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LNP023 (Iptacopan)

Clinical Trial Protocol 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

Document type:	Amended Clinical Trial Protocol
EUDRACT number:	2019-004665-40
Version number:	02 (Clean)
Clinical Trial Phase:	III
Release date:	23-Nov-2021

Clinical Trial Protocol Template Version 3.0 (31-Jan-2020)

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List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
b.i.d.	bis in die/twice a day
BMF	Bone Marrow Failure
BTH	Breakthrough hemolysis
BUN	Blood Urea Nitrogen
CDS	Core Data Sheet
CK	Creatinine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus Disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EORTC QLQ-C30	European Organization For The Research And Treatment Of Cancer Quality Of Life Questionnaire
EVH	Extravascular Hemolysis
EOS	End of Study
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQol - 5 Dimensions- 5 Level
eSAE	Electronic Serious Adverse Event
ESA	Erythropoiesis Stimulating Agent
eSource	Electronic Source
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	Hour
HIF-PHI	Hypoxia-inducible factor prolyl hydroxylase inhibitors
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life

i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVH	Intravascular Hemolysis
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LLOQ	Lower Limit Of Quantification
MAVE	Major Adverse Vascular Event
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
OATP	Organic Anion-Transporting Polypeptide
ORN	Off-site Research Nursing
PGIS	Patient Global Impression of Severity
P-gp	Permeability glycoprotein
p.o.	oral(ly)
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
PPD	Premature Participant Discontinuation
PRO	Patient Reported Outcomes
PT	prothrombin time
QD	Once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RAP	The Report and Analysis Plan
RBC	Red Blood Cell(s)
RDC	Remote Data Capture
REB	Research Ethics Board
REP	Roll-over Extension Program
RU	Resource Utilization
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sCR	serum creatinine
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin

TD	Study Treatment Discontinuation
ULN	Upper Limit of Normal
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product or control drug (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as EOS of the last participant as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis

Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

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Protocol summary

Protocol number	CLNP023C12302
Full Title	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
Brief Title	Study of efficacy and safety of twice daily oral LNP023 in adult PNH patients with residual anemia despite anti-C5 antibody treatment
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this Phase 3 study is to determine whether LNP023 is efficacious and safe for the treatment in PNH through demonstration of superiority of LNP023 compared to anti-C5 antibody treatment in adult PNH patients presenting with residual anemia despite treatment with anti-C5 antibody therapy
Primary Objective(s)	The primary objectives are 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. • 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. 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 Major Adverse Vascular Events (MAVEs), on the odds of being a responder, with the endpoints defined as a composite of • An increase in Hb levels from baseline ≥ 2 g/dL • Hb levels ≥ 12 g/dL both assessed between Day 126 and Day 168 and of not requiring RBC transfusions between Day 14 and Day 168.
Secondary Objectives	• To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment in transfusion avoidance as the proportion of participants who remain free from transfusions by assessing the proportion of participants not receiving any packed red blood cell transfusions per protocol established criteria between Day 14 and Day 168 • To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in average change in hemoglobin by assessing the 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 by assessing the 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 by assessing the change from baseline in reticulocyte count (109/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 by assessing the 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) of participants with breakthrough hemolysis reported between Day 1 and Day 168

	• To assess rates of MAVEs (incl. thrombosis) of LNP023, compared to anti-C5 antibody treatment occurring between Day 1 and Day 168 • The assessment of safety and tolerability of LNP023 compared to anti-C5 antibody treatment
Study design	This study is a multi-center, randomized, open-label, active comparator-controlled, parallel group study, which is comprised of a screening period, a 24-week, active controlled, parallel group treatment period and a 24-week LNP023 treatment extension period.
Study population	Approximately ninety one (91) patients diagnosed with PNH, who are treated with a stable regimen of anti-C5 antibody (Standard of Care (SoC); either eculizumab or ravulizumab) for at least 6 months prior to Randomization, but still presenting with residual anemia (i.e., Hb < 10 g/dL) will be enrolled.

Key Inclusion criteria	• Male and female participants ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with RBCs and WBCs granulocyte/monocyte clone size ≥ 10%
	• Stable regimen (dose and intervals) of anti-C5 antibody treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization
	• Mean hemoglobin level <10 g/dL
	  • Over a minimum of 4 months before screening visit
	  • Confirmed by central laboratory assessment during screening
	• Vaccination against Neisseria meningitidis infection is required prior to the start of treatment. If the patient has not been previously vaccinated, or if a booster is required, vaccine should be given according to local regulations, at least 2 weeks prior to first dosing.
	• If not received previously, vaccination against Streptococcus pneumoniae and Haemophilus influenzae infections should be given, if available and according to local regulations. The vaccines should be given at least 2 weeks prior to first dosing.

Key Exclusion criteria	• Participants on a stable eculizumab dose but with a dosing interval of 11 days or less or participants on stable ravulizumab dose but with a dosing interval of less than 8 weeks. • Known or suspected hereditary complement deficiency at screening • History of hematopoietic stem cell transplantation • Patients with laboratory evidence of bone marrow failure (reticulocytes <100x109/L; platelets <30x109/L; neutrophils <500x106/L). • Active systemic bacterial, viral (incl. COVID-19) or fungal infection within 14 days prior to study drug administration • A history of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus. • Major concurrent comorbidities including but not limited to severe kidney disease (e.g., eGFR < 30 mL/min/1.73 m^2,dialysis) , advanced cardiac disease (e.g., NYHA class IV), severe pulmonary disease (e.g., severe pulmonary) hypertension (WHO class IV), or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participant's participation in the study.
Study treatment	LNP023 Anti-C5 antibodies (either eculizumab or ravulizumab)
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 patient discontinues treatment (treatment policy).
Efficacy assessments	• Hemoglobin, reticulocytes, LDH and other PNH-related laboratory parameters • Red blood cell transfusions • Breakthrough hemolysis

	• Patient Reported Outcomes (PRO)–FACIT-Fatigue • Major Adverse Vascular Events (MAVEs) incl. thrombosis
Key safety assessments	• Laboratory evaluations in blood and urine • Adverse event monitoring • ECG • Coagulation panel/thrombosis • Reproductive and thyroid hormones monitoring
Other assessments	An assessment of patient-reported outcomes is planned in this trial using European Organization For The Research And Treatment Of Cancer Quality Of Life Questionnaire (EORTC QLQ-C30), EuroQol - 5 Dimensions- 5 Level (EQ-5D-5L), and Patient Global Impression of Severity of fatigue (PGIS). Exploration of the meaningfulness of the change demonstrated in patient report outcomes will be performed with an optional Patient Interview.
Data analysis	All efficacy analyses will use the full analysis set (FAS) that includes all patients randomized into the study. Primary efficacy estimands represented by the following endpoints: • Proportions of participants achieving a sustained increase in hemoglobin levels from baseline ≥ 2 g/dL between Day 126 and Day 168 in the absence of transfusions between Day 14 and Day 168 • Proportions of participants achieving sustained hemoglobin levels ≥ 12 g/dL between Day 126 and Day 168 in the absence of transfusions between Day 14 and Day 168 Superiority of LNP023 compared to anti-C5 antibody treatment will be determined using an odds ratio and tested by a simultaneous weighted permutation test derived from a conditional logistic model accounting for the stratification factors used at randomization and with adjustment for baseline hemoglobin levels and sex, used in the analysis of the two endpoints. Besides the odds ratio a marginal logistic model adjusting for stratification factors and covariates will be used to compare the proportions of both treatments using standardization. Secondary efficacy estimands represented by the following endpoints: • Proportions of participants who are transfusion free by protocol specified criteria between Day 14 and Day 168 • Differences in average change from baseline in hemoglobin levels between Day 126 and Day 168 estimated under the hypothetical condition of being free from transfusion between Day 14 and Day 168 • Differences in average score changes from baseline evaluated between Day 126 and Day 168 of FACIT-Fatigue • Differences in average changes from baseline in reticulocyte counts evaluated between Day 126 and Day 168 • Differences in average percent change from baseline in LDH evaluated between Day 126 and Day 168 • Rates of breakthrough hemolysis between Day 1 and Day 168 • Rates of MAVEs between Day 1 and Day 168 Following successful rejection of the hypotheses associated with the primary estimands, the secondary estimand hypotheses will be tested applying weighted Simes' tests with pre-defined weights allocated to the different levels of secondary hypotheses. The testing procedure applies alpha propagation rules according to the principles of graphical procedures for multiplicity adjustment. The estimands of interest as well as methods for obtaining comparisons are described in detail in the corresponding sections.
Key words	LNP023, eculizumab, ravulizumab, anti-C5, PNH, LDH, hemoglobin, anemia

1 Introduction

1.1 Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hemolytic disorder characterized by complement-mediated intravascular hemolysis, bone marrow failure (BMF) and severe thrombophilia (Risitano 2012). It begins with the clonal expansion of a hematopoietic stem cell that has acquired a somatic mutation in the phosphatidylinositol N-acetylglucosaminyltransferase subunit A (PIGA) gene (Brodsky 2014). Consequently, PNH blood cells lack the glycophosphatidylinositol (GPI) anchor protein and are deficient in the membrane-bound complement inhibitory proteins CD55 and CD59. As a result, PNH type red blood cells (RBCs) are attacked by complement leading to complement mediated lysis.

The clinical spectrum of PNH varies and signs and symptoms include anemia, thrombosis, smooth muscle dystonia, fatigue, hemoglobinuria, chronic kidney disease and pulmonary hypertension. The clinical presentation is driven by uncontrolled complement activation on CD55 and CD59 deficient PNH type RBCs culminating with hemolysis and the release of free hemoglobin, and platelet activation (Hill et al 2013). Hemolysis results in release of intracellular hemoglobin and lactate hydrogenase (LDH) into the circulation. Irreversible binding to and inactivation of nitric oxide (NO) by hemoglobin and inhibition of NO synthesis with consequent vasoconstriction and tissues ischemia, result in abdominal pain, dysphagia, erectile dysfunction, platelet activation and a prothrombotic status (Brodsky 2014, Hill et al 2013). Thromboembolism is the leading cause of morbidity and mortality in patients with PNH and can occur at any site; although venous is more common (80–85%), it can also be arterial (15–20%) (Hillmen et al 2007).

Eculizumab and Ravulizumab (engineered from eculizumab with prolonged dosing interval) are approved anti-C5 antibody therapies for the treatment of PNH and the current Standard of Care (SoC) where available. The introduction of eculizumab has significantly reduced the thromboembolic risk of PNH patients improving morbidity and mortality and largely improved the quality of life (QoL) of PNH patients.

Although the anti-C5 antibody treatment is generally effective in treating intravascular hemolysis (IVH), there remains a high unmet medical need for PNH. Different authors reported heterogeneous hematological response with eculizumab and a substantial proportion of patients not achieving normal or near normal hemoglobin levels (McKinley et al 2017, DeZern et al 2013, Hill et al 2010, Risitano et al 2009). In the study of Risitano and colleagues, approximately one third of patients treated with eculizumab achieved normal or near normal hemoglobin levels (hemoglobin $\geq$ 11 g/dL) without requiring red blood cell transfusions (Risitano et al 2009).

Until recently, well defined response categories to complement inhibitor therapy have not been established. A classification of hematological response with anti-complement agents has been proposed by the Severe Aplastic Anemia (SAA) Working Party of the European group for Bone Marrow Transplantation (EBMT) (Risitano et al 2019). The classification has been applied to a large cohort of 93 PNH patients retrospectively and results have been reported (Debureaux P-E 2019) after the first six months of treatment with eculizumab (n=80).

- Only thirteen percent (13%) of patients achieved a complete or major response (defined as no transfusion with normal hemoglobin (≥ 12g/dL) without (complete response) or with residual significant IVH / increased erythropoietic response (major response)).
- Thirty four percent (34%) of patients achieved a good response (defined as no transfusion with mild anemia (hemoglobin ≥ 10 to < 12 g/dL) with or without residual significant IVH and BMF ruled out).
- Fifty four percent (54%) of patients had hemoglobin < 10g/dL with or without the need of transfusions and residual IVH, respectively and BMF ruled out.

The heterogeneous response to eculizumab or other anti-C5 antibody treatment can, in part, be explained through its mechanism of action inhibiting only the terminal part of the complement cascade. Therefore, deposition of C3 fragments on the cell surface of PNH type erythrocytes lacking CD55 is not impacted, rendering the cells susceptible to extravascular hemolysis. This is inconspicuous in untreated PNH patients, because signs and symptoms of intravascular hemolysis dominate. However, extravascular hemolysis eventually emerges once the therapeutic inhibition with anti-C5 agents prevents intravascular hemolysis. In fact, it can become the main mechanism of hemolysis in patients treated with eculizumab (Risitano et al 2009) and C3 mediated extravascular hemolysis represents an unmet medical need. Residual chronic anemia greatly impacts the patients' QoL that currently can only be treated with red blood cell transfusions (McKinley et al 2017) with possible complications such as iron overload.

In addition, a rare polymorphism at the eculizumab binding site of C5 mainly occurring in Japanese and Han Chinese patients has been reported resulting in complete resistance to eculizumab. Nishimura and colleagues identified 11 out of 345 (3.2 %) Japanese patients treated with eculizumab sharing the same single polymorphism, thus making this subset an ultra-rare disease (Nishimura et al 2014).

[redacted]

1.2 Purpose

The purpose of this Phase 3 study in PNH patients presenting with residual anemia despite treatment with anti-C5 antibody, is to determine whether LNP023 is efficacious and safe for the treatment of PNH through demonstration of superiority of LNP023 compared to anti-C5 antibody treatment. This Phase 3 study has a 24-week randomized, active comparator controlled, open-label study period and a 24-week open-label treatment extension period. Efficacy will be evaluated by the proportion of participants achieving the primary hemoglobin response criteria in the absence of red blood cell transfusions, as well as other hematological response endpoints, transfusion avoidance, breakthrough hemolysis rates and fatigue scores (FACIT-Fatigue, a patient reported outcome questionnaire).

The results of the analysis performed once the last participant has completed the 24-week randomized treatment period will form the basis of the data package for regulatory filing.

2 Objectives and endpoints

Table 2-1 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 (109/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) of LNP023, compared to anti-C5 antibody treatment	• Occurrences of MAVEs occurring between Day 1 and Day 168
• 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]

Objective(s)	Endpoint(s)
[redacted]	[redacted]

Table 2-2 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	• 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.

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 $\geq$ 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 primary estimand is that it will capture both the hematological benefit of the study drug as 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 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).

Further details can be found in Section 12.

The two primary estimands share the following attributes:

- Population: Patients with PNH who are on a stable regimen of SoC (anti-C5 antibody treatment) and have residual anemia (Hb < 10 g/dL). Further details about the population are provided in Section 5.
- 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). Further details about the investigational treatment and control treatment are provided in Section 6.
- Intercurrent events: Transfusions 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.
- 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 transfusions 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.

For the purpose of efficacy assessment, a supplementary estimand has been added considering the use of rescue therapy as treatment failure. The supplementary estimand will have the same population, treatment of interest, summary measure as the primary estimand and the analysis and details are stated in Section 12.4.6.

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.

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 in Section 12 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.

3 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 3-1):

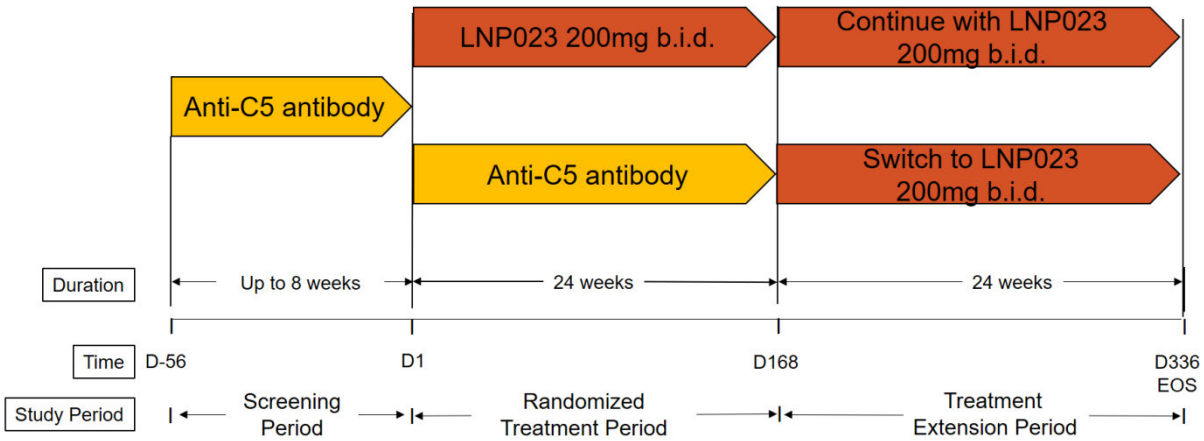
- A screening period lasting up to 8 weeks (unless there is a need to extend it for vaccinations required for inclusion, vaccinations should be started at the earliest possible to avoid extension of the screening period)
- A 24-week randomized, open-label, active controlled, parallel group treatment 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 3-1 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 EOS (End of Study) 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, as applicable.

By signing the ICF, the participants will provide access to the following records: hemoglobin levels reported at least during the last 4 months; the numbers of transfusions and unit numbers of packed-RBC received in the last 12 months prior to Screening; Major Adverse Vascular Events (MAVEs) reported prior to 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 defined in Section 5.1. Vaccines should cover as many serotypes as possible (including meningococcal serotypes A, C, Y, W-135 and B). To minimise participant burden, the use of multivalent vaccines is recommended as locally available and per local guidelines and regulations (e.g. quadrivalent vaccine for *N. meningitidis* which covers serotypes A, C, Y and W-135 and Pneumovax-23 which covers 23 *S. pneumoniae* serotypes). For the vaccination type and booster requirements use local guidelines, and locally available vaccines (and refer to the package insert of those, or local guidelines). The screening period may be extended to allow vaccination procedures to be completed, in case of multiple vaccination needs and local/country requirements. This is applicable for vaccinations only, while all the other screening assessments must be performed as indicated in the Assessment Schedule Table 8-1.Vaccinations should be started at the earliest possible to avoid extension of screening period. There is a possibility that administration of a vaccine to a patient with PNH could stimulate complement production and worsen hemolysis. In order to mitigate this possibility, it may be preferred to start treatment with iptacopan within 2 weeks after vaccination. In this case, the 2-weeks post-vaccination period should be covered by treatment with prophylactic antibiotics.

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.

The absolute reticulocytes count will be measured at Screening to determine eligibility with regards to exclusion criterion # 6. Due to the kinetics of maturation of reticulocytes into mature red blood cells and turnaround time from reticulocytes sample collection and analysis by central laboratory, local reticulocytes testing can be performed at the same time as the central testing during the Screening period. 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) should be included in the eCRF to document eligibility.

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

Investigators should refer to the locally approved label of eculizumab and ravulizumab for recommendation of use and in accordance with local practice.

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 having received at least one packed red blood cell (pRBC) transfusion in the 6 months prior to randomization.

Participants will be randomized to one of the two treatment arms in a 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 and corresponding assessments according to schedule described in Table 8-1.

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 dose of 200 mg b.i.d. Please refer to Section 6 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.

Please refer to Section 8.3.2 which provides details about the protocol-specific guidelines for participants to receive a packed-RBC transfusion in the randomized treatment period.

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 Participants should complete all visits and assessments up to Week 24 visit.

Because of the known risk of complement inhibitor treatment for infections with encapsulated bacteria, most importantly *Neisseria meningitidis*, all participants will be provided with a Participant Safety Card. Participants will be instructed to be vigilant for any clinical sign of bacterial infections and to contact the investigator or local physician immediately in case of suspicion of infection and start of antibiotic treatment as soon as possible.

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 End of Study 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 schedule described in Table 8-2.

The **participants in the LNP023 arm**, who benefit from treatment and are taking LNP023 at Week 24 visit (i.e. did not permanently discontinue study medication), will be offered to continue the oral treatment during the treatment extension period, with study visits and assessments according to schedule detailed in Table 8-2. For participants not agreeing to continue in the treatment extension period after completing Day 168 visit, End of Study will be after completing recommended procedures defined in Section 9.1.1.

For participants permanently discontinuing LNP023 treatment during the treatment extension period, please refer to Section 9.1.1

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 program (REP), which will provide access to LNP023 and enable long-term safety monitoring. For participants not agreeing to continue in the Roll-over extension program (REP) after completing Day 336 visit, End of Study will be after completing recommended procedures defined in Section 9.1.1

4 Rationale

4.1 Rationale for study design

CLNP023C12302 is designed as a multicenter, open-label, randomized, active-comparator controlled, parallel group study for demonstration of superiority of LNP023 at a dose of 200 mg b.i.d. orally compared to intravenous anti-C5 antibody treatment on hematological response parameters and patient reported outcome measures for fatigue, in patients with PNH that present with residual anemia despite treatment with a stable regimen of anti-C5 antibody treatment (SoC).

The study population consists of PNH patients with residual anemia defined by a mean hemoglobin value below 10 g/dL (with approx. 40% requiring RBC transfusions in the past 6 months) for inclusion in the study despite treatment with SoC, i.e., anti-C5 antibody treatment of eculizumab or ravulizumab. This represents a population for which there remains a need for improved efficacy. In a retrospective analysis of a cohort of 93 PNH patients classifying hematological response to eculizumab treatment, it has been shown that after 6 months of eculizumab treatment (n=80), 54% of participants have a hemoglobin value of less than 10 g/dL with or without the need of RBC transfusions during that period

(Debureaux P-E et al 2019). The 54% included patients meeting the criteria for partial, minor or no hematological response according to the novel classification of hematological response to eculizumab (Risitano et al 2019).

Approximately 40% of randomized participants are required to have received at least one packed red blood cell (pRBC) transfusion in the 6 months prior to randomization. In the eculizumab registration trials TRIUMPH and SHEPHERD, transfusion independence has been achieved in 51% of eculizumab treated patients after 26 weeks of treatment (Hillmen et al 2006) and 51% of eculizumab treated patients after 52 weeks of treatment (Brodsky et al 2008), respectively. More recently, transfusion avoidance rates after 26 weeks of treatment were reported with 66.1% and 73.6% in eculizumab and ravulizumab treated patients respectively (Lee et al 2019).

The randomization will be stratified based on prior anti-C5 antibody treatment (eculizumab or ravulizumab) and by the presence or not of transfusion dependence (any transfusion administered in the 6 months prior to Randomization), both factors that could impact hematological response.

A multicenter setting has been chosen to ensure adequate recruitment and enrollment into the study in this rare indication. A randomized, active-comparator controlled study design for the main treatment period has been selected to appropriately assess LNP023's efficacy and safety and demonstration of superior efficacy compared to anti-C5 antibody treatment in support of its registration.

The randomization ratio of 8:5 has been chosen in order to maximize the number of PNH participants who are treated with LNP023 and increase the efficacy and safety data collected with LNP023 in this rare population. The initiation of LNP023 treatment has an overlap of 1 (eculizumab) or 2 (ravulizumab) weeks with prior anti-C5 antibody treatment to ensure that participants are not at risk of breakthrough hemolysis while minimizing potential carry-over effects of prior anti-C5 antibody treatment.

An open-label design is appropriate for the selected primary and majority of secondary efficacy endpoints, which are objectively measured (i.e. hematological response parameters, hemoglobin, LDH, reticulocytes, transfusion avoidance and breakthrough hemolysis). Protocol-specific guidelines (see Section 8.3.2) were defined to reduce potential bias in the determination of endpoints including transfusion avoidance.

The randomized treatment period of 24 weeks is considered appropriate to assess the effect of LNP023 on the primary and secondary efficacy endpoints as well as on safety and tolerability, similar to the treatment duration of the Phase 3 studies with eculizumab and ravulizumab (Lee et al 2019; Kulasekararaj et al 2019). Because the comparator arm includes both eculizumab and ravulizumab, the potential carry-over effects of the longer acting ravulizumab were taken into account by the choice of 24 weeks randomized treatment period instead of e.g. 16 weeks reported in the PEGASUS trial with only eculizumab as comparator (ClinicalTrials.gov Identifier: NCT03500549).

Two hematological responder endpoints will be used for the primary efficacy analysis of the randomized treatment period:

1. A hematological responder defined as a participant achieving an increase from baseline in hemoglobin levels ≥ 2 g/dL (assessed during the last 6 weeks of the 24 weeks randomized treatment period) without the need of RBC transfusions from Day 14 to Day 168. This endpoint comprises 1) a sustained improvement in hemoglobin of at least 2 g/dL from baseline and 2) transfusion independence for treatment success, both clinically important treatment goals in PNH. The choice of an increase of at least 2 g/dL in hemoglobin in the absence of transfusions is because it approximates an increase that can be achieved with the administration of a RBC transfusion (1-2 units), thereby considered clinically relevant.
2. 2. A hematological responder defined as a participant achieving hemoglobin levels ≥ 12 g/dL (assessed during the last 6 weeks of the 24 weeks randomized treatment period) without the need of RBC transfusions from Day 14 to Day 168. This endpoint comprises 1) hemoglobin normalization and 2) transfusion independence for treatment success, also both clinically important treatment goals in PNH.

An interval of six weeks at the end of the randomized treatment period with four assessments, and 3 out of 4 meeting the criterion, has been selected to demonstrate a durable hematological response. Furthermore the last six weeks of the 24 weeks randomized treatment period are used for determining hematological response (≥ 2 g/dL hemoglobin increase from baseline; hemoglobin ≥12 g/dL) to ensure that it reflects the actual treatment effect of either LNP023 or anti-C5 antibody treatment.

Considering that some patients may present with very low hemoglobin levels (e.g. < 7 g/dL), and thereby require a red blood cell transfusion during the first two weeks of the randomized treatment period, transfusions administered during these first 2 weeks will not be considered for the transfusion avoidance definition.

Secondary efficacy endpoints include transfusion avoidance and breakthrough hemolysis, a patient reported outcome measure for fatigue (FACIT-Fatigue) as well as changes in reticulocytes and LDH and MAVEs. They were selected to supplement the primary efficacy endpoints and are clinically meaningful endpoints for hemolytic PNH.

A treatment extension period of 24 weeks will provide further safety and efficacy data on LNP023 in PNH patients.

4.2 Rationale for dose/regimen and duration of treatment

The dose of 200 mg LNP023 b.i.d. as continuous treatment has been selected for this study primarily based on the available efficacy and safety data obtained at the time of interim analyses from the two ongoing Phase 2 PNH studies and is supported by PKPD modeling results.

In the CLNP023X2201 study in patients with active hemolysis despite treatment with eculizumab, LNP023 at a dose of 200 mg b.i.d. was administered to 10 PNH participants (cohort 1) and at a dose of 50 mg b.i.d. to 6 PNH participants (cohort 2). An interim analysis (IA) was conducted after 10 participants (cohort 1) completed at least 13 weeks of treatment with LNP023 200 mg b.i.d. add-on treatment to eculizumab.

In the CLNP023X2204 study in PNH patients not treated with eculizumab/complement inhibition, participants were randomized to LNP023 monotherapy in two sequences with forced titration after 4 weeks from LNP023 25 mg b.i.d. to 100 mg b.i.d (sequence 1) or LNP023 50

mg b.i.d. to 200 mg b.i.d. (sequence 2). An IA was conducted after the first 8 patients were randomized and 7 patients completed Week 8 visit assessments.

The dose of 200 mg b.i.d. is expected to provide optimal efficacy required for PNH as monotherapy with an adequate safety profile based on the following key findings of the two interim analyses:

- Participants treated with LNP023 200 mg b.i.d. (as add-on to eculizumab) had clinical benefits not achieved with eculizumab that included control of IVH demonstrated by LDH reduction, control of EVH demonstrated by reduction of bilirubin, reticulocytes and increase in haptoglobin resulting in normalization of hemoglobin in the majority of patients in the absence of red blood cell transfusions. The hematological response participants achieved with LNP023 200 mg b.i.d. add-on therapy was maintained with LNP023 monotherapy during the extension period (at the time of the IA) when eculizumab treatment was discontinued in 5/10 participants who continued with LNP023 monotherapy. Following the IA, several additional participants discontinued eculizumab treatment. C3 deposition was fully reversed by addition of LNP023 at a dose of 200 mg b.i.d. and survival of PNH red blood cells prolonged further supporting control of EVH by LNP023 at a dose of 200 mg b.i.d. There was sustained inhibition of the complement alternative pathway and profound and sustained reduction of Fragment Bb demonstrating target engagement.
- Participants receiving LNP023 monotherapy showed that LNP023 at dose levels ≥ 25 mg b.i.d. had LDH reduction of more than 60% from baseline in all participants and early transfusion-free hemoglobin increase in the majority of participants. Other hemolysis relevant laboratory values indicated that LNP023 administered as monotherapy controls both, intra (LDH reduction) and extravascular hemolysis (decrease of reticulocytes and bilirubin, increase in haptoglobin).

Preliminary information from cohort 2 in CLNP023X2201 suggests that the LNP023 dose of 50 mg b.i.d. may not provide optimal efficacy required for LNP023 monotherapy in PNH. There was suboptimal response in most participants requiring up-titration to the dose of 200 mg b.i.d.

LNP023 at a dose of 200 mg b.i.d. was safe and well tolerated by participants in both studies in PNH, as well as at the same dose in patients with IgA nephropathy (study CLNP023X2203) and C3 glomerulopathy (CLNP023X2202), supporting its use in this study.

The exposure-response model developed with data from the First In Human (FIH) study with LNP023 in healthy volunteers predicts that a dose of about 200 mg b.i.d. would be needed to achieve > 90% inhibition of the alternative pathway (Wieslab assay) in > 70% of subjects. Given the risk of hemolysis and breakthroughs in cases of insufficient inhibition of complement activity, full inhibition is desired and modelling results provide additional support for the choice of the dose of 200 mg b.i.d. for PNH. For further details, please refer to the LNP023 Investigator Brochure.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

For this study, an active control has been selected due to the life-threatening nature of the disease. To date the only approved, targeted therapies for treatment of PNH are eculizumab and

ravulizumab, two anti-C5 monoclonal antibodies inhibiting cleavage of C5 to C5a and C5b. The study allows inclusion of patients treated with either eculizumab or ravulizumab, at stable regimen. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose is a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose is based on body weight.

Eculizumab is the current Standard of Care (SoC) for PNH patients with hemolysis and the clinical program with eculizumab demonstrated prevention of intravascular hemolysis, hemoglobin stabilization, and reduction/avoidance of red blood cell transfusions (Brodsky et al 2008, Hillmen et al 2006) as well as reduction of the thromboembolic risk (Hillmen et al 2007). Its approval in 2007 and subsequent introduction has significantly changed the disease course where available and improved morbidity and mortality.

Ravulizumab (engineered from eculizumab with prolonged dosing interval) approved in 2019 for the treatment of PNH is expected to replace eculizumab as SoC, given the added convenience of an 8-week administration regimen. Data from two clinical trials demonstrated non-inferiority of ravulizumab to eculizumab (Lee et al 2019; Kulasekararaj et al 2019) providing justification for the choice of ravulizumab and eculizumab in the control arm.

While anti-C5 agents are effective in inhibiting intravascular hemolysis in most patients, only a small proportion of patients achieve normal to near normal hemoglobin values and there remains an unmet medical need to inhibit extravascular hemolysis not prevented by anti-C5 antibody treatment (please refer to Section 1.1). Participants are expected to continue with their stable anti-C5 antibody treatment regimen (which they were on during the six months prior to randomization) throughout the randomized treatment period. Any changes in dose and/or infusion interval should be avoided.

4.4 Purpose and timing of interim analyses/design adaptations

Periodic monitoring of safety data and emerging risk/benefit will be carried out by a Data Monitoring Committee (DMC). To this end, interim reports with analysis results using treatment group labels available only to the DMC will be generated by an independent statistical group not involved in the conduct of the trial. The randomization list will be made available in a firewalled area for the purpose of generating interim analysis reports.

4.5 Risks and benefits

The risks associated with the use of LNP023 are those inferred by its pharmacology and the results of preclinical safety studies. The most relevant risks are described below and a complete description of preclinical safety findings is available in the LNP023 Investigator Brochure. The safety results from the CLNP023X2201 study (PNH patients treated with eculizumab) as well as CLNP023X2204 study (anti-C5 treatment-naïve PNH patients) are summarized in the Investigator Brochure. LNP023 at a dose of 200 mg b.i.d. has been generally safe and well tolerated in these studies.

Appropriate eligibility criteria, as well as study specific stopping rules for the investigational drug with guidance to ensure continued treatment of PNH are included in this protocol. Recommended guidelines for monitoring of and management of infections are provided in

Section 6.6.2. The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures of participants including vaccinations prior to starting study treatment, close clinical monitoring with appropriate risk mitigation strategies, and periodic review of the safety data by an independent DMC. This study does not involve any risks regarding study procedures (e.g. no invasive research procedures). One theoretical risk which is specific to PNH patients is the risk of hemolysis following discontinuation of treatment with a complement inhibitor. This is managed by specific discontinuation procedures outlined in Section 9.1.1.

LNP023 did not show any mutagenic, teratogenic or genotoxic potential in completed standard battery of genotoxicity testing. In addition, LNP023 was tested in embryo-fetal development studies in rats and rabbits and no LNP023-related adverse fetal findings were detected in any of the studies. However, LNP023 has not been used in pregnant women, therefore, women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Based on the preliminary results from the CLNP023X2201 study as well as CLNP023X2204 study (Section 4.2 for details), patients randomized to LNP023 may have clinical benefits over and above the SoC including:

- Increase of hemoglobin to normal/near normal values in the absence of red blood cell transfusions
- Control of extravascular hemolysis
- Reduction of LDH

It is expected that the improved hematological response upon LNP023 treatment will translate into improved quality of life, most importantly an improvement in fatigue. More details about the preliminary results of the Phase 2 studies can be found in Section 1.1 and the Investigators Brochure. Patients randomized to anti-C5 antibody treatment may benefit from participating in this clinical trial and the possibility to switch to LNP023 treatment at the end of the randomized treatment period.

The main safety risk for complement inhibitors is considered to be infection caused by encapsulated bacteria. To date, no infections have been reported in preclinical studies with LNP023 and no infections caused by encapsulated bacteria have been reported in clinical trials.

Translational research has shown that the serological response to meningococcal infection is maintained during AP blockade but that it is markedly reduced after blockade of the classical pathway (CP) with C5-blockers like eculizumab. Serum bactericidal activity studies of serum from vaccinated patients against meningococci showed that C5 inhibitors block killing of meningococci, whereas AP inhibitors have less inhibitory effect on meningococcal killing (Konar and Granoff 2017). Vaccination is therefore predicted to be an effective mitigation strategy to reduce the risk for individuals treated with LNP023. Participants will be vaccinated against *meningococcal, pneumococcal* and *H. influenzae* infections according to local guidelines and availabilities, since these are all encapsulated bacteria.

Participants will also be closely monitored for signs and symptoms of infection (listed on a "Participant Safety Card" for participant awareness) and will be instructed to contact the investigator or a local physician if they experience these symptoms. The investigator will employ clinical judgement to determine an appropriate course of treatment. Antibiotic treatment should be started immediately for infections caused by encapsulated bacteria, with action taken with study medication considered on a case-by-case basis. Recommended guidelines for monitoring and management of infections are provided in Section 6.6.2. For immunocompromised participants with a higher risk of infections, precautionary actions (e.g. prophylactic antibiotics) should be considered by the investigator.

Other safety risks are based on preclinical data, with no relevant findings in clinical studies performed to date. There are potential risks of testicular effects, bone marrow toxicity with severe anemia, aorta mineralization and increase in heart weight and thyroid changes. The preclinical findings are described in more detail in the Investigator Brochure.

In the LNP023 clinical studies, there have been no serious testicular adverse events or changes from baseline in reproductive hormones reported to date. Since the testicular effects seen in preclinical studies have been shown to be mild and reversible with no notable effect on sperm or hormone levels in dogs, and a reasonable safety margin when comparing unbound concentrations achieved in the dog at the lowest dose where an effect was seen (LOAEL) and the concentrations achieved in man at the 200 mg twice daily dose, the relevance of the findings to man is considered questionable. Testicular AEs and reproductive hormone levels will continue to be monitored in Phase 3.

Although a severe bone marrow effect was seen pre-clinically in a single dog, it occurred at the highest dose level for which the exposure to LNP023 for unbound levels was more than 80-fold greater than that observed with the 200 mg b.i.d. dose of LNP023 in the clinic (see Investigator's Brochure). There have been no adverse events or blood chemistry values reported which are relevant to the bone marrow toxicity seen in the dog. Hematological parameters will continue to be monitored in Phase 3 studies.

Increases in heart weight and mineralization of the aortic wall were observed at dose levels ≥30 mg/kg/day in very young dogs (4 weeks old at the start of treatment, equivalent to 6-12 months of age in humans) after 52 weeks of treatment. These findings were not seen in adult dogs. Blood pressure decrease concurrent with heart rate increase was consistently observed in both young and adult dogs soon after dosing, but in adult dogs these effects diminished over time, whereas they persisted in the young dogs. Since the aorta mineralization and increased heart weight are considered to be seen only in young dogs because of an increased sensitivity related to age, the risk is considered unlikely to be relevant to adult patients.

Preclinical thyroid effects have been observed; however, they were minimal and reversible. There have been no clinically relevant thyroid adverse events or changes in thyroid hormone levels in clinical trials to date. Thyroid hormone levels will continue to be monitored in Phase 3 studies.

In addition, safety results from completed studies in 108 healthy volunteers exposed to LNP023 (84 to single doses and 24 to multiple doses over two weeks) indicated that treatment was well tolerated. Overall, no deaths or SAEs were reported, no imbalances from placebo in rates of

AEs and no AEs which led to study drug discontinuation. Similarly, the two Phase 2 studies in patients with PNH (29 patients exposed to LNP023), studies carried out in complement-driven renal disease (IgA nephropathy study, in which 87 patients were exposed to LNP023 and C3G studies, in which 27 patients were exposed to LNP023) confirmed that the safety profile was favorable and supported continuation of development.

In summary, the benefit risk relationship for LNP023 is positive supporting the start of this study.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

Patients diagnosed with PNH, who are treated with a stable regimen of anti-C5 monoclonal antibody treatment (Standard of Care; either eculizumab or ravulizumab) for at least 6 months prior to randomization, but still presenting with residual anemia (i.e., Hb < 10 g/dL) will be enrolled. Approximately 40% of participants having received at least 1 packed-RBC transfusions in the 6 months prior to randomization are to be enrolled. A total of approximately 91 participants will be randomized in the trial.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female participants ≥ 18 years of age with a diagnosis of PNH confirmed by *high-sensitivity flow cytometry* (Borowitz et al 2010) with RBCs and with WBCs granulocyte/monocyte clone size ≥ 10%.
3. Stable regimen (dose and intervals) of anti-C5 antibody treatment (either eculizumab or ravulizumab) for at least 6 months prior to Randomization.
4. Mean hemoglobin level <10 g/dL:
    - Documented by at least 2 measurements over a minimum of 4 months (medical history data) before Screening visit
    - And confirmed by central laboratory assessment during Screening and prior to Randomization:
        - By two hemoglobin measurements (mean <10 g/dL), two up to eight weeks apart, for patients not receiving a pRBC transfusion during Screening.
        - By one hemoglobin measurement (<10 g/dL) carried at the first Screening visit for patients receiving a pRBC transfusion after which he/she will be eligible.

5. Vaccination against *Neisseria meningitidis* infection is required prior to the start of treatment. If the patient has not been previously vaccinated, or if a booster is required, vaccine should be given according to local regulations, at least 2 weeks prior to first dosing. If treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment must be initiated.
6. If not received previously, vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* infections should be given, if available and according to local regulations. The vaccines should be given at least 2 weeks prior to first dosing. If LNP023 treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment must be initiated.
7. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are not eligible for inclusion in this study.

1. Participation in any other investigational drug trial or use of other investigational drugs at the time of enrollment, or within 5 elimination half-lives of enrollment, or within 30 days of enrollment whichever is longer; or longer if required by local regulations.
2. Participants on a stable eculizumab dose but with a dosing interval of 11 days or less or participants on stable ravulizumab dose but with a dosing interval of less than 8 weeks.
3. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
4. Known or suspected hereditary complement deficiency at screening.
5. History of hematopoietic stem cell transplantation.
6. Patients with laboratory evidence of bone marrow failure (reticulocytes $<100x10^9$/L, (or $<100x10^6$/mL); platelets $<30x10^9$/L, (or $<30x\ 10^6$/mL); neutrophils $<500x10^6$/L, (or $<500x10^3$/mL).
7. Active systemic bacterial, viral (incl. COVID-19) or fungal infection within 14 days prior to study drug administration.
8. Presence of fever ≥ 38 °C (100.4 °F) within 7 days prior to study drug administration.
9. Human immunodeficiency virus (HIV) infection (known history of HIV or test positive for HIV antibody at Screening).
10. A history of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus.
11. Major concurrent comorbidities including but not limited to severe kidney disease (e.g., eGFR < 30 mL/min/1.73 m^2, dialysis), advanced cardiac disease (e.g., NYHA class IV), severe pulmonary disease (e.g., severe pulmonary hypertension (WHO class IV)), or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participant's participation in the study.
12. Liver disease, such as active HBV or HCV infection defined as HBsAg positive or HCV RNA positive, or liver injury as indicated by: abnormal liver function tests at Screening:

- Any single parameter of ALT, GGT, alkaline phosphatase must not exceed 3×upper limit of normal (ULN)

13. Unstable medical condition including, but not limited to, myocardial ischemia, active gastrointestinal bleeding, coexisting chronic anemia unrelated to PNH, or unstable thrombotic event not amenable to active treatment as judged by the investigator at Screening.
14. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
15. Any medical condition deemed likely to interfere with the patient's participation in the study.
16. Concomitant use of any of the following medications is prohibited if not on a stable regimen for the time period indicated below prior to Screening and those listed in Section 6.2.2:
    - Erythropoiesis-stimulating agents (ESAs) or immunosuppressants for at least 8 weeks
    - Systemic corticosteroids given for hematological conditions (less than 1 mg/kg) for at least 4 weeks
    - Vitamin K antagonists (e.g., warfarin) with a stable international normalized ratio (INR) for at least 4 weeks
    - Low-molecular-weight heparin, and the direct oral anticoagulants (DOACs) rivaroxaban, apixaban and edoxaban, for at least 4 weeks
    - Iron supplements, vitamin B12, or folic acid for at least 4 weeks
    - Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) such as roxadustat for at least 8 weeks
17. Female patients who are pregnant or breastfeeding, or intending to conceive during the course of the study.
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and for 1 week after stopping LNP023, 5 months after stopping eculizumab and 8 months after stopping ravulizumab. **Effective contraception methods include**:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 m prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant

- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository
- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

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

19. Ongoing drug or alcohol abuse that could interfere with patient's participation in the trial

6 Treatment

Participants will be randomized in an 8:5 ratio to either LNP023 monotherapy given orally b.i.d. (where the anti-C5 antibody treatment will be stopped – See below for timing), or intravenous anti C5 antibody treatment (continuing with the same dose as that received prior to randomization).

LNP023 first administration (Day 1 visit)

The timing of the first LNP023 administration will provide a seamless switch from prior anti-C5 antibody treatment to LNP023, allowing for some overlap of exposure to anti-C5 antibody treatment when starting the oral agent while limiting the potential risk of breakthrough hemolysis, as the LNP023 exposure builds-up.

- First LNP023 dose administration of participants on prior eculizumab regimen must occur at days 7 to 8 after last infusion
- First LNP023 dose administration for participants on prior ravulizumab regimen must occur at days 41 to 43 after the last infusion

Participants will then continue taking 200 mg LNP023 b.i.d. monotherapy.

Anti-C5 first administration in the study (Day 1 visit)

Participants assigned to the comparator arm will continue receiving the anti-C5 infusion as per their stable regimen. It will be ensured that the participants and their physicians have relevant educational material and eculizumab or ravulizumab specific Participant Safety cards. However, the day of the next administration of anti-C5 for the 'study start' should coincide with 'Day 1' study day. The investigator is encouraged to 'count back' from the schedule date for the planned infusion.

Treatment Extension period: LNP023 administration for comparator group

At Week 24 visit, participants in the comparator arm will receive the last anti-C5 infusion, and will start with the first LNP023 dose administration the morning after the visit (Day 169).

With participants starting in the treatment extension period taking LNP023 starting on Day 169, the visit schedule will be harmonized, with the exception of Day 175, where only participants formerly assigned to the comparator arm will return for PK and safety assessments.

6.1 Study treatment

6.1.1 Investigational and control drugs

In this study, the "study treatment" includes the investigational drug, LNP023, and the active comparators of anti-C5 antibodies (either eculizumab or ravulizumab).

Table 6-1 Investigational and control drug

Investigational/ Comparator	Pharmaceutical dosage form	Route of administration	Supply type
LNP023, 200 mg	Hard gelatin capsule	Oral use	Open label, patient specific kits
Eculizumab, 300 mg/30mL	Concentrate solution for infusion	Intravenous infusion	Open label, vial
Ravulizumab, 300 mg/30 mL	Concentrate solution for infusion	Intravenous infusion	Open label, vial
Ravulizumab, 300 mg/3 mL**	Concentrate solution for infusion	Intravenous infusion	Open label, vial
Ravulizumab, 1100 mg/11 mL**	Concentrate solution for infusion	Intravenous infusion	Open label, vial
LNP023, 10* mg	Hard gelatin capsule	Oral use	Open label, patient specific kits

*used only during tapering down of LNP023 dose – see Section 9.1.1 for details

**If available commercially and provided by manufacturer

The investigational drug, LNP023 as 10 mg and 200 mg capsules, will be prepared by Novartis and supplied to investigator sites as open-label participant packs.

Eculizumab and ravulizumab will be provided locally by the study site, subsidiary or designee as commercially available or by Novartis, in each participating country according to local practices and local regulations.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

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 orally b.i.d. (approximately 56 participants), or i.v. anti-C5 antibody treatment (approximately 35 participants continuing with the same stable regimen as that prior to randomization), respectively.

6.1.4 Treatment duration

The duration of the randomized Treatment period is 24 weeks. If a participant's treatment with LNP023 is discontinued and participant is switched back to the prior anti-C5 antibody treatment, every effort will be made to continue with the study assessments up to the Week 24 visit.

The treatment extension period will last up to 24 weeks, where participants randomized to LNP023 arm during the randomized treatment period will be offered to continue with LNP023 treatment, and participants randomized to anti-C5 arm will be offered to switch to LNP023 monotherapy. If a participant permanently discontinues LNP023 during the treatment extension period, the Investigator should follow the recommended procedures for discontinuation (see Section 9.1.1). If possible, participant should continue with the study assessments up to the Week 48 visit.

After completion of the treatment extension period, participants may receive post-trial access (PTA) by joining the Roll-over extension program (REP) to allow participants access to LNP023 and to enable long-term safety monitoring. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms. Please refer to Section 8.3.2 for the red blood cell transfusions and protocol specific guidelines for its administration.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Erythropoiesis-stimulating agents (ESAs) and hypoxia inducible factors prolyl hydroxylase inhibitors (HIF-PHIs) are allowed to be used if on stable dose at least 8 weeks before Screening.

During the study, it is recommended to adjust the dose and/or discontinue dosing of ESAs and/or HIF-PHIs based on participant's hemoglobin level as per local guidelines and practice. As a general guide, it is recommended to reduce the ESA and/or HIF-PHIs dose by 50% if hemoglobin is ≥ 12 g/dL and/or to stop ESA and/or HIF-PHIs dosing if hemoglobin is ≥ 13 g/dL. Use particular caution in participants with coexisting cardiovascular disease, stroke and chronic kidney disease.

LNP023 has been shown to have a weak inhibition potential for the liver uptake transporter OATP1B1. Calculation revealed that the exposure (AUC) of respective sensitive substrates may be increased by <1.5 fold. Although the expected effect on the exposure of respective co-medications is small and may not be clinically relevant it is recommended to combine LNP023 with sensitive OATP1B1 substrates or those having a narrow therapeutic index with caution or apply a staggered dosing (see below). A list of OATP1B1 substrates to be used with caution will be provided to the investigators.

LNP023 has also been shown to inhibit the efflux-transporter P-glycoprotein (P-gp) on the intestinal level but not the liver. Therefore, the direct oral anti-coagulation drugs apixaban, rivaroxaban and edoxaban which are P-gp substrates should be used with caution. For edoxaban a staggered dosing (see below) is recommended, in particular for participants with impaired kidney function.

For narrow therapeutic index (NTI) immunosuppressants (e.g. cyclosporine, sirolimus, tacrolimus on a stable dose) which are substrates for the efflux transporter P-gp with no alternative treatment available a staggered dosing approach is recommended. This can be accomplished by administering the respective co-medication >3hrs following oral administration of LNP023. Alternatively, compounds with a short Tmax of around < 2 hours (i.e., fast absorption) can be given >1hr prior to LNP023. The staggered dosing will avoid increases in systemic exposure of co-administered drugs due to P-gp inhibition by LNP023 at the intestinal level. For participants receiving immunosuppressants (stable dose) and if their exposure is no longer monitored, it is advisable to resume therapeutic drug monitoring after start of treatment with LNP023 (single assessment).

6.2.2 Prohibited medication

Use of the treatments listed below are not allowed during LNP023 administration.

- Live vaccines are prohibited for the entire study treatment duration
- Preclinical studies have shown that systemic disposition of LNP023 is primarily mediated by metabolic clearance, predominantly by CYP2C8 and to a smaller extent by direct glucuronidation. In addition, some contribution from direct renal (approximately 20%) and direct biliary excretion (around 5 to 10%) is anticipated. LNP023 is also a substrate for the organic anion-transporting polypeptide (OATP) hepatic uptake transporter (see above). To ensure participant safety, co-medications that inhibit multiple disposition mechanisms of

LNP023 (e.g. Gemfibrozil) are prohibited. The same applies to strong CYP2C8 inhibitors (main clearance pathway) such as clopidogrel.

- Gemfibrozil (a potent inhibitor of metabolizing enzymes CYP2C8, UGT1A and liver uptake transporter OATP1B1) must be interrupted at least 48 hours before first LNP023 dose until end of LNP023 treatment (and replaced with another appropriate medication used for that indication)
- Strong inhibitors of CYP2C8 such as clopidogrel must be interrupted 7 days before first LNP023 dose until end of LNP023 treatment (and replaced with another appropriate medication used for that indication)

- Medications that are either "sensitive substrates" for the efflux transporter P-gp or have a narrow therapeutic index (NTI) and are substrates for P-gp should not be administered with LNP023 (interrupted 48 hours before first LNP023 dose). Typical examples are digoxin, quinidine, paclitaxel, fentanyl and phenytoin. However, if no alternative treatment is available, a staggered dosing approach is recommended (refer to Section 6.2.1.1). The anti-coagulation drug dabigatran which is also a P-gp substrate should not be used in combination with LNP023 and a staggered dosing is also not recommended.

Concomitant medication listed under exclusion criterion 16 is prohibited, if not on a stable regimen prior to Screening, for the time periods indicated.

6.2.3 Rescue medication

Rescue medication is allowed to treat serious complications such as thrombosis with anti-thrombotic treatment and management of this complication as per local guidelines and practice. For significant breakthrough hemolysis requiring rescue medication in the opinion of the investigator, rescue medication is allowed and should be managed as per local guidelines and practice.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.3.2 Treatment assignment, randomization

During screening and after hemoglobin eligibility is confirmed, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment (for LNP023, and when applicable for anti-C5) to be dispensed to the participant.

Randomization should occur as closely as possible to the planned Day 1 (see Section 6) while taking into consideration availability of assigned treatment arm on site.

The randomization numbers will be generated ensuring that treatment assignment is unbiased and concealed from participants and investigator staff as is described in the following: A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by the type of prior anti-C5 antibody treatment (eculizumab or ravulizumab) and based on transfusion history as reported during the last 6 months prior to randomization (i.e. transfusion received / not received).

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Treatment will be open to participants, investigator staff, and the CTT. The CTT will have access to standard reports of participants profiles and other listings as necessary to fulfill data review activities and patient safety. No aggregated data reports by treatment groups will be created and made available to the CTT. Dummy treatment assignments will be used to test statistical analysis programs and the randomization list will be kept strictly confidential until the database lock at the end of the randomized treatment period. During the randomized treatment period, the randomization list will be released only to a firewalled area to those designated to access it to serve the purposes of creating reports for the DMC or the PK analysis.

6.5 Dose escalation and dose modification

LNP023 will be administered at 200 mg b.i.d. and anti-C5 antibody treatment will be administered at the stable regimen participants were on in the prior 6 months before randomization for the duration of the study. There are no dose adjustments planned for LNP023 or anti-C5 antibody treatment.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by providing detailed instructions to the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant safety and the validity of the study. The participant must also be instructed to immediately contact the investigator if he/she is unable for any reason to take the study treatment as prescribed and appropriate actions will be taken.

Compliance for LNP023 will be assessed by the investigator and/or study personnel using capsule counts and information provided by the participant. This information should be captured in the source document at each visit.

Participants on LNP023 will be given the opportunity to use a generic reminder application (app) that will synchronize with the participant mobile phone calendar to remind participants to take their medication. The participants may choose to report compliance to the study site staff through the app. The use of this application and the compliance reporting feature are entirely voluntary and not mandated for use.

For the comparator arm, study treatment is administered intravenously under the supervision of the Investigator or designee, thereby ensuring compliance with study medication administration.

All study treatments dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

Infections

The participants and treating staff need to be instructed to be vigilant for any clinical signs of bacterial infections (e.g., malaise, chills, fever, nausea, photophobia, generalized muscle and joint pain) and to measure the body temperature at minimum at the times of symptoms of presumed infection. Participants will be instructed to contact the study physician immediately in case of suspicion of infection or elevated body temperature (> 38.3°C by oral or tympanic method) for a 'phone directed' triage.

In case of a suspected bacterial infection, participants should be immediately considered for emergency evaluation and empirically treated with an appropriate antibiotic course.

In case of any (bacterial and non-bacterial incl. COVID-19) severe infection, interruption of LNP023 dosing could be considered, on a case-by-case basis. However, every effort should be taken to keep the participant on study treatment unless the risk outweighs the benefit in the opinion of the investigator.

If LNP023 treatment is to be permanently discontinued, please refer to Section 9.1.1 for the appropriate actions.

If the participant is in the anti-C5 antibody treatment arm at the time of diagnosis of a serious bacterial infection, they should be treated immediately with appropriate antibiotics and any

guidance in the local label for the anti-C5 inhibitor should be followed.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

LNP023 Participant Safety Card

All participants will be provided with a Participant Safety Card. Participants will be instructed to be vigilant for any clinical sign or symptom of serious bacterial infection and to contact the investigator or local physician immediately in case of suspicion of infection, in which case antibiotic treatment should be started as soon as possible.

Comparator Participant Safety Card

All participants randomized to continue on eculizumab or ravulizumab will be provided with the specific relevant Participant Safety card if they do not already have one. Participants will be instructed to be vigilant for any clinical sign or symptom of meningococcal infection and to contact the investigator or local physician immediately in case of suspicion of meningococcal infection, in which case antibiotic treatment should be started as soon as possible.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to continue administration of the study treatment even without performing an on-site visit.

The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1-month supply. In this case, regular phone calls or virtual contacts (as per scheduled visits or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

LNP023

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

Anti-C5 antibody treatment (eculizumab, ravulizumab)

Preparation and dispensation should follow the locally approved label and local practice. During the 24-week randomized Treatment Period, participants randomized to anti-C5 antibody treatment must continue with same dose and schedule as they were before entering the study.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels (comparators) or in the Investigator's Brochure (LNP023).

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

LNP023

Participants should take LNP023 at the dose of 200 mg twice per day (in the morning and in the evening) at approximately the same times each day and ideally with 12-hours interval between morning and evening dosing. On study visit days, the participants should not take that day's morning dose until instructed by the site staff following the completion of all study assessments.

Table 6-2 LNP023 dose and treatment schedule

Dose level	Posology	LNP023 dose strength
200 mg b.i.d.	1 capsule twice daily	200 mg

Participants should take LNP023 irrespective of food intake. Each dose should be taken with a glass of water.

Participants should be instructed to swallow capsules whole and not to chew or open them.

If vomiting occurs during the course of treatment, participants should not take the study treatment (LNP023) again before the next scheduled dose.

Participants should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 4 hours after the approximate time of the usually daily dosing. That dose should be omitted and the participant should continue treatment with the next scheduled dose.

Anti-C5 antibody treatment (eculizumab, ravulizumab)

Preparation and dispensation should follow the locally approved label and local practice. Participants randomized to anti-C5 antibody treatment must continue with same dose and schedule as they were before entering the study. A specific eculizumab or ravulizumab Participant Safety card and relevant educational material will be provided to participants receiving anti-C5 therapy, and study investigator.

All kits of study treatment will be recorded in the IRT system.

7 Informed consent procedures

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

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

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) (and/or CDS for marketed drugs). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may

conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

The following informed consents are included in this study:

- Main study consent, which also includes:
  - An additional signature page for participants moving to Treatment extension period
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - A subsection that requires a separate signature for the 'Optional Consent for Patient Interview'
- Informed Consent Optional for genetic research
- Informed Consent Form for Optional Off-site Research Nursing (ORN) visits during a pandemic
- Informed Consent Form for Optional Off-site Research Nursing (ORN) visits for Week 2 (Day 14) and/or Week 6 (Day 42) visits or in special circumstances
- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

The study includes an optional DNA component which requires a separate signature if the participant agrees to participate. It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments (DNA) will in no way affect the participant's ability to participate in the main research study.

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

8 Visit schedule and assessments

The assessment schedule (Table 8-1 and Table 8-2) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Unless specified (i.e. post dose PK samples), all assessments should be performed prior to dose administration the day of visits.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Tables 8-1 and Table 8-2) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

At the investigator's discretion, and based on benefit-risk considerations of the participant's clinical condition, and the local availability of services, some qualifying participants may be offered the option to receive home nursing to perform Week-2 and /or Week-6 visits. These off-site visits will be offered in certain countries and sites if Sponsor, Investigator and local regulations and conditions allow.

Participants, that the investigator identifies as suitable benefitting from off-site visits, must provide (a separate) consent in the optional Off-site Research Nursing Informed Consent. The participants are under no obligation to participate in off-site visits, as they can decide to continue with on-site visits at the study site.

The off-site visits will comply with all assessments indicated in Table 8-1 for those visits.

The off-site visits will be carried out by a third-party vendor centrally sourced by the Sponsor that can provide qualified research nurses who will perform study assessments under the oversight of the Investigator. The qualified nurses will be under the delegation of the investigator. The investigator will retain accountability for participant's oversight and all medical decisions (i.e. protocol specified medical procedures, AE/SAE assessment and reporting, changes in medication, etc.).

Participants who discontinue LNP023 treatment during the randomized treatment period should continue in the study up to Week 24 visit, completing all scheduled visits assessments. The same applies to anti-C5 antibody treatment. Please, refer to Section 9.1.1 for details on the recommended procedures to follow in case of permanent discontinuation.

Participants who discontinue LNP023 treatment during the treatment extension period of the study for any reason, should continue in the study up to the Week 48 visit completing all scheduled visit assessments. The same guidance for managing LNP023 permanent discontinuation as in the randomized treatment period applies.

At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster or in special circumstances, that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. tele consult) or visits by home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the disruption or until it is safe for the participant to visit the site again. For more details refer to Section 8.6.

Table 8-1 Assessment schedule - Randomized treatment period

Period	Screening		Randomized treatment period											
Visit Name	**Screening**	**Screening Hb confirmation**	**Day 1**	**Day 7**	**Day 14**	**Day 28**	**Day 42**	**Day 56**	**Day 84**	**Day 112**	**Day 126**	**Day 140**	**Day 154**	**Day[9] 168**
Days	**-56 to -1**	**-56 to -1**	**1**	**7 ±1**	**14 ±1**	**28 ±1**	**42 ±3**	**56 ±3**	**84 ±3**	**112 ±3**	**126 ±3**	**140 ±3**	**154 ±3**	**168 ±3**
Weeks	**-8 to -1**	**-8 to -1**	**1**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**18**	**20**	**22**	**24**
Informed consent	X													X[11]
Entry criteria	X	X												
Demography	X													
Medical history/current medical conditions	X													
Vaccination history & Vaccination	X													
Alcohol and Smoking history	X													
Hepatitis B, C and HIV screen	X													
Physical examination	S		S			S								S
Blood pressure and pulse rate	X		X	X	X	X	X	X	X	X	X	X	X	X
Body height	X													
Body weight	X		X					X		X				X
Body temperature	X		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[1]	S		S						S					S
Clinical Chemistry (full)	X		X					X		X				X
Clinical Chemistry (abbreviated)				X	X	X	X		X		X	X	X	
Hematology (full)[2]	X	X (Hb only)	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation/Markers of thrombosis	X		X			X		X	X	X		X		X
Panel of hormones blood samples	X		X			X		X	X	X		X		X

Period	Screening		Randomized treatment period											
Visit Name	**Screening**	**Screening Hb confirmation**	**Day 1**	**Day 7**	**Day 14**	**Day 28**	**Day 42**	**Day 56**	**Day 84**	**Day 112**	**Day 126**	**Day 140**	**Day 154**	**Day[9] 168**
Days	**-56 to -1**	**-56 to -1**	**1**	**7 ±1**	**14 ±1**	**28 ±1**	**42 ±3**	**56 ±3**	**84 ±3**	**112 ±3**	**126 ±3**	**140 ±3**	**154 ±3**	**168 ±3**
Weeks	**-8 to -1**	**-8 to -1**	**1**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**18**	**20**	**22**	**24**
[redacted]	X		X			X		X		X		X		X
[redacted]				X		X								X
Urinalysis (dipstick)	X		X			X		X		X		X		X
Urine Albumin/Creatinine ratio			X						X					X
Breakthrough hemolysis							X							
[redacted]	X		X	X	X	X	X	X	X	X	X	X	X	X
[redacted]							X							
12-lead Electrocardiogram (ECG)	X		X						X					X
Adverse Events							X							
Major Adverse Vascular Events							X							
Concomitant medications								X						
[redacted]								X						
Surgical and medical procedures								X						
Patient reported outcomes		X[4]	X	X[5]	X		X		X		X	X	X	X
[redacted]														X[10]
IRT	X	S[6]	X	X	X	X	X	X	X	X	X	X	X	X
LNP023 Dispensing			X			X		X	X	X		X		X
Eculizumab Dispensing			X		X	X	X	X	X	X	X	X	X	X
Ravulizumab Dispensing			X					X		X				X
Study Drug Administration[7]								X						
[redacted]			X[8]											
[redacted]			X											X

Period	Screening		Randomized treatment period											
Visit Name	**Screening**	**Screening Hb confirmation**	**Day 1**	**Day 7**	**Day 14**	**Day 28**	**Day 42**	**Day 56**	**Day 84**	**Day 112**	**Day 126**	**Day 140**	**Day 154**	**Day[9] 168**
Days	**-56 to -1**	**-56 to -1**	**1**	**7 ±1**	**14 ±1**	**28 ±1**	**42 ±3**	**56 ±3**	**84 ±3**	**112 ±3**	**126 ±3**	**140 ±3**	**154 ±3**	**168 ±3**
Weeks	**-8 to -1**	**-8 to -1**	**1**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**18**	**20**	**22**	**24**
Disposition		X												

X = assessment to be recorded in the clinical database or received electronically from a vendor

S = assessment to be recorded in the source documentation only

[1]At screening, a serum pregnancy test will be performed, while during the study urinary pregnancy tests will be performed

[2]Local reticulocytes testing can be performed at the same time as the central testing during the Screening period. 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

[redacted]

[4]First PRO completion should occur at a visit during screening period prior to Randomization and before any other assessment at that visit.

[5]Only FACIT-F [redacted] questionnaires will be carried out at this visit

[6]Randomization after eligibility confirmed. All laboratory results must be available and reviewed prior to randomization to ensure patient's eligibility.

[7]Study drug Administration: LNP023 to be administered b.i.d. daily to participants assigned to LNP023 arm. Participants assigned to the comparator arm will continue receiving the anti-C5 infusion as per their stable regimen at the study center.

[redacted]

[9]For participants not agreeing to continue in the treatment extension period after completing Day 168 visit, End of Study will be after completing recommended procedures defined in Section 9.1.1. For participants prematurely discontinuing study treatment before Day 168 but remaining in the study for abbreviated visits, please refer to Section 9.1.1 for the close monitoring and additional assessments/visits to be performed in between abbreviated visits.

[redacted]

[11]The extension period should be presented/re-discussed with the participant and additional signature obtained if participant agrees to continue in the extension period

Table 8-2 Assessment Schedule - Treatment Extension period

Period	**Treatment Extension Period**						
Visit Name	**[Day 175]** ***x-comparator only*** **	**Day 196**	**Day 224**	**Day 252**	**Day 280**	**Day 308**	**Day336/EOS[3]**
Days	**175 ± 1**	**196 ± 5**	**224 ± 5**	**252 ± 5**	**280 ± 5**	**308 ± 5**	**336 ± 5**
Weeks	**25**	**28**	**32**	**36**	**40**	**44**	**48**
Blood pressure and pulse rate	X	X	X	X	X	X	X
Physical examination							S
Body weight							X
Body temperature	X	X	X	X	X	X	X
Pregnancy test							S
Clinical Chemistry (full)			X				X
Clinical Chemistry (abbreviated)	X	X		X	X	X	
Hematology (full)	X	X	X	X	X	X	X
Coagulation/markers of thrombosis		X	X	X	X	X	X
Panel of safety hormones blood samples		X	X		X		X
[redacted]		X	X		X		X
[redacted]	X	X					X
Urinalysis (dipstick)	X	X	X	X	X	X	X
Urine Albumin/Creatinine ratio				X			X
Breakthrough hemolysis	X						
[redacted]	X	X	X	X	X	X	X
RBC transfusion	X						
12-lead Electrocardiogram (ECG)							X
Adverse Events	X						
Major Adverse Vascular Events	X						
Concomitant medications	X						
[redacted]	X						

Period	**Treatment Extension Period**						
Visit Name	**[Day 175]** ***x-comparator only*** **	**Day 196**	**Day 224**	**Day 252**	**Day 280**	**Day 308**	**Day336/EOS[3]**
Days	**175 ± 1**	**196 ± 5**	**224 ± 5**	**252 ± 5**	**280 ± 5**	**308 ± 5**	**336 ± 5**
Weeks	**25**	**28**	**32**	**36**	**40**	**44**	**48**
Surgical and medical procedures	X						
Patient reported outcomes		X	X	X	X	X	X
IRT	X	X	X	X	X	X	X
LNP023 Dispensing		X	X	X	X	X	
Study Drug Administration[2]	b.i.d. from Day 169						
Disposition	X						

**Visit [Day 175] will be completed only by those participants that were taking comparator treatment on Week-24 visit and progressing into the treatment extension period

X = assessment to be recorded in the clinical database or received electronically from a vendor

S = assessment to be recorded in the source documentation only

[redacted]

[2]Study drug Administration: LNP023 to be administered b.i.d. daily to all participants in the treatment extension period.

[3]For participants not agreeing to continue in the roll-over extension program (REP) after completing Day 336 visit, End of Study will be after completing recommended procedures defined in Section 9.1.1. For participants prematurely discontinuing study treatment before Day 336 but remaining in the study for abbreviated visits, please refer to Section 9.1.1 for the close monitoring and additional assessments/visits to be performed in between abbreviated visits

8.1 Screening

Screening activities (Table 8-1) must be initiated only after the participant has signed the ICF.

Rescreening participants

It is permissible to re-screen a participant if the participant fails the first screening; however, each case must be discussed and agreed with Novartis on a case-by-case basis.

In the case where a safety laboratory assessment (this excludes Hemoglobin laboratory assessment) at screening is outside of the range specified in the entry criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion eCRFs must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (Section 10.1.3). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.1.2 Hemoglobin assessments and transfusion during Screening

When signing the Informed Consent Form, the participants allows the retrospective review and reporting of hemoglobin values at least during the last 4 months prior to screening. The mean/average of at least 2 values must be below 10 g/dL to proceed with screening activities.

During the screening period, mean hemoglobin <10 g/dL will be confirmed by central laboratory assessment prior to randomization evaluated by two hemoglobin measurements, (mean <10 g/dL), two up to eight weeks apart; or by one hemoglobin measurement (<10 g/dL) from the first assessment for patients receiving a pRBC transfusion after the first assessment.

Transfusion administered based on hemoglobin during the Screening period

If, in the Investigator's judgment, a participant conditions meets the conditions for transfusion as per local requirements, the participant must be transfused with packed-RBC.

If a participant receives a packed-RBC transfusion following the first assessment carried out for the Screening visit (central laboratory), he/she will be eligible without an additional hemoglobin assessment by the central laboratory.

Transfusion administration will be recorded on a dedicated CRF page, where signs and symptoms are also reported as needed. If a participant refused to receive a blood transfusion, the CRF page must be completed indicating that the packed-RBC was not administered per participant's decision.

8.1.3 Absolute Reticulocytes Count during Screening

The absolute reticulocytes count will be measured at Screening to determine eligibility with regards to exclusion criterion # 6. Due to the kinetics of maturation of reticulocytes into mature red blood cells and turnaround time from reticulocytes sample collection and analysis by central laboratory, local reticulocytes testing can be performed at the same time as the central testing during the Screening period. 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) should be included in the eCRF to document eligibility.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Participants demographic: full date (only if required and permitted) or year of birth or age, sex, race/predominant ethnicity (if permitted) and baseline characteristic data will be collected on all participants. Participant race/ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Relevant medical history/current medical conditions will include: date for diagnosis of PNH (and age or disease duration will be derived up to the date of screening); vaccination history; MAVE history (dates and type); the packed-RBC transfusion received in the last 12 months prior to Screening; relevant medical history; smoking and alcohol history will also be collected.

Prior concomitant medications (including vitamins, herbal preparations, over the counter medications, and those medications highlighted in the entry criteria, as well as start date of anti-C5 treatment) **and procedures** (any therapeutic intervention including surgery, biopsies, or non-pharmacological therapy) taken prior to Screening will be recorded in the CRFs.

Prior anti-C5 antibody treatment regimen for PNH (eculizumab or ravulizumab), which must be stable for the 6 month preceding randomization, will be recorded in a dedicated CRF page.

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

8.3 Efficacy

Efficacy/pharmacodynamics assessments are specified below. Please refer to Table 8-1 and Table 8-2 for timepoints when these assessments are performed. Section 2 shows the correlation of the assessments with the objectives.

8.3.1 Hemoglobin, reticulocytes, LDH and other PNH-related laboratory parameters

Blood samples for hematology, clinical chemistry and [redacted] will be collected according to Table 8-1 for the randomized treatment period.

The following laboratory parameters will be assessed: Hemoglobin [redacted], reticulocyte count and bilirubin (as markers for extravascular hemolysis), LDH (as a marker for intravascular hemolysis), [redacted]

During the treatment extension period, the assessment will be carried out as per Table 8-2.

Please refer to central laboratory manual regarding sample collection, numbering, processing and shipment.

8.3.2 Red blood cell transfusion

The need for administration of red blood cell transfusion will be monitored continuously during the randomized treatment period.

To standardize criteria for administration, transfusion criteria have been established and will apply starting from Day 1 of the study.

Packed RBC transfusions will be administered to participants in the following cases:

- Hemoglobin level ≤ 9 g/dL with signs /and or symptoms of sufficient severity to warrant a transfusion
- Hemoglobin of ≤ 7 g/dL, regardless of presence of clinical signs and/or symptoms

The level of hemoglobin, the number and unit of transfusion administered as well as the signs and/or symptoms if applicable will be recorded in the CRFs. Symptoms typically associated with or precipitating participant's need for transfusion are listed below:

- Severe or worsening of fatigue
- Severe or worsening dyspnea / shortness of breath
- Palpitation/angina (or worsening symptoms)
- Change in mental status (syncope, light-headedness, confusion, stroke, transient ischemic attack)

If a participant meets the transfusion criterion, the Investigator will determine the appropriate number of units of packed-RBC to be transfused.

The hemoglobin value on which the investigator will base the need for administering a packed-RBC transfusion may be from the local laboratory due to the turnaround time for central lab results. However, the investigator must collect a separate sample for hemoglobin assessment by the central laboratory for analysis at the same time as taking a sample for local lab analysis.

It is recommended that the transfusion is administered within 2-3 days of the assessment of the hemoglobin/event that triggered the requirement. In case the investigator or participant decides not to give or receive a transfusion despite meeting the criteria specified above, the reason should be clearly documented in the CRF page.

During the treatment extension period, the need for administration of red blood cell transfusion will be monitored continuously until the end of study visit following the same criteria and guidance described above.

8.3.3 Breakthrough hemolysis

The occurrence of breakthrough hemolysis will be monitored continuously during the randomized treatment period.

The criteria for clinical breakthrough is defined in Table 8-3 below if either one of the two clinical criteria is met, in presence of the laboratory evidence of intravascular hemolysis and should be reported in the 'Breakthrough hemolysis' CRF page in addition to the AE page.

In contrast to clinical breakthrough as defined, the isolated laboratory evidence of increased intravascular hemolysis, without meaningful decrease in hemoglobin and without other clinical signs or symptoms of hemolysis (per Table 8-3), is defined as subclinical breakthrough hemolysis, and should **not** be reported in the 'Breakthrough hemolysis' CRF page.

Table 8-3 Breakthrough definition

	Clinical criteria		Laboratory criteria
	Hemoglobin levels	**Signs or symptoms**	**LDH level**
Clinical breakthrough *	Decrease equal to or more than 2 g/dL (compared to the latest assessment, or within 15 days)	Gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs & symptoms	> 1.5-times ULN and increased as compared to the last 2 assessments
Subclinical breakthrough	Decrease less than 2 g/dL (compared to the latest assessment, or within 15 days)	No clinical signs or symptoms, except moderate hemoglobinuria	> 1.5-times ULN and increased as compared to the last 2 assessments
LDH: lactate dehydrogenase; ULN: Upper Limit of Normal; *The breakthrough is defined clinical if either one of the two clinical criteria is demonstrated, in presence of laboratory evidence of intravascular hemolysis (LDH level)			

During the treatment extension period, breakthrough hemolysis will be monitored continuously until the end of study visit following the same criteria and guidance described above.

The assessment could be based on the local laboratory results. However, the Investigator should also collect at the same time a sample for the central laboratory assessment of hemoglobin and LDH, whenever possible.

8.3.4 Patient Reported Outcomes (PRO) – FACIT-Fatigue

The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. It will be used to assess patient-reported fatigue. FACIT-Fatigue is one of many different FACIT scales part of a collection of Health-Related Quality of Life (HRQoL) questionnaires referred to as the FACIT Measurement System (Webster et al 2003, Yellen et al 1997). The use of the FACIT-F in PNH patients has been reported in several publications and is sensitive to changes in disease status, allowing demonstration of statistically significant and clinically meaningful results

(Kulasekararaj et al 2019, Ueda et al 2018, Brodsky et al 2008, Ueda et al 2018, Brodsky et al 2008). All FACIT scales are scored so that a high score is better. As each of the 13 items of the FACIT-F Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best. For additional Patient Reported Outcomes (PROs) assessed in the study, please refer to Section 8.5.1.

The PROs will be completed by participants on an electronic PRO device (ePRO), before any other procedure or assessment at study visits at the screening and Day 1 visits. The questionnaires should be completed in the language with which the respondent is most familiar. The participant should be given sufficient space and time to complete the questions. The participant should be made aware that completed questionnaires are not reviewed by the investigator/ study personnel.

Following the Day 1 visit, the participant will take home the ePRO device to be able to complete the PROs at home prior to visits to the clinic site. Detailed instructions describing administrative procedures of the PROs including participant completion via ePRO will be provided to the sites.

If a participant is not able to self-administer the ePRO or refuses to complete the questionnaires, this should be documented in the source documents. A participant inability or refusal to complete a questionnaire(s) is not a protocol deviation.

8.3.5 [redacted]

[redacted]

8.3.6 Major Adverse Vascular Events (MAVEs)

Assessments of MAVEs occur according to Table 8-1 and Table 8-2 and will be reported in the dedicated CRF page, in addition to the AE page. The description of the MAVEs including diagnosis (i.e., ultrasound, angiogram, magnetic resonance imaging, etc.), date of diagnosis. Start date, end date (if applicable) and status (ongoing / resolved) will be collected in the CRFs. A MAVE is defined as per the list below.

- Acute peripheral vascular occlusion

- Amputation (non-traumatic; nondiabetic)
- Cerebral arterial occlusion/cerebrovascular accident
- Cerebral venous occlusion
- Dermal thrombosis
- Gangrene (non-traumatic; nondiabetic)
- Hepatic/portal vein thrombosis (Budd-Chiari syndrome)
- Mesenteric/visceral arterial thrombosis or infarction
- Mesenteric/visceral vein thrombosis or infarction
- Myocardial infarction
- Pulmonary embolus
- Renal arterial thrombosis
- Renal vein thrombosis
- Thrombophlebitis / deep vein thrombosis
- Transient ischemic attack
- Unstable angina
- Other, please specify

8.3.7 Appropriateness of efficacy assessments

The efficacy assessments including laboratory parameters hemoglobin (to determine the degree of anemia), LDH (as marker for intravascular hemolysis), reticulocytes, bilirubin and haptoglobin (as markers for extravascular hemolysis), and the need of red blood cell transfusions are important parameters for assessing treatment response in PNH. In fact, hemoglobin, the need of RBC transfusions are the determining parameters for classifying treatment response to complement inhibitor therapy with LDH and reticulocytes as ancillary parameters (Risitano et al 2019). Breakthrough hemolysis is a phenomenon reported with eculizumab and also ravulizumab, therefore is part of the efficacy assessments in this study. Although the incidence of MAVEs is expected to be very low in the study population, it is important to assess it for a new complement inhibitor treatment. The majority of these efficacy assessments have been used in the eculizumab and ravulizumab registrations studies and will provide clinically relevant results for PNH.

The FACIT-Fatigue Scale will measure various aspects of fatigue, one of the most debilitating and commonly reported symptom generally among PNH patients (Hill et al 2007), and among patients currently treated with eculizumab (Socie et al 2019). The use of the FACIT-F in PNH patients has been reported in several publications and is sensitive to changes in disease status, allowing demonstration of statistically significant and clinically meaningful results (Kulasekararaj et al 2019, Ueda et al 2018, Brodsky et al 2008). It has been well validated in general populations (Webster et al 2003; Yellen et al 1997) and content validity has been completed specifically in PNH patients (Weitz et al 2012).

8.4 Safety

Safety assessments are specified below with the assessment schedules (Table 8-1 and Table 8-2) detailing when each assessment is to be performed.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, or in special circumstances that limits or prevents on-site study visits, and in case that an Off-site Research Nursing (ORN) visits are planned at that site (see Section 8.6), regular phone or virtual calls may occur (as per scheduled visits) for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

For details on AE collection and reporting, refer to AE Section 10.1.1.

Table 8-4 Assessments and specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated, based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include BP and pulse measurements. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured with an appropriately sized cuff. If the value reported is out of range, a repeat sitting measurements will be made at 5 - 10 minute later and the second measurement will be used/entered in the CRFs.
Height and weight	Height in centimeters (cm) is collected at Screening only; body weight (to the nearest 0.1 kilogram (kg) assessed in indoor clothing, but without shoes) will be measured as specified in Table 8-1 and Table 8-2.
Body temperature	The same route (temporal, tympanic, or axillary) and modality (temporal scanner, tympanic probe, thermometer) should be used for ongoing patient observations, as to allow for accurate temperature trend evaluation.

8.4.1 Laboratory evaluations

Unless specified in the table below, a central laboratory will be used for the analysis of the specimens collected. Details of collection, shipment, and reporting by the laboratory is provided to the investigator in the laboratory manual.

As per Section 4.6, if participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) may be used as defined in Table 8-8.

Clinically notable laboratory findings are defined in Appendix 1.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Table 8-5 Laboratory tests

Test Category	Test Name
Hematology - full list	Hematocrit, total Hemoglobin, Mean corpuscular hemoglobin, Haptoglobin, Reticulocytes counts, Red blood cells (RBC) count, RBC distribution width, RBC mean corpuscular volume, white blood cell (WBC) count with differentials and platelet count
Clinical Chemistry (full)	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, eGFR, hs-C-reactive protein (hsCRP), Serum creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) /Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting), Ferritin
Clinical Chemistry (abbreviated)	LDH, Albumin, ALT, AST, GGT, eGFR, hs-C-reactive protein, Serum creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN)/Urea, Ferritin
Urinalysis/urine dipstick assessments	Dipstick measurements for protein, bilirubin, blood, glucose, ketones, nitrites, pH, specific gravity and urobilinogen, and WBC/leukocytes will be performed at the site's local laboratory. If dipstick measurement results are positive (abnormal), results will be captured in the eCRF. Microscopy must be assessed locally following an abnormal dipstick test.
UACR Urine albumin creatinine ratio	UACR will be assessed from sample obtained during the visit (Central Laboratory analysis)
Coagulation/markers of thrombosis	Prothrombin time (PT), INR, activated partial thromboplastin time (aPTT). D-dimer and fibrinogen
Blood hormone levels	Triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH) and reverse T3; Follicle stimulating hormone (FSH), luteinizing hormone (LH), dihydrotestosterone (DHT) and testosterone
Pregnancy test	Serum / Urine pregnancy test (source)
Hepatitis markers	Hepatitis B Virus Surface Antigen, Hepatitis C Virus RNA
HIV	HIV seropositivity testing will be performed as detailed in the Central laboratory manual and in line with local regulatory requirements
[redacted]	[redacted]

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position and conducted as a 12-lead recording according to the assessment schedules in Table 8-1 and Table 8-2. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling (including PK sampling). The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Unless auto-calculated by the ECG machine, the investigator must calculate QTcF according to the following formula, where QT interval is in milliseconds (ms) and RR interval in seconds (s):

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Single 12-lead ECGs are to be collected with ECG machines available at the site. The original ECGs and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

For any ECGs with participant safety concerns (please refer to Appendix 1 for notable abnormalities), two additional ECGs must be performed to confirm the safety finding. If confirmed, a copy of the assessment should be sent to the Novartis global team for expedited review. Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events, as appropriate. Any identifier details must be redacted e.g. participant initials, date of birth.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing performed locally. Refer to the Assessment Schedule in Table 8-1 and Table 8-2 for timing of the required assessments. Additional pregnancy testing might be performed if requested by local requirements.

At screening, a serum pregnancy test will be performed, while during the study urinary pregnancy tests will be performed. Local pregnancy test and associated results will not be collected on CRF.

The participant should inform the investigator if they believe they might be pregnant. Please refer to Section 9.1.1 on recommendations for LNP023 therapy.

Assessments of fertility

Refer to Section 5.2 for criteria to determine women that are not of child bearing potential.

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

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Coagulation panel/thrombosis

Blood samples will be analyzed at the Central laboratory for the following panel: D-dimer, fibrinogen, prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT).

8.4.5 Reproductive and thyroid hormones monitoring

The assessments indicated below will be carried out as per the Assessment schedules in Section 8, and will be assessed in all participants.

Testosterone, follicle stimulating hormone (FSH), dihydrotestosterone (DHT), luteinizing hormone (LH), thyroid stimulating hormone (TSH) and thyroid hormones (T3, T3 reverse, T4) will be regularly monitored.

8.4.6 Urine albumin creatinine ratio (UACR)

At the scheduled study visit indicated in Table 8-1 and Table 8-2, a urine sample will be taken while the participant is at the site to measure albumin and creatinine, and calculate UACR.

8.4.7 Appropriateness of safety measurements

The safety assessments selected are appropriate for this indication/patient population and the potential risks associated with LNP023. The risk of (meningococcal) infection will be closely monitored throughout the study. Participant vigilance for early signs and symptoms of infection is required and supported by providing appropriate tools (e.g. Participant Safety Card, educational material) to enhance awareness and vigilance. Reproductive and thyroid-related hormones, vital signs and ECGs will be collected in order to evaluate the findings observed in preclinical toxicity studies.

8.5 Additional assessments

8.5.1 [redacted]

[redacted]

[redacted]

[redacted]

8.5.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	PK blood collection		
					[redacted]	[redacted]	[redacted]
				[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]				[redacted]		[redacted]

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8.5.3 [redacted]

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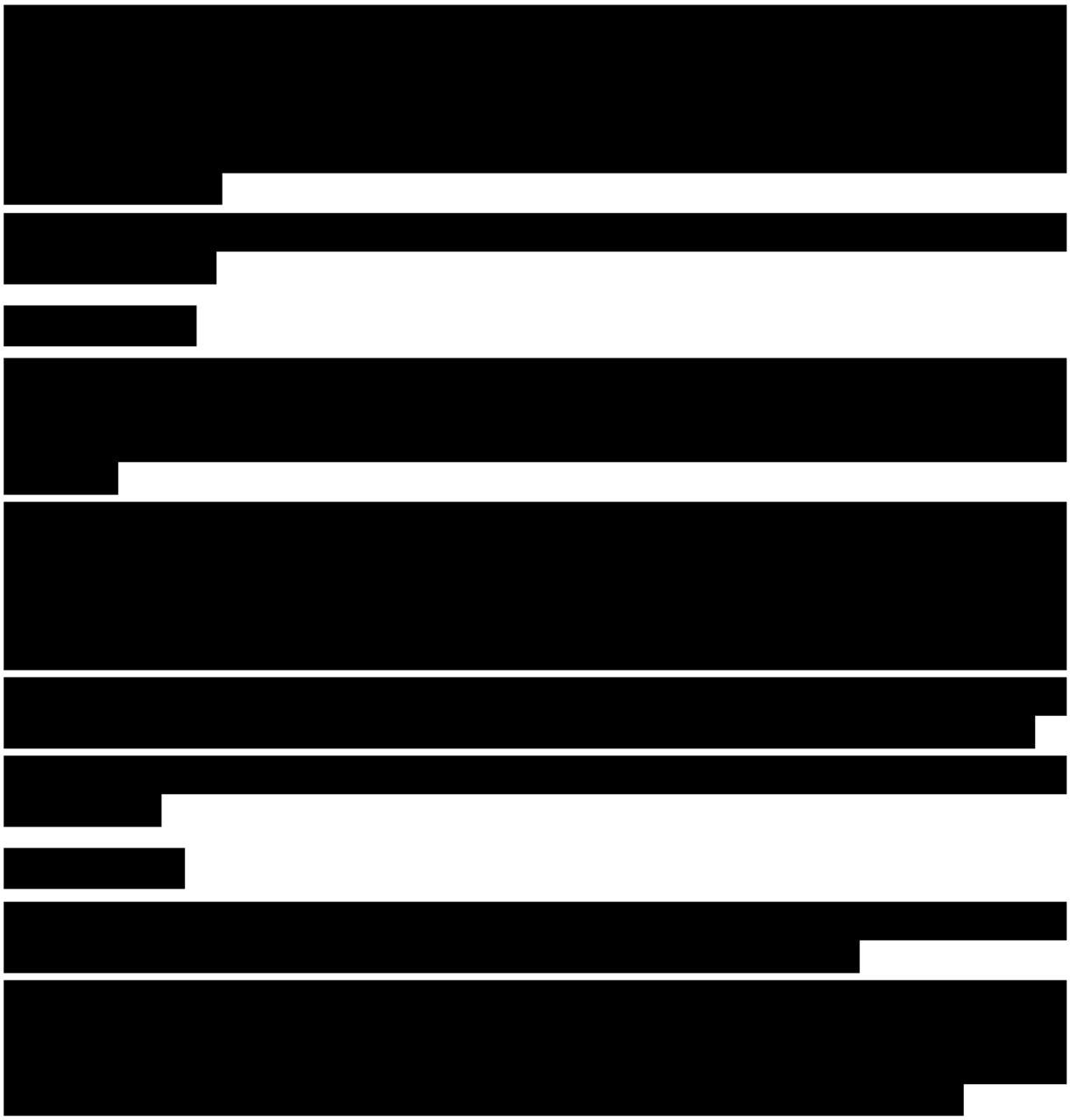


8.6 Off-site research nursing (ORN) visits

In addition to the option to receive off-site research nursing services to perform Week-2 and /or Week-6 visits (Section 8), at the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option of off-site research nursing visits to unburden the participant while ensuring patient safety, engagement and retention during pandemic or the emergency similar to that of a pandemic such as the physical inability of a participant to visit the site.

The off-site visits will be offered in certain countries and sites and may replace on-site visits if Sponsor, Investigator and local regulations and conditions allow.

Participants, that the investigator identifies as suitable benefitting from off-site visits, must provide (a separate) consent in the optional Off-site Research Nursing Informed Consent. The participants are under no obligation to participate in off-site visits, as they can decide to continue with on-site visits at the study site.

The off-site location is not a site location where the investigator will conduct the trial and where source data will be maintained, but is for example the participant's home or another safe location if assessed as suitable by the Off-site Research Nurse (ORN) and ultimately decided by the Investigator.

The off-site visit schedule will be determined in discussion between the participant, Investigator, and the Sponsor.

Conditions to enable off-site visits

Procedures conducted in an off-site location are carried out with the same level of scientific integrity as assessments conducted on-site.

The following conditions must be met for off-site visits to occur:

- Off-site visits may occur during the study duration for Week-2 and /or Week-6 visits or under exceptional circumstances and if agreed between investigator and Sponsor.
- The participant must have completed at least Day 1 visit (i.e., confirmed eligibility and completed all visit assessments).
- At least the first anti-C5 infusions must have occurred during the on-site period for participants on comparator arm (albeit performed as per local regulations and conditions)
- If a participant has begun off-site visits and s/he suffers from either (1) a severe AE or an SAE (possibly related to study medication), and/or (2) any concurrent medical conditions which, in the opinion of the Investigator, could cause unacceptable safety risks, then the participant must resume the on-site visits. The participant may resume the off-site visits when, based on the Investigator's judgment, there are no further safety risks for the participant.

Off-site research nursing (ORN) personnel

The off-site visits will use a third-party vendor (wherever possible) centrally sourced by the Sponsor or other similar services available locally and agreed by Novartis, that can provide qualified research nurses who will perform study assessments under the oversight of the Investigator. Qualified ORN will be under delegation of the investigator. The investigator will retain accountability for participants' oversight and all medical decisions (i.e. protocol specified medical procedures, AE/SAE assessment and reporting, changes in medication, etc.).

More details of the off-site research nursing process will be outlined in a separate manual provided to the sites participating in the off-site research nursing visits.

The ORN may collect and process Laboratory samples according to Table 8-8, which will then be shipped to the Central Laboratory. However, if results of these samples collected by ORN are obtained from the local laboratory then these results need to be entered in the appropriate local laboratory CRF pages.

Assessment will be performed following the timing indicated in the assessment Schedule (Table 8-1), but limited to the listing indicated below.

Table 8-8 List of the assessments to be performed during by off-site research nursing visit

Assessment list to be performed during ORN
Assessments*
Vaccination booster
Blood pressure and pulse rate
Body temperature
Breakthrough hemolysis event
PNH signs and symptoms
Adverse Events
Major Adverse Vascular Events
Concomitant medications
ER visits / re-hospitalization
Surgical and medical procedures
Study treatment administration / Checking availability
Blood samples to be collected **
Clinical Chemistry
Hematology
Coagulation/Markers of thrombosis
Panel of safety hormones blood samples
[redacted]
[redacted]
[redacted]
*Data collected are entered in the study CRF pages for the corresponding visit. **Results obtained from the local laboratory are entered in the appropriate local laboratory CRF pages. [redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Any situation in which study treatment might result in a significant safety risk to the participant

If a female on LNP023 becomes pregnant during the study, it is recommended to discontinue treatment. However, after an individual benefit-risk assessment by the investigator, LNP023 continuation may be considered in exceptional circumstances. Counseling should be provided to the participant on the appropriate treatment for PNH during pregnancy. The outcome of the discussion with the participant, reflecting benefit-risk considerations, should be documented in the participant's file.

If a female on anti-C5 therapy becomes pregnant during the study, the continuation of anti-C5 therapy may be considered following an individual benefit-risk assessment by the investigator. Guidance on pregnancy provided in the local label for the anti-C5 inhibitor should be followed.

If treatment with LNP023 has to be discontinued immediately, i.e. because of a significant safety risk which warrants immediately stopping LNP023 treatment, it is recommended to promptly re-initiate anti-C5 antibody treatment, as judged by the investigator.

Close monitoring of participants for signs and symptoms of hemolysis should be performed upon LNP023 discontinuation. It is recommended to monitor at minimum for: increase in LDH, decrease in hemoglobin level and [redacted] increase in serum creatinine, thrombosis, and change in mental status. If serious hemolysis occurs, the Investigator should consider the following supportive treatments (and record them in the appropriate CRF pages):

- Blood transfusion (packed RBCs),
- Or exchange transfusion if the PNH RBCs are >50% of the total RBCs by flow cytometry
- Corticosteroids
- Anticoagulation
- Any other supportive treatment or therapy as judged by the investigator.

A visit one week after permanent discontinuation of LNP023 should occur for the following assessments: LDH, creatinine, hemoglobin, coagulation/thrombosis markers (PT/INR, aPTT, D-dimer, and fibrinogen), [redacted], dipstick urinalysis, PNH signs and symptoms and all adverse events. All data collected will be entered in the appropriate CRF page.

If treatment with LNP023 has to be discontinued but it is not warranted to immediately discontinue LNP023 treatment, e.g., discontinuation due to participant/guardian decision, it is recommended to consider re-initiating the anti-C5 antibody treatment, as judged by the investigator. In addition, it should be considered to taper down LNP023 over a period of 14 days, as follows:

- 3 capsules of 10 mg LNP023 taken in the evening (once daily) for 7 days
- 1 capsule of 10 mg LNP023 taken in the evening (once daily) for 7 days

The investigator should consider the proposed monitoring and supportive treatments listed above in case serious hemolysis occurs. For LNP023 tapering, weekly visits are recommended while tapering, and one week after the last LNP023 dose for the following assessments: LDH,

creatinine, hemoglobin, coagulation/thrombosis markers (PT/INR, aPTT, D-dimer, and fibrinogen), [redacted], dipstick urinalysis, PNH signs and symptoms and all adverse events. All data collected will be entered in the appropriate CRF page.

Anti-C5 permanent discontinuation

For the permanent discontinuation of anti-C5, refer to the local label for recommended monitoring upon discontinuation.

Overall considerations

All dose changes must be recorded on the appropriate CRF.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section).

Where possible, they should return for the assessments indicated in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

Participants who permanently discontinue study medication during the randomized treatment period, should complete the visits as scheduled up to Week 24.

Participants who permanently discontinue study medication during the treatment extension period, should complete the visits as scheduled up to Week 48.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s premature discontinuation of study treatment and record this information.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments, including the need of RBC transfusions
- Safety laboratory assessments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant’s discontinuation from study treatment.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

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

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible (for an EOS visit) and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending

on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their End of Study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

After completion of the treatment extension period, participants may receive post-trial access (PTA) by joining the Roll-over extension program (REP) to allow participants' access to LNP023 and to enable long-term safety monitoring. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of each participant and identifying adverse events.

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

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

For participants who permanently discontinue LNP023 administration during the course of the study, or do not continue into the roll-over extension program (REP), AEs will be collected for 7 days after last dose of study drug or until EOS, whichever is longer.

For participants who roll-over to the REP, AEs will be collected in the database for this study until participant last study visit (Day 336/EOS).

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued at least until the last study visit.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

10.1.1.1 Adverse events of special interest

Adverse events of special interest (AESIs) are defined as events (serious or non-serious) which are of scientific and medical interest specific to Novartis's product or program, for which ongoing monitoring may be appropriate. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest are defined on the basis of potential safety risks for the product, class effects and data from preclinical studies.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical conditions(s)] which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an

emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAE's is collected and recorded on the (eSAE with paper back up) Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

For participants NOT entering the roll-over extension program (REP), any SAEs experienced by participants up to 30 days after EOS should be reported to the Novartis Safety office using a paper SAE form.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the stopping study treatment should be considered as described in Section 9.1.1, and the trial participant must be asked to read and sign the pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the study informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS) on a Pharmacovigilance Pregnancy Form. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must also be reported. After consent is provided, the pregnancy be followed-up for one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE immediately, without undue delay, under no circumstances later than within 24 hours of Investigator's awareness (Note: If more stringent, local regulations regarding reporting timelines prevail).

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1 in Appendix 2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are also outlined in Table 16-1. Repeat liver chemistry tests (i.e. ALT etc.) to confirm elevation.

These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), exposure to environmental chemical agents, alcohol use, recreational drug use, and special diets.
  - Exclusion of underlying liver disease

These investigations can include based on investigator's discretion:

- Imaging such as abdominal US, CT or MRI, as appropriate
- Considering gastroenterology or hepatology consultations.

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Data Monitoring Committee

This study will include a Data Monitoring Committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables of value for assessing benefit/risk to study participants, and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC. Analyses reviewed by the DMC will be performed by an independent statistical group that will have access to randomization codes in accordance to procedures described in the charter and its appendices.

10.2.3 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, i.e. not being members of the DMC and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

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

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be released and made available for data analysis of the randomized treatment period. Before this it will be made available in a restricted area to be accessed by the independent programmer and statistician who will prepare reports for the DMC. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

A clinical study report (CSR) will be produced for submission at the time the last participant has completed the randomized treatment period. This section describes the methods associated to this report.

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.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

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

The Full Analysis Set (FAS) comprises all participant 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.

The Safety Set 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 analysis set including the complete follow up of participants up to the completion of the treatment extension period will be defined in the corresponding SAP.

12.2 Participant 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.

12.3 Treatments

The Safety set will be used for the analyses of exposure to LNP023 and anti-C5 antibody treatment 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 and anti-C5 antibody treatment as well as the dose intensity and the relative dose intensity will be summarized by means of descriptive statistics using the safety set.

In addition, the duration of exposure (in days) reflecting the compared treatment strategies: LNP023 + transfusions and anti-C5 antibody treatment + transfusions, will be summarized to describe exposure corresponding to treatment policy.

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

12.4 Analysis of the primary endpoint(s)/estimand(s)

In the study protocol, 'absence of transfusions' or 'not requiring transfusions' refers to not receiving transfusions and not meeting the criteria for administration of transfusions as per Section 8.3.2.

12.4.1 Definition of primary endpoint(s)/estimand(s)

Here we define the two primary endpoints corresponding to the primary estimands. The 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 last six weeks (from Day 126 to Day 168) of the randomized treatment period, and
- The participant has not met the criteria (i.e. not received and not met the criteria for administration as per Section 8.3.2) for administration of RBC transfusions 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 participants who do not receive a transfusion between the first and second confirmatory measurement. In participants who

receive a transfusion after the first confirmatory measurement, the baseline will be the first measurement.

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

- The hemoglobin levels are ≥ 12 g/dL on three out of four measurements taken at the visits occurring in last six weeks (from Day 126 to Day 168) of the randomized treatment period, and
- The participant has not required (i.e. not received and not met the criteria for administration as per Section 8.3.2) any RBC transfusions between Day 14 and Day 168.

12.4.2 Statistical model, hypothesis, and method of analysis

The overall study Type I error is one-sided 0.025. 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:

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

versus

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

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

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 12.1.

To adjust for multiplicity of the simultaneous test of two primary endpoints, we will apply a weighted permutation test with equal weights to each of the two endpoints. In order to account for the correlation between the two primary endpoints due to the overlap in participants who would be positive for both criteria as well as for the small sample size, 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 from each fit with the actual treatment labels will be compared with the 1.25$^{\text{th}}$ percentiles 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 al1993).

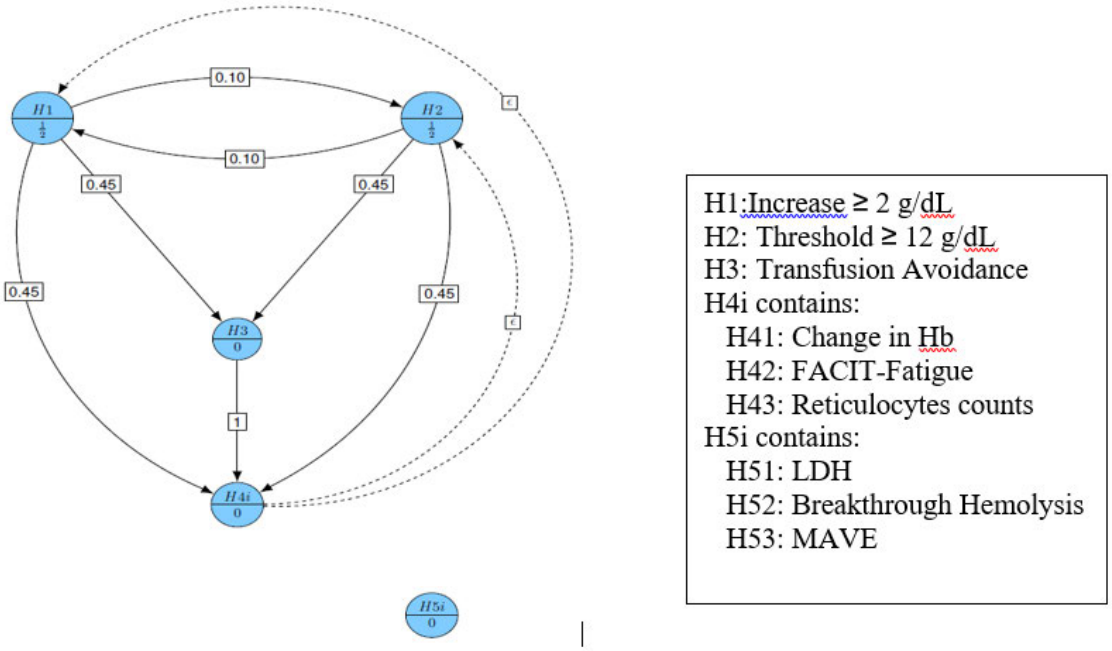
The summary measure provided will be the odds ratio derived as the coefficient for treatment effect from the conditional logistic regression. This corresponds to an overall estimate where the intercept parameter is dropped from the likelihood by conditioning on the within stratum non-responders. The estimated odds ratios and their confidence intervals will be provided for each of the two endpoints as well as the corresponding p-values.

The secondary endpoint hypotheses are described in Section 12.5. Figure 12-1 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 described above. 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.
3. Secondary endpoints in H5i: H51, H52, and H53 are tested after successful rejection of hypotheses in H1, H2, H3, and 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 not available in the abbreviated version here are provided in Appendix 3.

Figure 12-1 Graphical display of multiple testing procedure



12.4.3 Handling of remaining 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.

12.4.4 Handling of missing values not related to intercurrent event

For the primary response definitions, RBC transfusion will qualify the participant as a non-responder, hence missing hemoglobin data following having met the criteria for transfusion does not impact the primary analyses.

Missing hemoglobin data caused due to withdrawal from study in the event that a participant did not have a prior RBC transfusion, will be imputed based on pattern mixture models which aims to be consistent with inclusion of hemoglobin data under the treatment policy strategy following all other intercurrent events. The impact on the need for transfusion would then be derived from this imputation. Furthermore, the impact on hemoglobin levels will also take into account the treatment participants were on at the time of withdrawal from study.

- For participants withdrawing from study follow up after discontinuation of LNP023, the model implemented will recover a return to pre-treatment levels of Hb. This would be implemented by borrowing from the control group (anti-C5 antibody treatment) whose on treatment response would be considered similar to the pre-treatment levels in participants in the LNP023 arm.
- For anti-C5 randomized participants withdrawing from study, missing data will be imputed by borrowing from participants in the anti-C5 antibody treatment arm.
- For participants with intermittent missing data during study follow up where reasons for missingness are assumed to be unrelated to response or compliance status, their missing data will be handled with a missing at random approach and imputed consequently.

The full specification will be provided in the SAP.

12.4.5 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. An additional sensitivity analysis of the use of a conditional logistic regression model including covariates will be carried out using a Cochran-Mantel Haenszel test instead. This assessment will be detailed in the SAP.

12.4.6 Supplementary analysis

A supplementary analysis for each of the two primary endpoints considering the use of rescue therapy (as defined in Section 6.2.3) as treatment failure will be performed. The supplementary estimand will have the same population, treatment of interest, summary measure as the primary estimand in Section 2.1. The intercurrent events for the supplementary estimand will be the following:

Transfusions will be considered treatment failures whereas discontinuations of study medication for any reason will be handled with treatment policy strategy. Use of rescue medication (to treat serious complications such as thrombosis or for significant breakthrough hemolysis) will be defined as an intercurrent event and handled using a composite strategy: patients receiving rescue medication will be considered as treatment failure.

12.4.7 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 will be a covariate in the model, together with the rest of covariates specified for the primary analysis model. 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 will be handled within a penalized likelihood (Firth) approach.

The comparisons of proportions described above will be further displayed for subgroup categories defined by previous transfusion dependence, previous anti-C5 antibody treatment, length of time since diagnosis, age categories, sex, and baseline hemoglobin.

Potential impact of a new wave of COVID-19 infections affecting measurements have been minimized through the measures proposed in Section 8. 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 SAP 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.

12.5 Analysis of secondary endpoints/estimands

The secondary estimands described below 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. In addition to the analysis of the secondary estimands, we also show the hypothesis identifier used in Figure 12-1.

For all estimands defined in this section, we consider the same intercurrent events as for the primary estimands, except in the case when the intercurrent event itself is considered an endpoint. For RBC transfusions, the treatment given to it will depend on the endpoint and this is described below. In the case of discontinuation of study medication, breakthrough hemolysis

events, and MAVEs expected to be reflected in the endpoint the analysis will apply treatment policy, for all endpoints.

H3: **Transfusion avoidance** will be evaluated comparing the proportion of participants not receiving (i.e. not receiving and not met the criteria for administration as per Section 8.3.2) any RBC transfusion during Day 14 and Day 168, similarly to the comparison applied to the primary estimand by means of the odds ratio with standardized marginal proportions derived similarly (including in both cases the randomization strata and covariates).

H41: 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. This will be accomplished by the of use of imputed values based on a normal distribution whose mean is restricted to a range consistent with not having received an RBC transfusion and the within visit covariance matrix will borrow from the observed within participant covariance matrix, to replace hemoglobin values following a transfusion. The model for the comparison between treatments is a repeated measures model with an unstructured covariance structure, with stratification factors and including main effect of treatment, visit and baseline, and the interactions between visits and treatment and visits and baseline levels. Additional covariates will be age (as binary indicator) and sex. 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).

H42: The endpoint consists of **changes from baseline in scores of fatigue using the FACIT-Fatigue questionnaire** where baseline is defined as the mean of levels obtained pre-randomization (Screening visit) and the Day 1 value. As for the other endpoints, the longitudinal model will be a repeated measures model including test scores collected at all visits. The comparison between treatments will be an average of treatment estimates derived for visits occurring between Day 126 and Day 168. Main effects will be stratification factors and baseline covariates and interaction terms will be similar as those used to compare changes in hemoglobin.

H43: The comparison of the **change from baseline in reticulocyte counts** will be derived from a longitudinal repeated measures model including data collected throughout the study and where baseline is defined as the value on Day 1. In this model, stratification factors, baseline covariates as well as interaction terms will be the same as for changes in hemoglobin. 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.

H51: The treatment effect on **percent change from baseline in LDH** will be assessed using a longitudinal repeated measures model of log transformed ratio to baseline based on all observations collected during follow-up. The model is similar to the model described for all continuous endpoints. Treatment comparisons will be derived based on the average of the log transformed ratio in each treatment estimated between Day 126 and Day 168.

H52: The comparison of **rates of breakthrough hemolysis** will be carried out using a negative binomial model. Stratification factors and covariates will be included similarly as for the other endpoints.

H53: The comparison of **rates of Major Adverse Vascular Events** (**MAVE**) will be carried out using a negative binomial model. Due to the expected low frequency of occurrences, no covariates are planned to be included.

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.

In addition the comparison of changes from baseline in hemoglobin will also be carried out quantifying the effect of the treatments compared that is mediated by the use of RBC transfusions.

Missing data for secondary endpoints

Missing data during study follow up will be imputed following the same principles as for the primary estimands/endpoints. This treatment involves pattern mixture models for withdrawal from study follow up using the reason for withdrawal modeled to capture the impact on hematological response or the need for RBC transfusions. In case of intermittent missing data, when reasons for missingness were consistent with the assumption of missing at random, the missing observations will be imputed under this assumption.

The imputation approach used for hemoglobin data that were missing following a transfusion, in the case of intermittent missing data will be the same as for the hypothetical estimand. In the case of definitive withdrawal of study follow up following a transfusion only hemoglobin levels at visits during 30 days following the transfusion would be imputed under the this approach, while the hemoglobin and other measurements involved in the secondary estimands will be imputed using a pattern mixture model according to principles described in Section 12.4.4.

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.

Treatment Extension period

The efficacy endpoints of interest will still be the same as during the randomized treatment period, namely, proportions achieving response, hemoglobin, scores of FACIT-Fatigue, reticulocyte counts, LDH, as well as occurrences of breakthrough hemolysis and MAVEs throughout the 48 weeks of follow up. These analyses will be fully detailed in the extension SAP.

12.5.1 Safety endpoints

The analysis set used for all safety analyses will be the safety set (SAF). All tables will be presented by treatment group. The complete details of all safety summaries will be provided in

the SAP. The following mentions safety outcomes of interest and provides a non-exhaustive description of principles to be followed in the preparation of outputs.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. 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). In addition, a separate summary of death events including on treatment and post treatment deaths will be provided if appropriate.

The on-treatment period lasts from the date of first administration of study treatment to 7 days after the date of the last actual administration of LNP023 which covers slightly more than 5 times the estimated half-life of LNP023.

Adverse events

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 medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to discontinuation of study medication, and for LNP023 tapering if this is followed prior to complete study dose discontinuation.

The number (and proportion) of participants with adverse events of special interest/related to identified and potential risks will be summarized by treatment.

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.

Vital signs

Summary statistics will be provided by treatment and visit/time. Summary occurrence of abnormalities may be provided by treatment group if appropriate.

12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally.

Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced (by treatment group).

Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

Laboratory data for participants with relevant abnormalities will be listed by participant, treatment group, and visit/time relative to the start of study medication. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification may be provided as appropriate to compare baseline to the worst on-treatment value. Other displays using based on fold increases or decreases of interest will be provided as appropriate.

12.5.2 [redacted]

12.5.3 Patient reported outcomes

In addition to the analyses below, a comprehensive analysis of PRO will be provided as a separate PRO report and documented in a separate statistical analysis plan.

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. Changes in scores of fatigue using the FACIT-Fatigue questionnaire are a secondary endpoint and the analysis is described in Section 12.5. This section briefly describes supportive analyses of FACIT-Fatigue as well as supportive analyses using a secondary clinical outcome instrument.

Among the other PRO outcomes measured, the QLQ-C30 global health status, fatigue, and in particular physical functioning sub-scales are considered of value and will certainly add to the interpretation of results using the FACIT-Fatigue questionnaire. In addition, the PGIS (Patient Global Impression of Severity) which is an anchor instrument will be used to calibrate the scale of the assessments using FACIT-Fatigue. Participants will as well complete EQ-5D-5E that will be used to support Health Technology Assessment evaluations and are outside the scope of the analyses in this section.

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. Note that the PGIS planned to be included in the study will ask the following question: "How would you rate your overall symptoms of fatigue during the past 7 days?" Participants in the study will select one of the following response choices: no symptoms, mild, moderate, severe, very severe." The use of PGIS to calibrate baseline severity scale and subsequent changes will match unit changes in PGIS to changes in FACIT-Fatigue scores to determine responder status.

Further, responder analyses derived from changes in FACIT-Fatigue will be performed. Response is defined as at least a 5-point improvement in the FACIT-Fatigue total score from baseline at a patient-level. Given the greater variability at the patient-level, a 5-point change is recommended as a meaningful important difference. Response data will be analyzed using Generalized Linear Mixed Model (GLMM) including terms for treatment, stratification factors, visit, treatment by visit interaction, and baseline score, with logit as link function. Individual patient random effects will be included in the model. The odds ratio between treatment arms at each scheduled time point will be estimated and treatment comparisons of interest will be derived as the comparison of average odds ratios for visit occurring between Day 126 and Day 168, and the estimated comparison will be derived together with a two-sided 95% confidence interval.

The above analyses will include data from participants with an evaluable baseline and at least one post baseline score. Handling of missing forms due to missed visits will follow the principles applied to all other missing data throughout the study.

Changes in the sub-scales of the EORTC-QLQ30 that were identified above will be analyzed following the same principles as for FACIT-Fatigue.

Participants' responses to the interview will be qualitatively analyzed and reported descriptively in a separate report. Results will be used in the analysis of PRO measures.

The analyses of patient reported outcomes described here will be detailed in a Statistical Analysis Plan (SAP) for PROs.

Descriptive statistics and displays by visit will be produced.

Results for EQ-5D-5E will be summarized appropriately, and whenever possible applying principles consistent with the analysis to be provided for the other measurements.

12.6 [redacted]

[redacted]

12.7 Interim analyses

No formal interim analyses of efficacy are planned in this study. 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 to be determined in the 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 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 a Charter to be finalized prior to FPFV in the study. The Charter will include 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. The analyses to be provided to the DMC will also be specified in the appendix to the Charter.

12.8 Sample size calculation

12.8.1 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. 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 $\geq$ 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 exact 2x2 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.

12.8.2 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.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

Renal alert values

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

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

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment. Causes and possible interventions should be considered.

ECG alert values

- Resting heart rate sinus rhythm < 30 or a HR decrease ≥ 25% or
- HR > 130 [bpm]
- QRS >120 or increase >25% compared to predose baseline [msec]
- QTcF >500 or increase >60 compared to predose baseline [msec]
- Ventricular tachycardia
- New complete heart block (Grade III AV block) or Mobitz II AV block

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding.

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Definitions of Triggers, Actions and Follow-up requirements for liver events

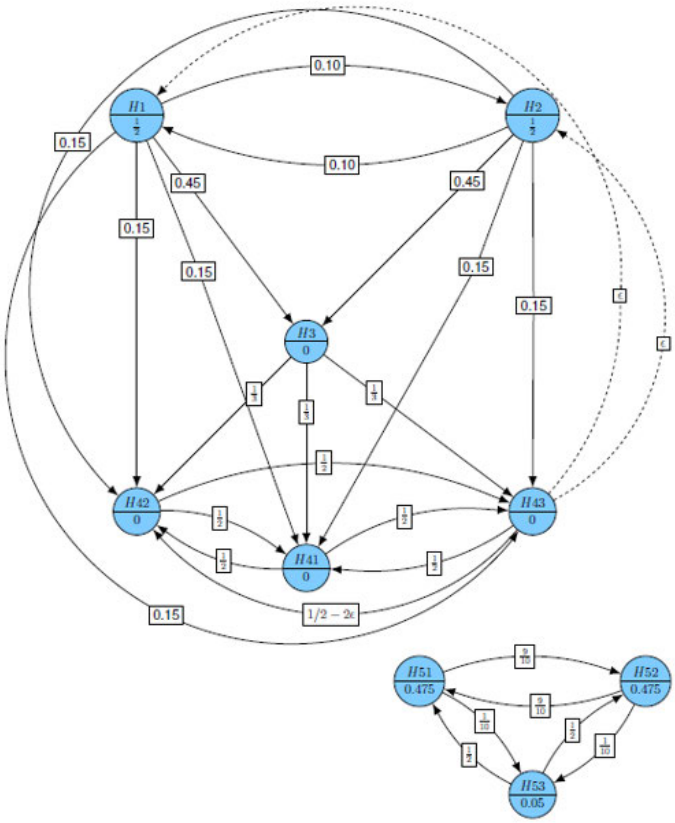
Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case (Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN – or 3 x ULN in the presence of bone pathology)	• Discontinue the study treatment immediately (if possibly related to study treatment) • Hospitalize, if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory value) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP, GGT, CK and GLDH (frequency at Investigator discretion) • Monitor for symptoms[b] • Report outcome[c]
ALT		
> 8 × ULN	• Interrupt the study treatment (if possibly related to study treatment) • Hospitalize if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT (frequency at Investigator discretion) • Monitor for symptoms[b] • Report outcome[c]
> 3 × ULN and INR > 1.5 (in the absence of anticoagulation) If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	• Interrupt the study treatment (if possibly related to study treatment) • Hospitalize if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
> 5 to ≤ 8 × ULN If elevated at baseline: > 3 x baseline or > 300 U/L (whichever occurs first)	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality (investigate alternative etiologies)a • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
> 3 × ULN to ≤ 5 × ULN	• Interrupt the study treatment (if possibly related to study treatment)	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution

Criteria	Actions required	Follow-up monitoring
(accompanied by symptoms)[b] If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	• Hospitalize if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	(frequency at Investigator discretion) • Monitor for symptoms[b] • Report outcome[c]
> 3 to ≤ 5 × ULN (patient is asymptomatic)[b] If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the participant	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology) >3 x ULN in the presence of bone pathology	• Repeat LFT within 48 hours • If elevation persists, establish causality (investigate alternative etiologies)[a] • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Liver events		
Jaundice	• Interrupt the study treatment (if possibly related to study treatment) • Hospitalize the participant • Establish causality (investigate alternative etiologies)[a] • Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion) • Monitor symptoms[b] • Report outcome[c]
Any AE potentially indicative of a liver toxicity[d]	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality (investigate alternative etiologies)a • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	Investigator discretion
[a] Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease		

Criteria	Actions required	Follow-up monitoring
[b]Severe fatigue, malaise (general), abdominal pain (right upper quadrant), nausea, vomiting or rash with eosinophilia [c]Resolved = return to Day 1 values; Condition unchanged = stable values at three subsequent monitoring visits at least 2 weeks apart; Condition deteriorated = values worsen or liver transplantation; and Fatal. [d]These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms. TBL: total bilirubin; ULN: upper limit of normal		

16.3 Appendix 3: Full 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



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

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 above. 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.

Approval Signatures

Compound: LNP023
Document Title: CLNP023C12302-protocol v02
Document Name: 02.01.0201 Protocol - v02
Document Version: 2.0

Username	User ID	Signing Reason	Date
[redacted]	[redacted]	Content Approval	2021-11-26 15:11:24 (UTC)
[redacted]	[redacted]	Content Approval	2021-11-26 16:05:22 (UTC)
[redacted]	[redacted]	Content Approval	2021-11-26 16:31:03 (UTC)

Document electronically signed