations, will be flagged and excluded from all analyses including listings.

6 Reference

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