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Novartis Research and Development

LNP023

Clinical Trial Protocol CLNP023X2204

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

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	complement alternate pathway
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
bid	Bis In Die (Twice daily)
BMI	Body Mass Index
BP	Blood pressure
CFR	U.S. Code of Federal Regulations
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
COA	Clinical Outcome Assessments
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
DAR	dose administration record
DHT	Dihydrotestosterone
CV	coefficient of variation
DNA	Deoxyribonuclein acid
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of study
EoT	End of treatment
eSource	Electronic Source
FB	Factor B
FDA	Food and Drug Administration
FDP	Fibrinogen degradation products

FAS	Full Analysis Set

FSH	Follicule-Stimulating hormone
GPI	Glycosylphosphatidylinositol
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

HV	Healthy volunteers
IA	Interim analysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
LDH	lactate dehydrogenase
LH	Luteinizing hormone

MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
ng	Nanogram(s)
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
PRO	Patient reported outcome
PT	prothrombin time
q.d.	Quaque die (once a day)

QTcF	Fridericia QT correction formula
REP	Roll-over extension program
RBC	red blood cell(s)
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SoC	Standard of Care
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSH	Thyroid stimulating hormone
ULN	upper limit of normal

WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of child bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject 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.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Run in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject’s medications or other intervention)
Screen Failure	A subject who is screened but is not treated or randomized
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

Study treatment	Any drug or combination of drugs 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 subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Protocol summary

Protocol number	CLNP023X2204
Full Title	A multi-center, randomized, open-label, efficacy, safety, pharmacokinetics and pharmacodynamics study, assessing multiple LNP023 doses in adult patients with paroxysmal nocturnal hemoglobinuria and active hemolysis
Brief title	Efficacy study, assessing multiple LNP023 doses in PNH patients
Sponsor and Clinical Phase	Novartis II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The study purpose is to evaluate the efficacy and safety of LNP023 in PNH patients with active hemolysis, without concomitant complement inhibition (e.g., eculizumab). Blockade of the alternative complement pathway with oral LNP023 has the potential to prevent both intra- and extravascular hemolysis, and therefore, may offer therapeutic benefits compared with eculizumab therapy. Additionally, the oral route of administration offers patients an advantage compared to the intravenous administration of eculizumab.
Primary Objective(s)	To assess the effect of LNP023 on the reduction of PNH associated hemolysis.
Secondary Objectives	To assess the dose-response effect of LNP023 on the reduction of PNH associated hemolysis. To assess the effect of LNP023 on markers of intravascular and extravascular hemolysis. To assess the safety and tolerability of LNP023 in PNH patients. To assess the plasma pharmacokinetics (PK) of LNP023 To assess the effect of LNP023 on markers associated with risk of thrombosis.
Study design	This is a non-confirmatory, randomized, open-label, multicenter, efficacy, safety, pharmacokinetic and pharmacodynamic study assessing CCI LNP023 doses, in adult PNH patients with active hemolysis. Total study duration from screening until EOS is approximately 2.5 years. This three-period study includes: a screening phase of up to 8 weeks, a baseline visit, Day 1 (first day that the investigational drug is given), a 4-week treatment period of LNP023 at the first dose in the assigned sequence (Period 1), an 8-week treatment period at the second dose in the assigned sequence (Period 2), an approximately 2 year extension Period 3. Patients joining the roll-over extension program (REP) (Section 9.2) will transition into the REP immediately after completion of Period 3. Patients not joining the REP after period 3 will undergo a taper down period of 2 weeks, an end of study visit one week after last LNP023 administration, and a safety follow up call performed 30 days post end of treatment (last LNP023 dose).

	Patient will be randomized to sequence 1 or sequence 2 in ratio 1:1. Commercially Confidential Information
Population	Ten adult, male and female PNH patients with active hemolysis, are planned to complete the study. Patients who drop out the study for reasons other than safety or efficacy can be replaced.
Key Inclusion criteria	• Male and female patients at least 18 years old at baseline. • Diagnosis of active PNH based on documented clone size of ≥10% by RBCs and/or granulocytes, measured by GPI-deficiency on flow cytometry (screening or medical history data acceptable). • LDH values ≥ 1.5 x upper limit of the normal range (ULN) for at least 3 measurements over a maximum of 8 weeks prior to Day 1 (Screening, baseline or medical history data acceptable). • Hemoglobin level < 10.5 g/dL at Baseline. • For Period 3 of the study, patients who as per judgment of Investigator benefit from LNP023 treatment based on reduced hemolytic parameters as compared to Screening and Baseline. • Vaccinations against *N. meningitidis, S. pneumoniae* and *H. influenzae* is required at least 4 weeks prior to first dosing with LNP023 (existing vaccinations should provide effective titers at time of LNP023 treatment start). If LNP023 treatment has to start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment must be initiated.
Key Exclusion criteria	• Patients treated with eculizumab or any other complement inhibitor less than 3 months prior to study Day 1 • Known or suspected hereditary or acquired complement deficiency. • History of currently active primary or secondary immunodeficiency. • History of splenectomy. • History of bone marrow/ hematopoietic stem cell or solid organ transplants (e.g., heart, lung, kidney, liver). • Evidence of malignant disease, or malignancies diagnosed within the previous 5 years. • Patients with laboratory evidence of bone marrow failure (reticulocytes < 60x10E9/L, or platelets < 50x10E9/L, or neutrophils < 1x10E9/L) verified both at screening and baseline.

	• History of recurrent meningitis, history of meningococcal infections despite vaccination, as verified at both screening and baseline. • Presence or suspicion (based on judgment of the investigator) of active infection within 2 weeks prior to first dose of LNP023, or history of severe recurrent bacterial infections. • A positive HIV, Hepatitis B (HBV) or Hepatitis C (HCV) test result at screening. • Patients on immunosuppressive agents such, as but not limited to, cyclosporine, tacrolimus, mycophenolate or mycophenolic acid, cyclophosphamide, methotrexate or IV immunoglobulins, less than 8 weeks prior to first treatment with LNP023, unless on a stable regimen for at least 3 months prior to first LNP023 dose. • Systemic corticosteroids unless on a stable dose for at least 4 weeks before randomization. Severe concurrent co-morbidities not amenable to active treatment; e.g., patients with severe kidney disease (CKD stage 4, dialysis), advanced cardiac disease (NYHA class IV), severe pulmonary arterial hypertension (WHO class IV), or unstable thrombotic event, as judged by the investigator, both at screening and baseline (unless baseline was skipped). • Any medical condition deemed likely to interfere with the patient's participation in the study, or likely to cause serious adverse events during the study. • History of hypersensitivity to the study treatment or its excipients or to drugs of similar chemical classes. • Female patients who are pregnant or breastfeeding, or intending to conceive during the course of the study. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after stopping of investigational drug.
Study treatment	LNP023
Efficacy assessments	Key efficacy assessments: • Serum LDH • Hemoglobin concentration and red blood cell counts
Pharmacodynamic assessments	PNH cells: • C3 deposition • PNH type III cells • PNH clone size
Pharmacokinetic assessments	The PK of LNP023 in the treated population will primarily be characterized by following parameters: Cmax, Tmax, Ctrough, AUClast and or AUCtau. Additional parameters may be calculated
Key safety assessments	Adverse event monitoring, physical examinations, ECG, monitoring of laboratory markers in blood and urine, number of transfusions, patient diary

Other assessments	Commercially Confidential Information
Data analysis	The primary efficacy variable for assessing the effect of LNP023 is response rate; where a patient will be considered a responder if LDH is below ULN or the percentage reduction from baseline in serum LDH is at least 60% at any time up to and including week 12 for that patient. In a proof of concept paradigm, a positive sign of efficacy is when the estimated response rate is at least 50%. For example, this criterion will be met when 5 out of 10 patients are considered responders. Commercially Confidential Information The same mixed modelling approach will be used for other continuous response variables. Skewed data will be transformed in order to meet underlying normality and homoscedasticity assumptions. In case early escalation gives data only to two weeks for some patients, the modelling will be adjusted to suit.
Key words	PNH, hemolysis, LDH, hemoglobin

1 Introduction

1.1 Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a life threatening condition caused by a somatic mutation in hematopoietic stem cells, leading to loss of cell surface complement regulatory proteins (CD55 & CD59) on all progeny cells, including red blood cells (RBCs).

Hemolysis in PNH is due to complement-dependent intravascular hemolysis, which normally is blocked by CD59 (protectin), preventing the final stage of complement assembly. Without the glycosylphosphatidylinositol (GPI) anchor, expression of CD59 on the cell surface is reduced allowing for C5b-9 formation and erythrocyte lysis (Brodsky 2014). C3-coated erythrocytes can also undergo complement-mediated destruction by reticuloendothelial macrophages in the liver and spleen (opsonophagocytosis). In healthy subjects, this extravascular hemolysis is blocked by CD55, which prevents assembly of the C3 and C5 convertases on the cell surface and hence blocks C3 deposition of the cells.

Eculizumab is an approved anti-C5 antibody therapy that targets intravascular hemolysis, used in PNH patients and is considered the standard of care (SoC) where available. However:

a. it is not available for all PNH patients in all countries; furthermore, in those countries where it is marketed, access to treatment may be limited; and
b. it has been demonstrated that approximately 40% of the patients treated with eculizumab still exhibit signs of active hemolysis based on consistently elevated lactate dehydrogenase (LDH) levels (Peffault de Latour et al 2015).

Due to its mode of action, almost no patient treated with eculizumab achieves normal hemoglobin levels, even in the absence of any bone marrow failure (Peffault de Latour et al 2015). The ongoing hemolysis is a burden for the patients leading to severe anemia, iron deficiency, and pain due to vasospasm and fatigue.

LNP023 is a novel oral small molecular weight compound that inhibits factor B (FB) of the complement alternative pathway (AP). Factor B (FB) is a key protease of the complement alternative pathway (AP) that can bind to C3b to form C3bB which is further cleaved to C3bBb representing the active C3 convertase. Blockade of the FB with oral LNP023 has the potential to prevent both intra- and extravascular hemolysis, and therefore, may offer therapeutic benefits compared with eculizumab therapy. Additionally, the oral route of administration may offer patients an advantage compared to the intravenous administration of eculizumab.

In preclinical studies, LNP023 has excellent efficacy and a good safety profile.

For further details, please refer to the Investigator Brochure.

1.2 Purpose

The study purpose is to evaluate the efficacy and safety of LNP023 in PNH patients with active hemolysis, without concomitant complement inhibition (e.g., eculizumab).

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the effect of LNP023 on the reduction of PNH associated hemolysis.	• Percentage of patients with 60% reduction in LDH or LDH below upper limit of normal (ULN) up to 12 weeks of treatment.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the dose-response effect of LNP023 on the reduction of PNH associated hemolysis.	• LDH, and other relevant parameters such as but not restricted to hemoglobin and red blood cell count up to week 4 for each dose.
• To assess the effect of LNP023 on markers of intravascular and extravascular hemolysis.	• Potentially all of, but not restricted to, • total and free hemoglobin, • carboxyhemoglobin, • reticulocytes, • C3 fragment deposition, • haptoglobin, • bilirubin, • red blood cell count, • platelet counts, • ferritin, • PNH type III red blood cells (RBC) • PNH clone size
• To assess the safety and tolerability of LNP023 in PNH patients.	• All safety parameters including: blood chemistry, hematology, urinalysis, ECG evaluation, vital signs, adverse events, transfusions, patient diary.
• To assess the plasma pharmacokinetics (PK) of LNP023	• Non-compartmental analysis of LNP023 PK parameters including, but not limited to Cmax, AUC, Ctrough and Tmax.
• To assess the effect of LNP023 on markers associated with risk of thrombosis.	• Assessments including, but not limited to, fibrinogen, prothrombin time, activated partial thromboplastin time, thrombin time, fibrin D-dimer

Objective(s)	Endpoint(s)
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

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3 Study design

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

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

Active hemolysis is defined by an LDH value ≥ 1.5x ULN. At least 3 pre-treatment LDH measurements each separated by at least a week over a maximum of 8 weeks prior to study Day 1 of the study should be ≥ 1.5x ULN , in order to include the patients in the study. LDH medical history data can be taken into consideration for inclusion purposes but at least one value must be from the study central laboratory. If medical history data is not available, the screening period may consist of several visits for LDH verification.

Total study duration from screening until EOS is approximately 28 months. This three-period study includes:

- a screening phase of up to 8 weeks,
- a baseline visit,
- Day 1 (first day that the investigational drug is given),
- a 4-week treatment period of LNP023 at the first dose in the assigned sequence (Period 1),
- an 8-week treatment period at the second dose in the assigned sequence (Period 2),
- an approximately 2 year treatment extension period for patients who respond to the LNP023 treatment (Period 3)
- taper down period of 2 weeks applicable only for patients discontinuing LNP023 treatment (Week 13 for non-responders or Week 109 for responders).

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- an EoS visit that will take place 1 week after the last LNP023 administration for patients not joining the roll-over extension program (REP). For patients joining the REP (Section 9.2), the last treatment visit will become the EoS visit.

A safety follow-up call 30 days after the last administration of LNP023 will be performed for patients not joining the REP.

Figure 3-1 Study design

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

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Subjects who meet the eligibility criteria at screening will continue to randomization and baseline evaluations. All baseline safety evaluation results must be available prior to randomization and dosing (note: local LDH levels are acceptable for the purpose of confirming eligibility prior to randomization). Local laboratories may be used to confirm eligibility of the patient at baseline, however, all baseline samples should also be sent to central laboratory for analysis. Baseline visits can be conducted on the same day as the last screening visit, in case the last screening visit is not more than 7 days prior to Day 1. All baseline assessments need to be performed at this time.

Pharmacokinetic, safety and other study assessments will be conducted according to the study schedule (see corresponding sections). Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring.

All patients need to complete vaccinations against *N. meningitidis*, *S. pneumoniae* and *H. influenzae* at least 4 weeks prior to starting LNP023 treatment. After initial immunization, booster doses of the vaccinations should be administered according to the label of the vaccination used. The screening period may be extended to allow vaccination procedures to be completed. This is applicable for vaccinations only and all the other screening assessments should be performed within the period described in the Assessment Schedule. However, if LNP023 treatment has to start earlier than 4 weeks post-vaccination, prophylactic antibiotic treatment must be initiated (Section 6.6.2). In addition, to reduce risk of infection, antibiotics will be required for patients with any sign of infection.

Body temperature should be measured daily in Period 1 and Period 2 and at minimum at the time of symptoms of infection during treatment Period 3. A diary will be completed by the patient to record, amongst other data, elevation of body temperature on days when no study visit is planned. The investigator shall review diaries at every visit. Patients will be instructed

to contact their physician immediately if body temperature rises to >38.3°C. For details, please refer to Section 6.6.2.

Please refer to the Assessment Schedule for details regarding assessments to be performed.

4 Rationale

4.1 Rationale for study design

The design of this study addresses the primary objective of assessing the effect of LNP023 on PNH associated hemolysis and takes into account the rarity of this disease and the objective nature of the measurement.

The main key study design elements are described below:

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- This is a non-placebo-controlled study since the absence of a placebo response for LDH in this patient population has been demonstrated (Hillmen et al 2006), and is expected given the nature of the primary outcome measure (LDH). In addition, when considering available treatment options, restricting PNH patients to placebo treatment may be considered unethical.

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- Treatment extension of approximately 2 years for patients responding to LNP023 treatment was included to assure treatment of the patients who otherwise have limited treatment options
- The taper down period of 2 weeks was included to mitigate potential risk of increased hemolysis after LNP023 discontinuation

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- Treatment comparisons within patient are included with the advantage that within patient variation is assumed to be less than between patients

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4.2 Rationale for dose/regimen and duration of treatment

4.2.1 Dose regimen and dose span

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4.2.2 Minimal treatment duration of each dose

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

Not applicable

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, early stopping rules, periodic review of the safety data, and guidance for the investigators in the Investigator's Brochure. The most relevant risks are described below. A complete list of toxicological findings is available in the Investigator's Brochure. Women of child bearing potential (WOCBP) 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 highly effective contraception requirements outlined in the Section 5.2 (Exclusion Criteria).

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4.5.1 Blood sample volume

Less than 500 mL of blood is planned to be collected from each study patient during 19 weeks of Period 1 and Period 2 of the study. Up to approximately 450 mL is planned to be collected from each study patient during approximately 2 years of Extension Period 3. Total maximum blood volume collected during the study will not exceed 950 mL.

Additional samples may be required for safety monitoring. Timings of blood sample collection are outlined in the Assessment schedule. A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information are available in laboratory manual.

See the section on the potential use of residual samples.

4.5.2 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 Population

Ten adult, male and female PNH patients with active hemolysis, are planned to complete the study. Additional patients might be enrolled to replace patients who discontinue the study or treatment for reasons other than safety or lack of efficacy.

The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible patients.

Patient selection is to be established by checking through all eligibility criteria at screening and/or baseline as specified below. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

5.1 Inclusion criteria

Subjects 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 patients at least 18 years old at baseline.
3. Diagnosis of active PNH based on documented clone size of ≥10% by RBCs and/or granulocytes, measured by GPI-deficiency on flow cytometry (screening or medical history data acceptable).

4. LDH values ≥ 1.5 x upper limit of the normal range (ULN) for at least 3 measurements over a maximum of 8 weeks prior to Day 1 (Screening, baseline or medical history data acceptable).
5. Hemoglobin level < 10.5 g/dL at Baseline.
6. For Period 3 of the study, patients who as per judgment of Investigator benefit from LNP023 treatment based on reduced hemolytic parameters as compared to Screening and Baseline.
7. Vaccinations against *N. meningitidis, S. pneumoniae* and *H. influenzae* is required at least 4 weeks prior to first dosing with LNP023 (existing vaccinations should provide effective titers at time of LNP023 treatment start). If LNP023 treatment has to start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment must be initiated.
8. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

5.2 Exclusion criteria

Subjects 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, whichever is longer; or longer if required by local regulations.
2. Patients treated with eculizumab or any other complement inhibitor less than 3 months prior to study Day 1
3. Known or suspected hereditary or acquired complement deficiency.
4. History of currently active primary or secondary immunodeficiency.
5. History of splenectomy.
6. History of bone marrow/ hematopoietic stem cell or solid organ transplants (e.g. heart, lung, kidney, liver).
7. Evidence of malignant disease, or malignancies diagnosed within the previous 5 years.
8. Patients with laboratory evidence of bone marrow failure (reticulocytes < 60x10E9/L, or platelets < 50x10E9/L, or neutrophils < 1x10E9/L) verified both at screening and baseline.
9. History of recurrent meningitis, history of meningococcal infections despite vaccination, as verified at both screening and baseline.
10. Presence or suspicion (based on judgment of the investigator) of active infection within 2 weeks prior to first dose of LNP023, or history of severe recurrent bacterial infections.
11. A positive HIV, Hepatitis B (HBV) or Hepatitis C (HCV) test result at screening.
12. Patients on immunosuppressive agents such, as but not limited to, cyclosporine, tacrolimus, mycophenolate or mycophenolic acid, cyclophosphamide, methotrexate or IV immunoglobulins, less than 8 weeks prior to first treatment with LNP023, unless on a stable regimen for at least 3 months prior to first LNP023 dose.
13. Systemic corticosteroids unless on a stable dose for at least 4 weeks before randomization.
14. Severe concurrent co-morbidities not amenable to active treatment; e.g., patients with severe kidney disease (CKD stage 4, dialysis), advanced cardiac disease (NYHA class IV), severe pulmonary arterial hypertension (WHO class IV), or unstable thrombotic

event, as judged by the investigator, both at screening and baseline (unless baseline was skipped).

15. Any medical condition deemed likely to interfere with the patient's participation in the study, or likely to cause serious adverse events during the study.
16. History of hypersensitivity to the study treatment or its excipients or to drugs of similar chemical classes.
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 highly effective methods of contraception during dosing and for 1 week after stopping of investigational drug.

    Highly effective contraception methods include:

    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). 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 tubal ligation at least six weeks before taking investigational drug. 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 months prior to Screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - Use or oral (estrogene and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate below 1%), for example hormone vaginal ring or transdermal hormone contraception.

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

    If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or 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. Refer to Section 8.4.4 (Pregnancy and Assessments of Fertility).

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects

6 Treatment

6.1 Study treatment

Patients will receive study medication at study center for days when visits are planned and at home during remaining study days. Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the SOM.

As per Section 4.5.2, 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 administer 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. In this case, regular phone calls or virtual contacts (frequency as per planned visit) will occur between the site and the participant for instructional purposes, safety monitoring, and 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.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Drug	Pharmaceutical Dosage Form	Route of Administration	Design	Sponsor (global or local)

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6.1.2 Additional study treatments

No additional treatment beyond investigational drug are included in this trial.

6.1.3 Treatment arms/group

Subjects will be randomized at baseline to sequence 1 or sequence 2.

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6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study.

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the specific case report form (CRF) page.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

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

6.2.1.1 Vaccinations

All patients need to complete vaccinations against *N. meningitidis*, *S. pneumoniae* and *H. influenzae* at least 4 weeks prior to starting LNP023 treatment. Vaccinations will be performed according to local recommendations for patients with complement deficiencies, if prior vaccination cannot be confirmed. The choice of vaccine(s) should take into account the serotypes prevalent in the geographic areas in which study patients will be enrolled.

After initial immunization, booster doses of the vaccinations should be administered according to the label of the vaccination used. The screening period may be extended to allow vaccination procedures to be completed. This is applicable for vaccinations only and all the other screening assessments should be performed within the period described in the Assessment Schedule.

6.2.1.2 Prophylactic antibiotics

In case LNP023 treatment has to start earlier than 4 weeks post-vaccination, prophylactic antibiotic treatment must be initiated. In addition, to reduce risk of infection, antibiotics will be required for patients with any sign of infection (see Section 6.6.2).

6.2.1.3 Permitted concomitant therapy requiring caution and/or action

LNP023 has been shown to have a weak inhibition potential for the liver uptake transporter OATP1B1 and respective calculations revealed that the exposure (AUC) of sensitive substrates may be increased by about 1.25 fold. It is therefore recommended to use respective co-medications with a narrow therapeutic index with caution.

As LNP023 is also an OATP1B1/3 substrate, co-administration with strong inhibitors may potentially lead to minor exposure increase (<1.5 fold) for LNP023.

6.2.2 Prohibited medication

Use of the medications displayed in the table below is NOT allowed.

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The investigator should consult with Novartis medical expert prior treating a patient with this type of co-medication.

Table 6-2 Prohibited medication

Medication	Prohibited period	Action to be taken
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6.2.3 Rescue medication

If required as per judgment of the Investigator, another medication targeting underlying pathophysiology of the disease might be used as a rescue medication. Please refer to Section 6.6.2 for recommended handling of adverse events (AE).

6.2.4 Restriction for study subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section:

- Need to adhere to assessment schedule and visit window
- Body temperature measurement
- Intake of study medication and recording any missing dosages in the patient diary
- Using contraception as specified in Section 5.2

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the Site Operations Manual.

6.3.2 Treatment assignment, randomization

Treatment sequence assignment will be blinded and randomized. Following randomization of the patient, study will be open-labelled.

6.4 Treatment blinding

Following blinded random assignment of treatment sequence to patient, treatment will be open to subjects, investigator staff, persons performing the assessments, and the CTT.

Table 6-3 Blinding and unblinding plan

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6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and

the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using capsule counts and information provided by the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

All study patients will be clinically managed as if in severe neutropenia regardless of their actual neutrophils count. Specifically, the patients and treating staff need to be instructed to be vigilant for any clinical signs of infections (e.g., malaise, chills, fever, nausea, photophobia, bone pain) and to measure the body temperature daily in study Period 1 and 2 and at minimum at the times of symptoms of infection in Period 3. Patients 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 infection, patients should either be admitted for emergency evaluation or empirically treated with oral fluoroquinolone plus amoxicillin/clavulanate (or plus clindamycin if penicillin allergic), unless fluoroquinolone prophylaxis was used before fever developed (Flowers et al 2013).

6.6.3 Randomization list

Randomization list will be provided to relevant study personnel of clinical centers participating in the study.

6.7 Preparation and dispensation

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

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

As per the treatment assigned to the subject, investigator staff will select the study treatment to dispense to the subject. The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the package to the subject, site personnel will detach the outer part of the label from the package and affix it to the subject’s source document.

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

7 Informed consent procedures

Eligible subjects 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 subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject 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 subject 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). This information will be included in the subject informed consent and should be discussed with the subject 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 subject.

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.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

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

Refer to the Site Operations Manual for a complete list of ICFs included in this study.

8 Visit schedule and assessments

Assessment schedule lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Please refer to Section 9.1 for guidance in case of treatment and/or study discontinuation.

As per Section 4.5.2, 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,

alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant ´ s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Epoch	Pre-Treatment		Treatment 1																Treatment 2									
Visit Name	Screening	Baseline[14]	Treatment																Treatment									
Visit Numbers[1]	1	2	101	102	103	104	105 [2]						106	107					201	202	203					204	205 [10]	
Days	-56 to -4	-3 to -1	1	2	8	15	16						22	29					36	43	57					71	85	
					±1	±1	±1						±1	±1					±1	±1	±1					±2	±2	
Time (post-dose)	-	-	-	-	-	-	pre-dose	0.25h	1h	2h	4h	6h	-	pre-dose	0.25h	1h	2h	4h	6h	-	-	pre-dose	0.25h	1h	2h	4h	6h	-	-
Informed consent	X																											
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Medical history/current medical conditions	X																											
Vaccinations	X																											
Hepatitis and HIV	S																											
Demography	X																											
Randomization[3]			X																									
Pregnancy test [4]	X	X												X								X					X	
Study drug[5]			X																	X								
Physical Examination		S	S	S			S						S	S					S	S							S	S
Body height and weight		X																										
Vital signs[6]	X	X	X	X	X	X	X						X	X					X	X	X					X	X	
ECG[6]	X	X	X	X	X	X								X							X						X		
Hematology[6]	X	X	X	X	X	X	X						X	X					X	X	X					X	X	
Clinical Chemistry[6]	X	X	X	X	X	X	X						X	X					X	X	X					X	X	
Urinalysis[6]	X	X	X	X	X	X							X	X					X	X	X					X	X	
Markers of thrombosis[6]	X	X			X	X								X						X	X					X	X	
Hormones[6]		X												X							X						X	
Incidence of transfusion	X																											
PK blood collection[6]				X		X	X	X	X	X	X	X	X	X^9	X^9	X^9	X^9	X^9	X^9	X	X	X	X	X	X	X	X	X	X
PNH clone size[7]	X																											
PNH cells[6, 12]		X				X								X								X						X
Commercially Confidential Information																												
Patient temperature and dosing diary			X																									
Adverse Events	X																											
Concomitant medications	X																											
Comments	X																											
Study completion																												

Epoch		Extension Treatment 3													EOS
Visit Name		Treatment													EOS
Extension Year 1	Visit Numbers[1]	301	302	303	304	305	306	307	308	309	310	311	312		
	Days	113 ±7	141 ±7	169 ±7	197 ±7	225 ±7	253 ±7	281 ±7	309 ±7	337 ±7	365 ±7	393 ±7	421 ±7	Down-titration	
Extension Year 2	Visit Numbers[1]	313	314	315	316	317	318	319	320	321	322	323	324 [13]	401	402	499 [11]
	Days	449 ±7	477 ±7	505 ±7	533 ±7	561 ±7	589 ±7	617 ±7	645 ±7	673 ±7	701 ±7	729 ±7	757 ±45	92 or 764 ±2	99 or 771 ±2	106 or 778 [15] ±3
Informed consent																
Commercially Confidential Information																
Medical history/current medical																
Vaccinations																
Hepatitis and HIV																
Demography																
Randomization[3]																
Pregnancy test [4]		X	X	X	X	X	X	X	X	X	X	X	X			X
Study drug[5]		X														
Physical Examination		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Body Weight													X [16]			X
Vital signs[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[6]													X [16]			X
Hematology[6]		X		X		X		X		X		X	X	X	X	X
Clinical Chemistry[6]		X		X		X		X		X		X	X	X	X	X
Urinalysis[6]		X		X		X		X		X		X	X	X	X	X
Markers of thrombosis[6]		X				X				X			X			X
Hormones[6]		X				X				X			X			X
Incidence of transfusion											X					
PK blood collection[6]				X		X				X			X	X	X	X
PNH clone size[7]																
PNH cells[6, 12]				X						X			X	X	X	

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Patient temperature and dosing diary	X
Adverse Events	X
Concomitant medications	X
Comments	X
Study completion	X [16]

[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] Visit structure given for internal programming purpose only

[2] Visit only applicable for Sequence 1 and 2 patients who do not have 40% reduction in LDH level at day 15

[3] Randomization should only occur once eligibility is confirmed.

[4] Serum pregnancy test required at screening and EOS, urine pregnancy test at further time points.

[5] LNP023 to be administered daily b.i.d

[6] To be completed pre-LNP023 dose, if applicable.

[7] Done only if no medical data is available that could be used for inclusion purpose

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[9] Samples collected only if patient did not complete PK sample collection at day 16

[10] Start of LNP023 down-titration for patients who do not participate in extension period 3

[11] A safety follow-up call 30 days after last treatment administered will be performed for patients not joining REP

[12] C3 deposition, clone size, type III PNH cells

[13] Start of LNP023 down-titration for patients who discontinue LNP023 treatment. EoS visit for patients joining REP

[14] Baseline visits can be conducted on the same day as the last screening visit, if the last screening visit is not more than 7 days prior to Day 1

[15] For patients not joining REP

[16] Assessments to be performed only for patients joining REP and complete study at EoT visit

8.1 Screening

In the case where a safety laboratory assessment at screening (and/or baseline) is outside of the range specified in the exclusion criteria, the assessment may be repeated twice prior to randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study. It is permissible to re-screen a subject if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the screening phase disposition page. The demographic information, informed consent, and reason for screen failure must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experiences a serious adverse event during the screening phase (see Section 10.1.3 for reporting details).

8.2 Subject demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all subjects include: age, gender, race, ethnicity, relevant medical history/current medical condition present before signing informed consent where possible, diagnoses and not symptoms will be recorded.

Hepatitis and HIV tests will be performed for samples collected at screening.

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

8.2.1 PNH Clone Size (for patient eligibility)

If no historic data is available a flow cytometry assay will be performed at screening to confirm diagnosis of PNH based on documented clone size of ≥ 10% by RBCs and/or granulocytes, measured by GPI-deficiency. Data will be entered into the eCRF.

8.3 Efficacy/Pharmacodynamics

8.3.1 LDH measurement

Serum LDH is a measure for intravascular hemolysis and is usually elevated in PNH patients. In order to help characterize disease status and progression, historical values of serum LDH prior to the informed consent signature (if available), may be recorded in the eCRF as part of the medical history assessment and to verify inclusion/exclusion criteria. The blockade of complement mediated lysis of erythrocytes is expected to result in reduction of serum LDH levels. LDH measured as a part of the study will be determined in serum by a validated assay. Detailed methodological description of the assay will be included in the bioanalytical data report. Please refer to Assessment Schedule for time points when clinical chemistry is analyzed. All the LDH values and local normal ranges collected during screening should be recorded in

the CRF. If available as a part of the patients' medical history, at least the 5 most recent LDH values recorded prior to screening visit should be recorded in the CRF in order to characterize the pre-treatment LDH profile over time.

8.3.2 Hemoglobin and red blood cell

Hemoglobin and red blood count will be assessed as a part of the standard central laboratory hematology panel at the timepoints specified in the Assessment Schedule.

8.3.3 PNH cells (C3 deposition, PNH type III cells and clone size)

Accumulation of C3 fragments on red blood cells make them prone to phagocytosis causing extravascular hemolysis. Level of C3 deposition on red blood cells will be quantified using flow cytometry. In addition both PNH type III cells and clone size will be evaluated. Whole blood samples will be collected at the clinical sites at the time point described in the Assessment Schedule and samples will be shipped to the analytical lab as described in a central laboratory manual. Detailed descriptions of the assays will be included in the bioanalytical data reports.

8.3.4 Appropriateness of efficacy measurements

The pathophysiology of PNH is directly linked to the complement-mediated destruction of the susceptible PNH red blood cells, which results in intravascular hemolysis, the primary clinical manifestation in all PNH patients. Eligibility for this trial therefore requires both, active hemolysis and anemia measured and confirmed by respective laboratory markers (i.e., lactate dehydrogenase (LDH) $\geq$ 1.5 ULN, hemoglobin $<$ 10.5 g/dL). Treatment with LNP023 is expected to mitigate intravascular hemolysis, as measured by LDH, number of red blood cells and reticulocytes, level of hemoglobin, bilirubin and haptoglobin. Clinically relevant reduction in intravascular hemolysis leads to measurable changes in the parameters mentioned and may result in increased transfusion avoidance, a reduced need for RBC transfusion and less anemia related symptoms such as fatigue.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

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

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. A short physical exam will include the examination of general appearance and vital signs. Complete physical examination should be performed at baseline, EoS and any other visit deemed necessary by Physician (triggered by safety results). Short examination will be performed at all the other visit as per Assessment Schedule. 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 included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.
Vital signs	Vital signs include blood pressure (BP), pulse measurements, and body temperature. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, with an appropriately sized cuff.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

8.4.1.1 Clinical Chemistry

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, ferritin, CRP, LDH, GGT, AST, ALT, CK, glucose, total cholesterol, and triglycerides data will be collected at timepoints specified in Assessment Schedule.

- Bilirubin: Bilirubin is released during hemolysis and is frequently increased in PNH patients. Serum levels will be determined using standard procedures. If the total bilirubin concentration is increased above 3 times above the baseline value, direct and indirect reacting bilirubin should be differentiated.
- Ferritin level will be measure at selected timepoints when blood is collected for clinical chemistry (see SoM for details): Ferritin levels have been reported to increase during treatment with eculizumab, and are a measure for iron overload. Serum levels will be determined using standard procedures.

8.4.1.2 Blood hormone levels

The hormones analyzed are: T3, T4, TSH, reversed T3, testosterone, FSH, LH and DHT.

8.4.1.3 Hematology

Total hemoglobin, free hemoglobin (at selected timepoints, please see SoM for details), carboxyhemoglobin, haptoglobin, hematocrit, red blood cell (RBC) count, reticulocyte count, white blood cell (WBC) count with differentials and platelet count will be measured.

8.4.1.4 Markers of thrombosis

Coagulation testing including prothrombin time (PT), reported as INR, activated partial thromboplastin time (aPTT), D-dimer, fibrinogen, and thrombin clotting time (at selected timepoints, please see SoM for details) will be measured.

8.4.1.5 Urinalysis

Dipstick measurements for protein, blood, and WBC/leukocytes will be performed.

If dipstick measurement results are positive (abnormal), results will be captured. Microscopy must be assessed following an abnormal dipstick test with results captured and provided by central laboratory as per agreed data transfer specifications.

8.4.2 Incidence of transfusions

The number and volume of blood transfusions will be counted and recorded in the eCRF. The history of transfusions administered within one year before baseline and the number of transfusions until EoS visit will be recorded.

8.4.3 Electrocardiogram (ECG)

Below parameters should be recorded: PR interval, QRS duration, heart rate, RR interval, QT interval, QTc.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Clinically significant abnormalities must be reported in the AE CRF.

8.4.4 Pregnancy and 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 tubal ligation must be retained as source document. 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:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH results should be used to confirm reproductive status of female patients.

8.4.5 Other safety evaluations

8.4.5.1 Patient diary

Patient diaries will be used to record any elevation of body temperature >38.3°C and also record any missed administration of LNP023.

Body temperature should be measured daily in Period 1 and 2 of the study and at minimum at the time of symptoms of infection in Period 3 of the study. The investigator shall review the diary at every visit. Patients 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 consultation.

In case of clinically significant abnormal values, these will be recorded in the AE CRF page (as per judgement of the investigator).

8.4.5.2 Clinical Outcome Assessments (COAs)

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8.4.6 Appropriateness of safety measurements

Complement activation in PNH is manifested as chronic hemolysis that leads to the release of free hemoglobin and the subsequent depletion of nitric oxide. Consumption of nitric oxide leads to vaso-occlusion and platelet activation and results in the common morbidities seen in PNH, such as fatigue, dyspnea, recurrent abdominal pain, dysphagia, chest pain and pulmonary hypertension. More importantly, chronic hemolysis renders PNH patients at a greater risk of thrombotic events, renal insufficiency and other organ damage, and premature mortality. Historically, supportive care measures used in PNH, such as transfusions, anticoagulation or long-term use of steroids and pain medication, leave patients with a poor quality of life (QoL) and are associated with adverse events.

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In preclinical and early clinical studies, LNP023 has excellent efficacy and a good safety profile. The important potential risks associated with LNP023 are mainly related to increased risk for infections which are mitigated by mandatory vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* including recommendations for continued monitoring of clinical signs and symptoms and respective antibiotic treatment recommendations.

Further information about the investigational drug can be found in the Investigator Brochure.

8.5 Additional assessments

8.5.1 Pharmacokinetics

PK samples will be collected at the time points defined in the Assessment Schedule.

Pharmacokinetic (PK) samples will be obtained and evaluated in all subjects at all dose levels.

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For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters of LNP023 will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher):

Plasma: Cmax,ss, Tmax,ss, AUCtau,ss, Cmin,ss, T1/2 at days defined in the schedule. Other pharmacokinetic parameters as appropriate. To denote parameters determined at steady state "ss" will be used.

The linear trapezoidal rule will be used for AUC calculation. Due to the limited PK sampling regression analysis of the terminal plasma elimination phase for the determination of T1/2 will likely not be possible. If the adjusted R2 value of the regression analysis of the terminal phase is less than 0.75, no values will be reported for T1/2 and AUCinf.

Further details on sample collection, numbering, processing and shipment will be provided in the lab manual and/or SOM.

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9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration. If possible taper-down should be implemented for patients who discontinue study treatment. Discontinuation of study treatment can be decided by either the patient, the investigator or Sponsor. Study treatment must be discontinued under the following circumstances:

- Patient decision - patient may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Pregnancy (see Section 5.2)
- Use of prohibited treatment as outlined in Table 6-2.
- If a liver or renal event occurs, follow the Hepatotoxicity Clinical Safety Standard Guideline or Renal Toxicity Clinical Safety Guideline, outlined in Appendix 1 and Appendix 2 regarding discontinuation of study treatment.
- Increases in QTcF to >500 ms or of >60 ms over baseline should be used as thresholds for patient discontinuation.
- Unsatisfactory therapeutic effect- decision to be taken after consultation with Sponsor.

If discontinuation of study treatment occurs, investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

Patients 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 Section 9.1.2, Withdrawal of Informed Consent). Where possible, patients who discontinue study treatment only should continue to return for study scheduled assessments.

If any patient discontinues study or study treatment with LNP023 they should be closely monitored for signs and symptoms of hemolysis.

The parameters below are suggested to be closely monitored:

- greater than 25% absolute decrease in PNH clone size (in the absence of dilution due to transfusion) in one week or less;
- increase in LDH level;
- an hemoglobin level of < 8 g/dL or a decrease of > 4 g/dL in one week or less;
- angina pectoris;
- change in mental status;
- a 50% increase in serum creatinine level; or
- thrombosis.

If serious hemolysis occurs after LNP023 discontinuation, the following procedures/treatments should be considered by the investigator:

- blood transfusion (packed RBC), or exchange transfusion if the PNH RBC are > 50% of the total RBCs by flow cytometry;
- anticoagulation; corticosteroids; or
- other rescue medication.

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

- new / concomitant treatments
- AE / SAE.

If they fail to return for EOS visit for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 9.1.3 (lost to follow-up).

9.1.1.1 Replacement policy

Patients can be replaced based on the case-by case after discussion with Sponsor in case the patient discontinued the study for a reason not related to safety or efficacy.

9.1.2 Withdrawal of informed consent

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

Does not want to participate in the study anymore, and

Does not allow further collection of personal data

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

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 subject are not allowed unless safety findings require communicating or follow-up.

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

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects 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 subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Study stopping rules

Novartis will review emergent safety reports on an ongoing basis to react as soon as there is a possibility that a stopping rule could apply. The Sponsor will review all SAE as individual cases and will also review summaries of non-serious AE for patterns and trends, and will first exclude any events determined to be clearly not related to LNP023 (e.g., SAE which occurred during the pre-treatment screening period, or disease-related SAE expected in the population under study). Enrollment in the study and dosing of affected patient(s) with LNP023 will be paused pending a full safety review by Novartis Study Team if any of the following occurs during the study:

- Three or more patients developing the same drug related SAE
- OR two or more patients developing any life-threatening drug related SAE
- OR one or more patient developing a fatal drug related SAE.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. 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 subject’s interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Based on the benefit of LNP023 treatment observed in the ongoing phase II studies (CLNP023X2201 and CLNP023X2204), a roll-over extension program (REP), study CLNP023C12201B, has been implemented to ensure long-term post-trial access for all PNH patients completing any of the phase II or phase III studies with LNP023. Study patients who completed study treatment and who demonstrated benefit from LNP023 treatment will have the option to join this roll-over extension program.

Study completion is defined as when the last subject finishes their study completion visit (EoT for patients joining the REP), 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.

Randomized and/or treated subjects not joining the REP should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 and the SoM. Documentation of attempts to contact the subject should be recorded in the source documentation.

Continuing care should be provided by the investigator and/or referring physician based on subject availability for follow-up.

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 subject or clinical investigation subject 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 individual subject 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF 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. its 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 subject

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:
   a. not recovered/not resolved
   b. recovered/resolved
   c. recovering/resolving
   d. recovered/resolved with sequelae
   e. fatal, or unknown

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

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 for at least 30 days following the last dose of study treatment.

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 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 subjects with the underlying disease.

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 subject 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 PNH
    - 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 subject'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 subject 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 subject 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.

All 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.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the

investigator folder provided to each site. The 30 day safety follow up will be completed as a part of the REP for patients joining roll-over extension.

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 within 24 hours of the investigator receiving the follow-up information. 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.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the 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). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the LNP0223 and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Intact pregnancy should be followed up until 1 month until 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, subject 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 collected in the DAR (dose administration record) eCRF 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 within 24 hours of Investigator's awareness.

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

Treatment error type	Document in Dose Administration (DAR) eCRF (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
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

Not applicable

10.2.1 Liver safety monitoring

To ensure subject 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 Appendix 2 for complete definitions of liver events, information on required follow up and actions required.

Liver chemistry repeats should be performed using the local or central laboratory.

10.2.2 Renal safety monitoring

Please refer to Appendix 3 for complete definitions of renal events, information on required follow up and actions required.

Renal chemistry repeats should be performed using the local or central laboratory.

11 Data Collection and Database management

11.1 Data collection

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

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 subject data for archiving at the investigational site.

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 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.

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused supplies to Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. 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 or delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or 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 subject 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 a centralized Novartis or delegated CRO, CRA organization. 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 subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 subjects will be disclosed.

12 Data analysis and statistical methods

The study analysis will be conducted on all patient data at the time the trial ends. As this is a multi-period study, all listings will include both study day and period day, especially when early escalation entails moving into a period earlier than on the standard study day. Statistical summaries and figures will also be aware of the same distinction where relevant.

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

12.1 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatments received.

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

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

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

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data, including disease characteristics, will be listed and summarized descriptively by treatment sequence for the full analysis set.

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and by preferred term, by treatment sequence for all patients.

12.3 Treatments

The full analysis set will be used for the analyses below. Categorical data will be summarized descriptively as frequencies. For description of continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

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

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

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary efficacy endpoint for assessing the effect of LNP023 is response rate, where a patient will be considered a responder if LDH is below ULN or the percentage reduction from baseline in serum LDH is at least 60% at any time up to and including Week 12 for that patient, whether or not

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12.4.2 Statistical model, hypothesis, and method of analysis

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

12.4.3 Handling of missing values/censoring/discontinuations

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

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12.5 Analysis of secondary endpoints

Assessment of plasma pharmacokinetics is a secondary endpoint but the analyses for it are described below in Section 12.5.3. Assessing the dose-response effect on LDH and other parameters associated with PNH associated hemolysis is the first secondary objective.

Mixed effect modelling will be performed for LDH.

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Baseline LDH will be calculated as the average of the last three screening values prior to randomization. The subject term will be considered as random so as to allow recovery of between subject information.

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The same mixed modelling approach will be used for other key continuous response secondary endpoint variables apart from LDH that are markers of intravascular and extravascular hemolysis, or are markers of thrombosis, as well as for PK parameters excluding Tmax (see Section 12.5.3). In these cases, except for PK parameters, the baseline covariate is the average of all pre-treatment values.

Data may be transformed in order to meet underlying normality and homoscedasticity assumptions. In case early escalation gives data only to two weeks for some patients, the modelling will be adjusted to suit, in the first instance looking only at Week 2 data for all patients.

12.5.1 Handling of missing values/censoring/discontinuations

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12.5.2 Safety endpoints

For all safety analyses, the full analysis set will be used.

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

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

Adverse events

All information obtained on adverse events will be displayed as described above taking into account the study design involving sequences,

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Listings will be down to patient level. The number (and percentage) of patients with treatment

emergent adverse events (events starting after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment dose group including split by first and second four weeks in second period, primary system organ class and preferred term.

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

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class. Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the dose level treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the dosing period.

Vital signs

All vital signs data will be listed by sequence, treatment dose group, subject, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided as described above. Individual overlaid profile plots over time with current dose level per patient color-coded will be presented.

12-lead ECG

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

All ECG data will be listed by sequence, treatment dose group, subject and visit/time. Abnormalities will be flagged. Summary statistics will be provided as described above. Individual overlaid profile plots over time with current dose level per patient color-coded will be presented.

Clinical laboratory evaluations

All laboratory data will be listed by sequence, treatment dose group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided as described above. Individual overlaid profile plots over time with current dose level per patient color-coded will be presented.

Other safety evaluations

All transfusion and patient diary data will be listed by sequence, treatment dose group, subject, and visit/time and relevant descriptive summaries will be formed.

12.5.3 Pharmacokinetics

LNP023 plasma concentration data will be listed by sequence, treatment dose group, subject, and visit/sampling time point.

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Pharmacokinetic parameters will be calculated from within four weeks of dosing only and will be listed by treatment dose group and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax, where median, minimum and maximum will be presented.

Table 12-1 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time / volume]
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Cmin	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (lz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives

A linear mixed effects model will be fitted to the log-transformed PK parameters (AUC0-24h, AUCinf, and Cmax) as described for dose-response analysis of LDH. For each PK parameter backtransformed estimates and confidence interval will be plotted against dose level.

During modeling of the pharmacokinetics of study treatment, the broad principles outlined in the FDA guidance will be followed (Guidance for Industry: Population Pharmacokinetics; http//www.fda.gov/cder/guidance/1852fnl.pdf).

12.6 Analysis of exploratory endpoints

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12.7 Interim analyses

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

With 10 subjects this study has 80% probability to meet the efficacy criteria of 5 or more successful patients out of 10 if the true response rate is 58%.

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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, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. 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 *(defined as last patient last visit)* 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 subjects 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 subject 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 subject 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 and vital signs

Alert criteria will be specified in the central laboratory documentation.

16.2 Appendix 2: Liver Event Definitions and Follow-up Requirements

Table 16-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known pathology)
Others	• Any clinical event of jaundice (if not clearly PNH disease related) • Any adverse event potentially indicative of liver toxicity

Table 16-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately (if not clearly PNH disease related) • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance*
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance*

*Liver event guidance for CRF completion is available in the Site Operations Manual

Table 16-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16.3 Appendix 3: Specific Renal Alert Criteria and Actions

Table 16-4 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-5 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

*Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.