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LNP023/Iptacopan

Clinical Trial Protocol CLNP023C12301

A multicenter, single-arm, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who are naive to complement inhibitor therapy

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List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Alternative pathway
aPTT	Activated Partial thromboplastin time
ARC	Absolute reticulocyte count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
b.i.d.	bis in die/twice a day
BMF	Bone marrow failure
BP	Blood pressure
BTH	Breakthrough hemolysis
BUN	Blood Urea Nitrogen
CDE	Center for Drug Evaluation
CI	Confidence Interval
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease -19
CP	Classical pathway
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed Tomography
CTT	Clinical Trial Team
CV	Coefficient of variation
d	Day
DAR	Drug Administration Record
DMC	Data Monitoring Committee
DHT	Dihydrotestosterone
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
[redacted]	[redacted]
EMA	European Medicines Agency
EOS	End of study

ePRO	Electronic Patient Reported Outcome
ESA	Erythropoiesis-stimulating agent
[redacted]	[redacted]
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
EU	European Union
EudraCT	European Union Drug Regulatory Authorities Clinical Trial
FAS	Full Analysis Set
FB	Factor B
FDA	Food and Drug Administration
FIH	First-In-Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
GPI	Glycophosphatidylinositol
H	Hour
Hb	Hemoglobin
HBV	Hepatitis-B-Virus
HBsAg	HBV surface antigen
HCV	Hepatitis-C-Virus
HIF-PHI	Hypoxia inducible factor prolyl hydroxylase inhibitor
HIV	Human immunodeficiency virus
HR	Heart rate
HRQoL	Health-Related Quality of Life
hsCRP	hs-C-reactive protein
IA	Interim Analyses
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
LDH	lactate dehydrogenase
LH	Luteinizing hormone
LLOQ	Lower limit of quantification

LOAEL	Lowest Observed Adverse Effect Level
MAVE	Major Adverse Vascular Events
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mL	Milliliter(s)
MRI	Magnetic Resonance Imaging
NO	Nitric oxide
NTI	Narrow therapeutic index
NYHA	New York Heart Association
OATP	Organic Anion-transporting Polypeptide
OATP1B1	Organic Anion-transporting Polypeptide 1B1
ORN	Off-site research nursing
PA	Posteroanterior
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PIGA	Phosphatidylinositol N-acetylglucosaminyltransferase subunit A
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
pRBC	packed Red blood cell transfusions
PRO	Patient Reported Outcomes
PT	Prothrombin time
PTA	Post-trial access
QMS	Quality Management System
QoL	Quality of life
QTcF	QT interval corrected by Fridericia's formula
RBC	Red blood cell(s)
REP	Rollover extension program
[redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
sCR	Serum creatinine
SD	Standard deviation
SMQ	Standardized MedDRA Query
SoC	Standard of care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T4	Thyroxine
TA	Transfusion avoidance
TBL	Total bilirubin

TSH	Thyroid stimulating hormone
UK	United Kingdom
ULN	Upper limit of normal
WBC	White blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications 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
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.

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

Amendment 3 (28-Mar-2022)

Amendment rationale

This amendment is being implemented to address the request from the Chinese Health Authority (CDE (Center for Drug Evaluation)) to collect additional historical data in Chinese trial participants. The retrospective data collection of laboratory values for hemoglobin, LDH and absolute reticulocyte count (ARC) over 6 months before screening for participants from China is intended to support the regulatory filing in China.

Major revisions are made to:

Section 8.2: Added that "For participants in China, historical data on hemoglobin, LDH and absolute reticulocyte count (ARC) laboratory values will be retrospectively collected for the 6 months preceding Screening."
The rest of changes in the current amendment have been implemented to correct errors in the Table 8-2 footnote and Section 10.1.2.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, if applicable.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment, if applicable.

Amendment 2 (23-Nov-2021)

Short summary of the amendment rationale and major changes

This amendment is being implemented to provide a more comprehensive evaluation of patients' hematological parameters by the central laboratory, by replacing the abbreviated hematology assessments with full hematology assessments. [redacted]

In addition, simplification of the analyses of the PRO have been introduced. A comprehensive analysis of PRO will be provided as a separate PRO report and documented in a separate statistical analysis plan.

Changes have also been made to provide additional clarity on AE/SAE reporting post-treatment discontinuation and to address new requirements regarding SAE reporting.

Major revisions are made to:

[redacted]

Section 8: (Assessment schedule) Abbreviated hematology assessments replaced with full hematology assessments. The visits impacted are: Day 7, 14, 42, 126 and 154 in the Core treatment period. Table 8-5 removed abbreviated hematology assessments accordingly.

Section 10.1: Provided additional clarity regarding requirements for AE and SAE reporting timelines.

Other changes to the protocol are:

- [redacted]
- Section 3 and Section 8.2: Transfusion history prior to screening, instead of prior to starting study treatment, will be collected.
- Section 4.5: Updated safety information.
- Footnote clarified in Table 8-1 and Table 8-2 for premature discontinuation.
- Section 12.5.4: [redacted] Clarified the reporting of additional analyses.

Changes to specific sections of the study protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, if applicable.

The changes herein are also reflected in the Informed Consent.

Amendment 1 (17-Aug-2021)

Short summary of the amendment rationale and major changes

This amendment is being implemented to address several requests from Health Authorities. The amendment provides more flexibility on timing of vaccination against encapsulated bacteria at study entry (vaccination of patients within 2 weeks of iptacopan initiation, at the discretion of the investigator and to accommodate to local practices), and the associated need for prophylactic antibiotic. Additionally, this amendment is also being implemented [redacted] and to specifically address new requirements regarding SAE reporting in Germany.

Furthermore, due to the use of (high dose) steroids as first line therapy in some countries, reduction of the maximum allowed dose at study entry reduces the risk of tapering down during the Core treatment period. Further updates have been made to certain exclusion criteria, provide new juvenile toxicity animal data, add the possibility for interim safety analyses when study is still ongoing, and add a supplementary estimand that considers use of rescue medication as a treatment failure.

Major revisions are made to:

[redacted]

Section 3: Updated the vaccination administration requirements at study entry as follows: the Investigator can decide to administer a vaccine within 2 weeks (up to Day 14) after starting iptacopan treatment. Prophylactic antibiotic must be given at the start of iptacopan and for at least 2 weeks after vaccination. Other relevant sections (Section 5.1 and Table 8-1) were updated accordingly.

Section 4.4 and Section 12.7: Added that interim safety analyses may be produced while the study is still ongoing, if required.

Section 4.5: Added new safety information.

Section 5.2:

Exclusion criteria #11: In order to further clarify severe kidney disease, eGFR<30 mL/min/1.73m^2 was added.

Exclusion criteria #16: Lowered the maximum daily allowed dose of systemic corticosteroids for hematological conditions from 0.5 to 0.25 mg/kg/d. Section 6.2.1.1 was updated accordingly.

Section 10.1.3: Updated requirement for SAE reporting timeline.

Sections 12.4, Section 12.4.1 and Section 12.5.1: Handling of transfusions for analysis has been clarified.

Section 12.4.2: Added a threshold for response rate obtained from primary analysis.

Section 12.4.6: A supplementary estimand has been added to consider the use of rescue therapy under intercurrent events as treatment failure, for the purpose of efficacy assessment. Deleted analysis using multi-state model since that may be produced outside the clinical study report.

[redacted]

[redacted]

Section 12.8.1: Added operating characteristics for planned sample size and added justification for determining the threshold for comparing results obtained from primary efficacy analysis.

Other changes to the protocol are:

- Updated List of abbreviations.
- Protocol summary updated in line with the protocol.
- In Section 3, clarification has been added to allow local laboratory testing for absolute reticulocytes count to assess participant's eligibility.
- In Section 6.2.3, cross reference to Section 9.1.1 was deleted.
- Section 8.1.3 has been added to allow local laboratory testing for absolute reticulocytes count to assess participant's eligibility.
- Hepatitis B Virus DNA analysis was removed from Table 8-5.
- Added 5 new references in Section 15.

The rest of changes in the current amendment have been implemented to correct errors or inconsistencies that were identified since the original protocol was finalized.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, if applicable.

The changes herein are also reflected in the Informed Consent.

Protocol summary

Protocol number	CLNP023C12301
Full Title	A multicenter, single-arm, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who are naive to complement inhibitor therapy
Brief title	Study of efficacy and safety of twice daily oral iptacopan in adult PNH patients who are naive to complement inhibitor therapy
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this single arm, open label study is to determine whether iptacopan is efficacious and safe for the treatment of PNH patients who are naïve to complement inhibitor therapy, including anti-C5 antibody
Primary Objective(s)	The primary objective is to assess the effect of iptacopan on proportion of participants treated with iptacopan achieving a sustained increase from baseline in hemoglobin levels of ≥ 2 g/dL in the absence of red blood cell transfusion. The primary clinical questions of interest are: What is the effect of iptacopan, regardless of discontinuations of study drug or occurrence of breakthrough hemolysis (BTH) or Major Adverse Vascular Events (MAVEs) on the primary endpoint (a composite of improvement in hemoglobin levels and absence of RBC transfusions), as assessed by the proportion of responders? The endpoints are defined as a composite of an increase in Hb levels from baseline ≥ 2 g/dL assessed between Day 126 and Day 168, and the absence of red blood cell (RBC) transfusions between Day 14 and Day 168.
Secondary Objectives	The secondary objectives are: To assess the effect of iptacopan on the proportion of participants achieving sustained hemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions. To assess the effect of iptacopan on transfusion avoidance (TA) defined as the proportion of participants who remain free from transfusions. To assess the effect of iptacopan on average change in hemoglobin. To assess the effect of iptacopan on average percent change in LDH. To assess the effect of iptacopan on the rate of breakthrough hemolysis (BTH). To assess the effect of iptacopan on average change in reticulocyte counts. To assess the effect of iptacopan on improving fatigue, using the FACIT-Fatigue questionnaire. To assess the rates of Major Adverse Vascular Events (MAVEs incl. Thrombosis). To assess safety and tolerability of iptacopan.
Study design	This study is a multicenter, single-arm, open-label trial, which is comprised of an up to 8-week screening period, a 24-week, open-label Core treatment period, and a 24-week Extension treatment period.
Study population	This study will enroll PNH patients with hemolysis (LDH > 1.5 upper limit of normal (ULN)) and anemia (hemoglobin <10 g/dL), who are naive to complement inhibitor therapy, including anti-C5 antibody treatment with

	approximately 40% of all participants having received at least one RBC transfusion within 6 months prior to starting study treatment. A total of approximately 40 participants will be starting study treatment.
Key Inclusion criteria	• Male and female participants ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with RBCs and white blood cells (WBCs) (granulocyte/monocyte) clone size ≥ 10%. • Mean hemoglobin level <10 g/dL confirmed by central laboratory assessment during Screening and prior to starting study treatment: • By two hemoglobin measurements (mean < 10 g/dL), two to eight weeks apart, for patients not receiving a RBC transfusion during Screening. • By one hemoglobin measurement (<10 g/dL) carried at the first Screening visit for patients receiving a RBC transfusion after which he/she will be eligible. • LDH > 1.5 x Upper Limit of Normal (ULN) for at least two central laboratory measurements two to eight weeks apart during the screening period. • Vaccination against *Neisseria meningitidis* infection is required, and is recommended at least 2 weeks prior to initiation of iptacopan treatment. However, administration of these vaccines less than 2 weeks prior to start of iptacopan treatment or up to 2 weeks (up to Day 14) after iptacopan initiation, is at the discretion of the investigator. If iptacopan treatment is started less than 2 weeks post-vaccination or before a specific vaccination is given, participant must be given prophylactic antibiotic at the start of iptacopan and for at least 2 weeks after vaccination. • If not received previously, vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* should be given (if available and according to local/national regulations), and are recommended at least 2 weeks prior to initiation of iptacopan treatment. However, administration of these vaccines less than 2 weeks prior to start of iptacopan treatment or up to 2 weeks (up to Day 14) after iptacopan initiation, is at the discretion of the investigator. If iptacopan treatment is started less than 2 weeks post-vaccination or before a specific vaccination is given, participant must be given prophylactic antibiotic at the start of iptacopan and for at least 2 weeks after vaccination.
Key Exclusion criteria	• Prior treatment with a complement inhibitor, including anti-C5 antibody. • Known or suspected hereditary complement deficiency at screening. • History of hematopoietic stem cell transplantation. • Patients with laboratory evidence of bone marrow failure (reticulocytes <$100x10^9$/L; platelets <$30x10^9$/L; neutrophils <$0.5x10^9$/L). • Active systemic bacterial, viral (incl. COVID-19) or fungal infection within 14 days prior to study drug administration. • A history of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus. • Major concurrent comorbidities including but not limited to severe kidney disease (e.g., eGFR<30 mL/min/1.73m^2, dialysis), advanced cardiac disease (e.g., New York Heart Association (NYHA) class IV), severe pulmonary disease (e.g., severe pulmonary hypertension (World Health Organization (WHO) class IV)), or hepatic disease (e.g., active hepatitis)

	that in the opinion of the investigator precludes participant's participation in the study.
Study treatment	Iptacopan
Treatment of interest	The investigational treatment iptacopan at a dose of 200 mg b.i.d regardless of whether the patient discontinues treatment (treatment policy).
Efficacy assessments	• Hemoglobin, reticulocytes, LDH and other PNH-related laboratory parameters • Red blood cell transfusions • Breakthrough hemolysis • Patient Reported Outcomes (PRO) – FACIT-Fatigue • Major Adverse Vascular Events (MAVEs) incl. thrombosis
Key safety assessments	• Laboratory evaluations in blood and urine • Adverse event monitoring • ECG • Coagulation panel/thrombosis • Reproductive and thyroid hormones monitoring
Other assessments	[redacted] Pharmacokinetic samples will be obtained and evaluated in all participants taking iptacopan.
Data analysis	All efficacy analyses will use the full analysis set (FAS) that includes all patients to whom study treatment has been assigned. Primary efficacy estimand represented by the endpoint: proportions of participants achieving a sustained increase in hemoglobin levels from baseline ≥ 2 g/dL between Day 126 and Day 168 in the absence of transfusion between Day 14 and Day 168. Effect of iptacopan will be determined using the probability of being a responder, standardized to the population of patients assigned to iptacopan in this study. The primary analysis of the primary endpoint will be a logistic regression model with covariates including sex, age (categorical), an indicator variable of baseline hemoglobin above 8 g/dL and an indicator of transfusion dependence at enrollment. The proportion of responders will be derived from the estimated marginal probabilities derived from the model fit as the mean of the individual logistic model predications, together with the 95% confidence intervals, where the standard error will be derived by the bootstrap method. Lower bound of the two-sided 95% confidence interval ≥ 15% is sufficient for demonstration that iptacopan improves hematological response in PNH patients with hemolysis and anemia in the absence of transfusions. Secondary efficacy estimands represented by the following endpoints: • Response defined as having hemoglobin levels ≥ 12 g/dL between Day 126 and Day 168 in the absence of red blood cell transfusion between Day 14 and Day 168 • Absence of administration of packed-red blood cell transfusions (pRBC) between Day 14 and Day 168

	• Change from baseline in hemoglobin (g/dL) as mean of visits between Day 126 and Day 168 • Percent change from baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168 • Occurrences of breakthrough hemolysis reported between Day 1 and Day 168 • Change from baseline in reticulocyte counts (10^9/L) as mean of visits between Day 126 and Day 168 • Change from baseline FACIT-Fatigue scores as mean of visits between Day 126 and Day 168 • Occurrences of MAVEs occurring between Day 1 and Day 168 Proportions of participants achieving sustained hemoglobin levels and remaining free from transfusions will be evaluated by means of standardized marginal proportions derived similarly to the estimation applied to the primary estimand. All continuous endpoints will be derived from a longitudinal repeated measures model. The estimations of rates of MAVEs and BTH will be carried out using negative binomial model.
Key words	LNP023, Iptacopan, PNH, LDH, hemoglobin, anemia

1 Introduction

1.1 Background

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

The clinical spectrum of PNH varies and signs and symptoms include: anemia, thrombosis, smooth muscle dystonia, fatigue, hemoglobinuria, chronic kidney disease and pulmonary hypertension. The clinical presentation is driven by uncontrolled complement activation on CD55 and CD59 deficient PNH type RBCs culminating with hemolysis and the release of free hemoglobin and platelet activation (Hill et al 2013). Hemolysis results in release of intracellular hemoglobin and lactate dehydrogenase (LDH) into the circulation. Irreversible binding to and inactivation of nitric oxide (NO) by hemoglobin and inhibition of NO synthesis with consequent vasoconstriction and tissues ischemia, result in abdominal pain, dysphagia, erectile dysfunction, platelet activation and a prothrombotic status (Hill et al 2013, Brodsky 2014). Thromboembolism is the leading cause of mortality in patients with PNH, accounting for between 40% and 67% of deaths with known causes (Hill et al 2013), impacting morbidity and life expectancy of PNH patients.

Eculizumab and ravulizumab (engineered from eculizumab with prolonged dosing interval) are approved anti-C5 antibody therapies for the treatment of PNH and have become the current standard of care (SoC) in European Union (EU), US and Japan, improving survival and quality of life (QoL). However, eculizumab and ravulizumab are not available to PNH patients in all countries and even where available, many patients do not have access, and the i.v. route of administration presents a burden to many patients.

Furthermore, in countries where eculizumab or ravulizumab is available, there remains a high unmet medical need for PNH. Heterogeneous hematological response has been reported with eculizumab and a substantial proportion of patients do not achieve normal or near normal hemoglobin levels (Risitano et al 2009, Hill et al 2010, DeZern et al 2013, McKinley et al 2017). The heterogeneous response to eculizumab or other anti-C5 therapies can, in part, be explained through its mechanism of action inhibiting only the terminal part of the complement cascade. Therefore, deposition of C3 fragments on the cell surface of PNH type erythrocytes lacking CD55 is not impacted, rendering the cells susceptible to extravascular hemolysis. This response is inconspicuous in untreated PNH patients, because signs and symptoms of intravascular hemolysis dominate. However, extravascular hemolysis eventually emerges once the therapeutic inhibition with anti-C5 agents prevents intravascular hemolysis. In fact, it can become the main mechanism of hemolysis in patients treated with eculizumab (Risitano et al 2009) and C3-mediated extravascular hemolysis represents an unmet medical need. Residual chronic anemia greatly impacts the patients' QoL that currently can only be treated with red blood cell transfusions (McKinley et al 2017) with possible complications such as iron overload.

In countries where anti-C5 antibody therapy is not available, therapy focuses on managing the clinical manifestations of PNH but do not target the underlying pathophysiology and have little impact on long-term outcomes in PNH patients (Risitano and Rotoli 2008). Hemolysis and anemia in PNH are treated with corticosteroids, androgens (for both chronic and acute hemolysis) and transfusions. Patients are usually given iron supplements, folate and vitamin B12 as supportive therapy for the increased erythropoiesis (Parker et al 2005). When PNH is associated with other bone marrow diseases such as aplastic anemia, immunosuppressive therapy has also been used (Risitano and Rotoli 2008). As thromboembolism is leading cause of death in PNH, anticoagulant therapy is used as a prophylaxis as well as in acute setting. Hematopoietic stem cell transplantation remains the only curative option, however its use is limited to specific cases due to the increased morbidity and mortality (De Latour et al 2012). With such supportive therapies, the median survival rate was approximately 10 years. Therefore, there is a high-unmet medical need for effective and targeted therapies addressing the underlying pathophysiology in PNH patients where anti-C5 is not available (Hillmen et al 1995, Socie et al 1996, De Latour et al 2008).

1.2 Purpose

The purpose of this single arm, open label study is to determine whether iptacopan is efficacious and safe for the treatment of PNH patients who are naive to complement inhibitor therapy, including anti-C5 antibody. The study will evaluate the effects of 200 mg iptacopan given twice daily (b.i.d) on a range of efficacy assessments relevant to PNH including hematological response endpoints, transfusion avoidance and breakthrough hemolysis (BTH) as well as patient reported outcome (PRO) for fatigue (FACIT-fatigue).

The 24-week Core treatment period (up to Day 168) of this study will be used to assess the key efficacy and safety analysis. The 24-week extension treatment period (up to Day 336) will provide long-term safety and efficacy data on iptacopan in PNH patients.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints for the Core treatment period

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the effect of iptacopan on proportion of participants treated with iptacopan achieving a sustained increase from baseline in hemoglobin levels of ≥ 2 g/dL in the absence of red blood cell transfusion	• Response defined as having an increase from baseline in Hb ≥ 2 g/dL assessed between Day 126 and Day 168, in the absence of packed red blood cell (pRBC) transfusions between Day 14 and Day 168
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the effect of iptacopan on the proportion of participants achieving sustained hemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions	• Response defined as having Hb levels ≥ 12 g/dL between Day 126 and Day 168 in absence of red blood cell transfusion between Day 14 and Day 168
• To assess the effect of iptacopan on transfusion avoidance (TA) defined as the proportion of participants who remain free from transfusions	• Absence of administration of packed-red blood cell transfusions between Day 14 and Day 168

Objective(s)	Endpoint(s)
• To assess the effect of iptacopan on average change in hemoglobin	• Change from baseline in hemoglobin (g/dL) as mean of visits between Day 126 and Day 168
• To assess the effect of iptacopan on average percent change in LDH	• Percent change from baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168
• To assess the effect of iptacopan on the rate of breakthrough hemolysis (BTH)	• Occurrences of breakthrough hemolysis reported between Day 1 and Day 168
• To assess the effect of iptacopan on average change in reticulocyte counts	• Change from baseline in reticulocyte counts (10^9/L) as mean of visits between Day 126 and Day 168
• To assess the effect of iptacopan on improving fatigue, using the FACIT-Fatigue questionnaire	• Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168
• To assess the rates of Major Adverse Vascular Events (MAVEs incl. thrombosis)	• Occurrences of MAVEs occurring between Day 1 and Day 168
• To assess safety and tolerability of iptacopan	• Safety assessments (including adverse events/serious adverse events, safety laboratory parameters, vital signs etc.) between Day 1 and Day 168
[redacted]	

[redacted]

Table 2-2 Objectives and related endpoints for the Extension treatment period

Objective(s)	Endpoint(s)
• To assess long term safety, tolerability and efficacy of iptacopan	• Safety assessments including adverse events/serious adverse events, safety laboratory parameters, vital signs etc. through End of Study visit • Efficacy endpoints including hematological response parameters, transfusion avoidance, BTH, FACIT-fatigue score, MAVEs through End of Study visit

2.1 Primary estimand

The primary clinical question of interest is:

What is the effect of iptacopan, regardless of discontinuations of study drug or occurrence of BTH or MAVEs, on the primary endpoint (a composite of improvement in hemoglobin levels and absence of RBC transfusions), as assessed by the proportion of responders?

This primary estimand captures both the hematological effect of the study drug (as evaluated by a clinically relevant increase of ≥ 2 g/dL in hemoglobin levels) and the absence of RBC transfusions which are regarded as treatment failure. Further details can be found in Section 12.

The attributes of the primary estimand are:

- Population: PNH Patients ≥ 18 years old with hemolysis (LDH > 1.5 ULN) and anemia (hemoglobin <10 g/dL), and who have not received any complement inhibitor therapy (including anti-C5 antibody). Further details about the population are provided in Section 5.
- Treatment of interest: the investigational treatment iptacopan at a dose of 200 mg b.i.d regardless of whether the patient discontinues treatment (treatment policy). Further details about the investigational treatment are provided in Section 6.
- Intercurrent events: Transfusions (after Day 14) will be considered treatment failures and as such captured in the endpoint. Discontinuations of study medication for any reason, BTH events, and MAVEs will be handled with a treatment policy strategy.
- The summary measure: the probability of being a responder, standardized to the population of patients assigned to iptacopan in this study.

2.2 Secondary estimands

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

events, and MAVEs whose impact is expected to be reflected in the respective endpoints, will be handled with a treatment policy strategy.

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

- Response defined as having Hb levels ≥ 12 g/dL between Day 126 and Day 168 in absence of red blood cell transfusion between Day 14 and Day 168. The summary measure is the same as for the primary endpoint.
- Absence of administration of packed red blood cell transfusions (pRBC) between Day 14 and Day 168. Proportions of participants not receiving any transfusions between Day 14 and Day 168 (Transfusion Avoidance). The summary measure is the same as for the primary endpoint.
- Changes from baseline in hemoglobin between Day 126 and Day 168 where transfusions occurring between Day 14 and Day 168 are treated within a hypothetical strategy (as if the participants had not received any transfusions). The summary measure is the mean change from baseline in hemoglobin levels assessed between Day 126 and Day 168.
- Percent change from baseline in LDH between Day 126 and Day 168 where the strategy applied to transfusions is treatment policy. The summary measure is derived from the mean log transformed ratio to baseline in LDH between Day 126 and Day 168.
- Rates of BTH occurring between Day 1 and Day 168. The summary measure is occurrences per year.
- Change from baseline in reticulocytes counts between Day 126 and Day 168 where the strategy applied to transfusions is treatment policy. The summary measure is the mean change from baseline in reticulocytes counts assessed between Day 126 and Day 168.
- Change from baseline in scores of fatigue using the FACIT Fatigue questionnaire between Day 126 and Day 168, where the strategy applied to transfusions is treatment policy. The summary measure is the mean change from baseline in scores of fatigue assessed between Day 126 and Day 168.
- Rates of Major Adverse Vascular Events (MAVE) occurring between Day 1 and Day 168. The summary measure is occurrences per year.

Estimand considerations in case of COVID-19 pandemic impact

The overarching principle for primary and secondary estimands, is answering questions of treatment effect of iptacopan that are valid in conditions when the COVID-19 pandemic is no longer present. Data capture and clinical evaluation activities include possible adaptations to restrictions for patient access to investigational sites in case of a new infection wave. The planned analyses in Section 12 could be supplemented by supportive analyses as well as sensitivity analyses if required by the presence of deviations from the normal methods of patient follow up and data capture.

3 Study design

Study CLNP023C12301 is a multicenter, single-arm, open-label trial in adult PNH patients who are naive to complement inhibitor therapy, including anti-C5 antibody treatment. This study is comprised of three periods (see Figure 3-1):

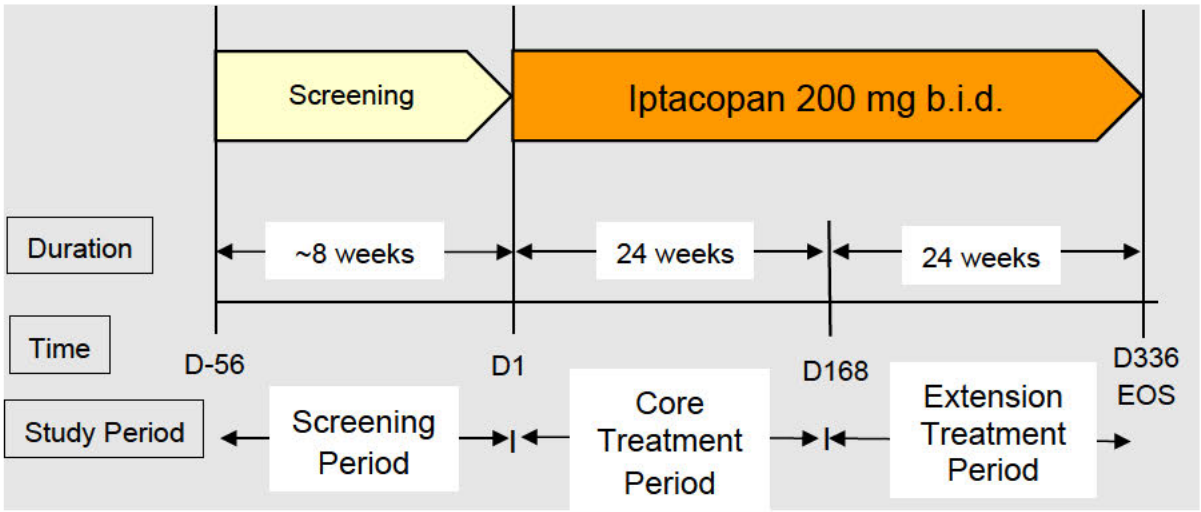
- A Screening period lasting up to 8 weeks (unless there is a need to extend it for vaccinations required for inclusion)
- A 24-week single arm, open-label Core treatment period for the primary efficacy and safety analysis
- A 24-week open-label, iptacopan treatment Extension period

This study will enroll PNH patients with hemolysis (LDH > 1.5 ULN) and anemia (hemoglobin <10 g/dL), who are naive to complement inhibitor therapy, including anti-C5 antibody treatment with approximately 40% of all participants having received at least one (1) packed-RBC transfusion within 6 months prior to starting study treatment.

A total of approximately 40 participants will be starting study treatment in the trial. All participants must provide written informed consent prior to start of any study-related activities.

The study design is shown in the schematic below.

Figure 3-1 Study design



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

Screening

Screening period starts at the time of Informed Consent Form (ICF) signing and lasts until the day preceding Day 1 of the Core treatment period.

Participants will be asked to review and sign the ICF prior to starting the screening assessments. After signing the ICF, inclusion and exclusion criteria will be assessed to verify participants' eligibility for starting study treatment in the study. This will be followed by the visit's assessments as outlined in Table 8-1, as applicable.

By signing the ICF, the participants will provide access to the medical records including numbers of transfusions, unit numbers of packed-RBC received in the last 12 months prior to Screening and history of Major Adverse Vascular Events (MAVEs).

Participants should be vaccinated as outlined in Section 5.1 Inclusion criteria. Vaccines should cover as many serotypes as possible (including meningococcal serotypes A, C, Y, W-135 and B). To minimize participant burden, the use of multivalent vaccines is recommended as locally available and according to local/national vaccination guidelines and regulations (e.g. quadrivalent vaccine for *N. meningitidis* which covers serotypes A, C, Y and W-135 and Pneumovax-23 which covers 23 *S. pneumoniae* serotypes). For the vaccination type and booster requirements, use local/national vaccination guidelines, and locally available vaccines (refer to the package insert of those).

The screening period may be extended in case of multiple vaccination needs. This is applicable for vaccinations only, while all the other screening assessments must be performed as indicated in the Assessment Schedule Table 8-1.

It is recommended to administer vaccines at least 2 weeks prior to initiation of iptacopan. However, administration of these vaccines less than 2 weeks prior to start of iptacopan or up to 2 weeks (up to Day 14) after iptacopan initiation, is at the discretion of the investigator. If iptacopan treatment is started less than 2 weeks post-vaccination or before a specific vaccination is given, participant must be given prophylactic antibiotic at the start of iptacopan and for at least 2 weeks after vaccination.

To fulfill the hemoglobin and LDH eligibility criteria, participant will have two different samples collected during the screening period and tested by the central laboratory prior to starting study treatment. In case the participant has received a RBC transfusion following the initial Screening visit, the participant is eligible based on the initial central hemoglobin if < 10g/dL.

The absolute reticulocytes count will be measured at Screening to determine eligibility with regards to exclusion criterion # 6. Due to the kinetics of maturation of reticulocytes into mature red blood cells and turnaround time from reticulocytes sample collection and analysis by central laboratory, local reticulocytes testing can be performed at the same time as the central testing during the Screening period. In the event that the absolute reticulocytes count as assessed by the central laboratory during the Screening period is below the protocol defined threshold (absolute reticulocytes $<100x10^9/L$) and only in this scenario, the results from the local lab testing can be used to determine participant's eligibility. The results of the local laboratory values (including reference ranges) should be included in the eCRF to document eligibility.

If eligibility criteria are not met due to any assessment, the participant should be considered as having failed the screening and does not proceed to the Core treatment period. However, the participant can be rescreened as described in Section 8.1.

Core treatment period

Participants who meet the eligibility criteria will proceed to the Core treatment period. Treatment with iptacopan at a dose of 200 mg b.i.d. will start on the first day (Day 1) and continue for 24 weeks with study visits and corresponding assessments according to the schedule described in Table 8-1.

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

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

For participants who permanently discontinue iptacopan administration, close monitoring and treatment proposals are indicated Section 9.1.1. Participants, if possible, should complete all visits and assessments up to Week 24 visit.

The Core treatment period will end with the completion of the Week 24 visit assessments. Upon completion of the Week 24 visit, participants may enter the Extension treatment period, as described below.

Extension treatment period

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

For participants permanently discontinuing iptacopan treatment during the Extension treatment period, Section 9.1.1 provides guidance for recommended procedures.

The Extension treatment period will last 24 weeks. After completion of the Extension treatment period, participants will be able to join the Roll-over extension program (REP), which will provide access to iptacopan and enable long-term safety monitoring. Post-trial access (PTA) will be provided until one of the following is met: participant no longer derives clinical benefit, investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

For participants not agreeing to continue in the Roll-over extension program (REP) after completing Day 336 visit, End of Study will be after completing recommended procedures defined in Section 9.1.1.

4 Rationale

4.1 Rationale for study design

CLNP023C12301 is a multicenter, single arm, open-label study designed to evaluate the efficacy and safety of iptacopan at a dose of 200 mg b.i.d. orally in adult PNH patients who are naive to any complement therapy, including anti-C5 antibody. A single arm design is chosen for this study for the following reasons:

- The study is the pivotal study to support the registration of iptacopan as treatment of PNH in countries where anti-C5 treatment (current SoC for PNH in countries where approved) is not available. As such, an active-comparator controlled design is not possible. The study will also provide supportive data for the global registration of iptacopan which will be based on a randomized controlled pivotal phase 3 trial comparing iptacopan vs anti-C5 treatment.
- A placebo-controlled design is deemed unethical with the compelling evidence of benefit of iptacopan in patients with PNH based on the IAs of the two Phase 2 PNH studies (LNP023X2201, LNP023X2204). Furthermore, a placebo arm is not considered appropriate with severe, life threatening diseases such as PNH.

The single arm, open-label design is widely used in rare diseases due to challenges associated with conducting studies in these patient populations (Bell and Smith 2014). Several measures have been included in the study design to minimize biases associated with this single arm open-label design, including

- Primary and majority of secondary, efficacy endpoints are objectively measured via laboratory assessments (i.e. hematological response parameters, hemoglobin, LDH, reticulocytes, transfusion avoidance and BTH).
- Protocol-specific guidelines (see Section 8.3.2) are defined to reduce potential bias due to events (such as transfusions) that may affect the main endpoints.

A hematological responder endpoint will be used for the primary efficacy analysis of the Core treatment period. A responder is defined as a participant achieving a hemoglobin increase from baseline $\geq$ 2 g/dL (assessed during the last 6 weeks of the 24 weeks Core treatment period) without the need of RBC transfusions from Day 14 to Day 168. This endpoint comprises 1) an improvement in hemoglobin of at least 2 g/dL from baseline and 2) transfusion independence for treatment success, both clinically important treatment goals in PNH. In the absence of a transfusion, an increase of 2 g/dL in hemoglobin has been chosen since it is approximates an increase that can be achieved with the administration of a RBC transfusion (1-2 units), thereby clinically relevant.

A treatment duration of 24 weeks is considered appropriate to assess the effect of iptacopan on the primary and secondary efficacy endpoints as well as on safety and tolerability. The 24-week treatment duration has been previously used in studies with PNH patients, including the recent Phase 3 studies with eculizumab and ravulizumab (Lee et al 2019, Kulasekararaj et al 2019). An interval of six weeks at the end of the Core treatment period with four assessments, and 3 out of 4 meeting the criterion, has been selected to demonstrate a durable and sustained hematological response. Moreover, the treatment duration of 24 weeks is implemented in the randomized iptacopan study in PNH patients (CLNP023C12302); thus ensuring alignment within the program.

A multicenter setting has been chosen to ensure adequate recruitment and representative patients' enrollment into the study in this rare indication.

The study population consists of PNH patients with hemolysis (LDH > 1.5 ULN) and anemia defined by a mean hemoglobin value below 10 g/dL; with approximately 40% of participants having received at least one RBC transfusion in the 6 months prior to starting study treatment.

Secondary efficacy endpoints include proportion of participants achieving sustained hemoglobin levels ≥ 12 g/dL, transfusion avoidance and BTH rates, a PRO measure for fatigue (FACIT-fatigue) as well as changes in reticulocytes and LDH. These endpoints were selected to supplement the primary efficacy endpoint and are clinically meaningful endpoints for PNH. Considering that some patients may present with very low hemoglobin levels (e.g. < 7 g/dL), and thereby require a RBC transfusion during the first two weeks of the Core treatment period, transfusions administered during these first 2 weeks will not be considered for the transfusion avoidance definition.

An extension period of 24 weeks will provide further safety and efficacy data on iptacopan in PNH patients.

4.2 Rationale for dose/regimen and duration of treatment

A dose of 200 mg iptacopan b.i.d. is chosen based on the available efficacy and safety data from the IA of the two ongoing Phase 2 PNH studies and is supported by Pharmacokinetic Pharmacodynamic (PKPD) modeling results. The dose of 200 mg b.i.d. is expected to provide optimal efficacy required for PNH as monotherapy with an adequate safety profile.

In the CLNP023X2204 study in patients not treated with eculizumab/complement inhibition, participants were randomized to iptacopan monotherapy in two sequences with forced titration after 4 weeks from iptacopan 25 mg b.i.d. to 100 mg b.i.d (sequence 1) or iptacopan 50 mg b.i.d. to 200 mg b.i.d. (sequence 2). An IA was conducted after the first 8 patients were randomized and 7 patients completed Week 8 visit. Results from this IA showed that:

- All participants (100%) had LDH reduction more than 60% from baseline.
- Early transfusion-free hemoglobin increase in the majority of participants. Other hemolysis relevant laboratory values indicated that iptacopan administered as monotherapy controls both, intra (LDH reduction) and extravascular hemolysis [redacted].

In the CLNP023X2201 study in patients with active hemolysis despite treatment with eculizumab, iptacopan was administered to 10 PNH participants at a dose of 200 mg b.i.d (cohort 1) and to 6 PNH participants at a dose of 50 mg b.i.d. (cohort 2). An IA was conducted after 10 participants (cohort 1) completed at least 13 weeks of treatment with iptacopan 200 mg b.i.d. add-on treatment to eculizumab. Results from this IA showed that participants treated with iptacopan 200 mg b.i.d. (as add-on to eculizumab) had clinical benefits not achieved with eculizumab that included:

- Control of both, intra- (LDH reduction) and extravascular hemolysis [redacted] with normalization of hemoglobin in the majority of patients in the absence of RBC transfusions.
- The hematological response achieved was maintained with iptacopan monotherapy during the extension period when in 5/10 participants (at the time of the IA) eculizumab treatment was discontinued and participants continued with iptacopan monotherapy. Following the IA, additional participants discontinued eculizumab treatment.
- C3 deposition fully reversed and survival of PNH RBC prolonged, providing additional evidence of the control of extravascular hemolysis by iptacopan. There was sustained inhibition of the complement alternative pathway and profound and sustained reduction of Fragment Bb demonstrating target engagement.
- Based on cohort 2 data following the IA, iptacopan dose of 50 mg b.i.d. may not provide optimal efficacy required for iptacopan monotherapy in PNH. There was suboptimal response in most participants requiring up-titration to the iptacopan dose of 200 mg b.i.d (add-on treatment to eculizumab).

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

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

Not applicable as this is a single arm study.

4.4 Purpose and timing of interim analyses/design adaptations

An independent Data Monitoring Committee (DMC) will conduct periodic monitoring of safety data and will assess risk/benefit for participants in the study. The reports compiled for DMC review will be provided by an independent statisticians and an independent programmer.

A clinical study report (CSR) will be produced for submission at the time the last participant has completed the Core treatment period. In addition, if deemed required (e.g. to support regulatory submissions to Health Authorities) interim safety analyses may be produced while the study is still ongoing. If there is an interim lock for safety analyses, [redacted]

4.5 Risks and benefits

The risks associated with the use of iptacopan are those inferred by its pharmacology and the results of preclinical safety studies. The most relevant risks are described below and a complete description of preclinical safety findings is available in the Investigator Brochure. The safety results from the Phase 2 PHN studies (CLNP023X2204 and CLNP023X2201) are summarized

in the Investigator Brochure. Iptacopan at a dose of 200 mg b.i.d. has been generally safe and well tolerated in PNH patients enrolled in these studies.

Appropriate eligibility criteria, as well as study specific stopping rules for the study drug and recommended procedures are included in this protocol (see Section 9.1.1). The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, including vaccinations prior to or up to 2 weeks after iptacopan initiation, close clinical monitoring with appropriate risk mitigation strategies, and periodic review of the safety data by an independent DMC. There is minimal risk to participants due to study procedures (mainly blood draws for laboratory assessments). One theoretical risk which is specific to PNH patients is the risk of hemolysis following discontinuation of treatment with a complement inhibitor. This is managed by specific discontinuation procedures outlined in Section 9.1.1. Additionally, there is the possibility that vaccinations could increase complement activation and worsen hemolysis.

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

The main safety risk for complement inhibitors is infections caused by encapsulated bacteria. To date, no infections have been reported in preclinical studies with iptacopan and one infection caused by encapsulated bacteria (pneumococcal pneumonia leading to sepsis) has been reported in a clinical trial patient with C3 glomerulopathy and a kidney transplant who was also taking cyclosporine, mycophenolate and prednisone.

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

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

immunocompromised participants with a higher risk of infections, precautionary actions (e.g. prophylactic antibiotics) should be considered by the investigator.

Other safety risks with iptacopan are based on preclinical data, with no relevant findings in clinical studies performed to date. These include potential risks of testicular effects, bone marrow toxicity with severe anemia, aorta mineralization and heart weight increase, and thyroid changes, summarized blow. Please refer to the Investigator Brochure for additional details on these preclinical findings.

In the iptacopan clinical studies, to date, there have been no serious testicular adverse events or clinically relevant changes from baseline in reproductive hormones reported.. In preclinical studies conducted in dogs, the testicular effects were mild and reversible with no notable effect on sperm morphology, numbers or motility, or hormone levels. In addition, considering the 17-fold safety margin between the unbound concentrations of iptacopan achieved in the dog at the lowest dose where an effect was seen (LOAEL), and the concentrations achieved in man at the 200 mg b.i.d. dose, the relevance of the findings to man is considered questionable. Testicular adverse events (AEs) and reproductive hormone levels will continue to be monitored in Phase 3 studies.

Although a severe bone marrow effect on erythropoiesis was seen pre-clinically in one dog, it occurred at the highest dose level, for which the exposure to iptacopan for unbound levels was more than 80-fold greater than that observed with the 200 mg b.i.d. dose of iptacopan in humans (see Investigator's Brochure). In clinical studies, there have been no adverse events or laboratory values compatible with this type of bone marrow toxicity. Hematological parameters will continue to be closely monitored in Phase 3 studies.

Minimal and reversible thyroid changes have been observed in preclinical studies. There have been no clinically relevant thyroid adverse events or changes in thyroid hormone levels in clinical trials to date. Thyroid hormone levels will continue to be monitored in Phase 3 studies.

Increases in heart weight and mineralization of the aortic wall were observed at dose levels $\geq$ 30 mg/kg/day in very young dogs (4 weeks old at the start of treatment, equivalent to 6-12 months of age in humans) after 52 weeks of treatment. These findings were not seen in adult dogs, even after chronic exposure (39 weeks). Blood pressure decrease concurrent with heart rate increase was consistently observed in both young and adult dogs at doses of 150 mg/kg/day, but in adult dogs these effects diminished over time whereas they persisted in the young dogs. It is not confirmed whether the aorta mineralization and increased heart weight are associated with these effects on blood pressure and heart rate but it is considered likely. Since these effects are seen only in very young dogs, likely because of an increased sensitivity related to their age, the risk of aorta mineralization and heart weight increase is considered unlikely to be relevant to adult patients. Increased heart rate and decreased blood pressure has not been seen following administration of iptacopan to humans to date.

Safety results from completed studies in 108 healthy volunteers exposed to iptacopan (84 to single doses and 24 to multiple doses over two weeks) indicated that treatment with iptacopan was well tolerated. Overall, there were no deaths, no serious adverse events (SAEs) or AEs leading to study drug discontinuation. Compared to placebo, no imbalance was observed in the rates of AEs.

Similarly, the two Phase 2 studies in PNH (29 participants exposed to iptacopan), as well as studies carried out in complement-driven renal diseases (IgA nephropathy study, n=87 participants exposed to iptacopan; C3G n=27 participants exposed to iptacopan) confirmed the favorable safety profile of iptacopan and supported the continuation of its development program.

Based on IA data from the CLNP023X2204 and CLNP023X2201 (Section 4.2), PNH patients treated with iptacopan may have clinical benefits including increases of hemoglobin to normal/near normal values in the absence of RBC transfusions, control of intra- and extravascular hemolysis, and reduction of LDH. Additionally, the benefit of iptacopan may exceed the ones reported with anti-C5 antibody, as per the IA results of Study LNP023X2201 (Section 4.2). It is expected that the improved hematological response with iptacopan treatment will translate into improved quality of life, most importantly an improvement in fatigue. Furthermore, participants may benefit from enrollment in a clinical study with close monitoring of their condition and frequent clinic visits and laboratory assessments as included in the assessment schedule.

In summary, the benefit-risk relationship for iptacopan in PNH is positive supporting the start of this study.

4.6 Rationale for Public Health Emergency mitigation procedures

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

5 Study Population

The study will enroll adult patients diagnosed with PNH who have never been treated with complement inhibitor, including anti-C5 antibody with approximately 40% of all participants having received at least one RBC transfusion within 6 months prior to starting study treatment. A total of approximately 40 male and female participants will be starting study treatment in the trial.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Male and female participants ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry (Borowitz et al 2010) with RBCs and WBCs (granulocyte/monocyte) clone size ≥ 10%.
3. Mean hemoglobin level <10 g/dL confirmed by central laboratory assessment during Screening and prior to start of study treatment:
   a. By two hemoglobin measurements (mean < 10 g/dL), two to eight weeks apart, for patients not receiving a RBC transfusion during Screening. Or

   b. By one hemoglobin measurement (<10 g/dL) carried out at the first Screening visit for patients receiving a RBC transfusion after which he/she will be eligible.
4. LDH > 1.5 x Upper Limit of Normal (ULN) for at least two central laboratory measurements two to eight weeks apart during the screening period.
5. Vaccination against *Neisseria meningitidis* infection is required, and is recommended at least 2 weeks prior to initiation of iptacopan treatment. However, administration of these vaccines less than 2 weeks prior to start of iptacopan treatment or up to 2 weeks (up to Day 14) after iptacopan initiation, is at the discretion of the investigator. If iptacopan treatment is started less than 2 weeks post-vaccination or before a specific vaccination is given, participant must be given prophylactic antibiotic at the start of iptacopan and for at least 2 weeks after vaccination.
6. If not received previously, vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* should be given (if available and according to local/national regulations), and are recommended at least 2 weeks prior to initiation of iptacopan treatment. However, administration of these vaccines less than 2 weeks prior to start of iptacopan treatment or up to 2 weeks (up to Day 14) after iptacopan initiation, is at the discretion of the investigator. If iptacopan treatment is started less than 2 weeks post-vaccination or before a specific vaccination is given, participant must be given prophylactic antibiotic at the start of iptacopan and for at least 2 weeks after vaccination.
7. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

5.2 Exclusion criteria

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

1. Participation in any other investigational drug trial or use of other investigational drugs at the time of enrollment, or within 5 elimination half-lives of enrollment, or within 30 days of enrollment, whichever is longer; or longer if required by local regulations.
2. Prior treatment with a complement inhibitor, including anti-C5 antibody.
3. History of hypersensitivity to iptacopan or any of its excipients or to drugs of similar chemical classes.
4. Known or suspected hereditary complement deficiency.
5. History of hematopoietic stem cell transplantation.
6. Patients with laboratory evidence of bone marrow failure (reticulocytes $<100x10^9$/L, platelets $<30x10^9$/L, neutrophils $<0.5x10^9$/L).
7. Active systemic bacterial, viral (incl. COVID-19) or fungal infection within 14 days prior to study drug administration.
8. Presence of fever ≥ 38 °C (100.4 °F) within 7 days prior to study drug administration.
9. Human immunodeficiency virus (HIV) infection (known history of HIV or test positive for HIV antibody at Screening).
10. History of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus.

11. Major concurrent comorbidities including but not limited to: severe kidney disease (e.g., eGFR<30 mL/min/1.73m^2, dialysis), advanced cardiac disease (e.g., NYHA class IV heart failure), severe pulmonary disease (e.g., severe pulmonary hypertension (WHO class IV)), or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participant's participation in the study.
12. Liver disease, such as active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection defined as HBsAg positive or HCV RNA positive, or liver injury as indicated by abnormal liver function tests at Screening:
    - Any single parameter of alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase must not exceed 3 × ULN.
13. Unstable medical condition including, but not limited to, myocardial ischemia, active gastrointestinal bleeding, coexisting chronic anemia unrelated to PNH, or unstable thrombotic event not amenable to active treatment as judged by the investigator at Screening.
14. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
15. Any medical condition deemed likely to interfere with the patient's participation in the study.
16. Concomitant use of any of the following medications is prohibited if not on a stable regimen for the time period indicated below prior to Screening and those listed in Section 6.2.2:
    - Erythropoiesis-stimulating agents (ESAs) for at least 8 weeks.
    - Any immunosuppressants for at least 8 weeks.
        - Systemic corticosteroids given for hematological conditions (less than 0.25 mg/kg/d) for at least 4 weeks (see Section 6.2.1.1 during the Core treatment period).
    - Vitamin K antagonists (e.g., warfarin) with a stable international normalized ratio (INR) for at least 4 weeks.
    - Low-molecular-weight heparin, and the direct oral anticoagulants rivaroxaban, apixaban and edoxaban, for at least 4 weeks.
    - Iron supplements, vitamin B12, or folic acid for at least 4 weeks.
    - Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) such as roxadustat for at least 8 weeks.
    - Androgens for at least 4 weeks.
17. Female patients who are pregnant or breastfeeding, or intending to conceive during the course of the study.
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of investigational drug and for 1 week after stopping of investigational drug. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking 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 participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For United Kingdom (UK): with spermicidal foam/gel/film/cream/vaginal suppository.
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

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

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

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

6 Treatment

6.1 Study treatment

All participants starting study treatment in this single arm open label study will receive LNP023 (iptacopan) 200 mg b.i.d.

6.1.1 Investigational drug

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

Table 6-1 Investigational drug

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
LNP023, 200 mg	Hard gelatin capsule	Oral use	Open label, patient specific kits	Sponsor (global)

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
LNP023, 10 mg*	Hard gelatin capsule	Oral use	Open label, patient specific kits	Sponsor (global)

* Used only during tapering down of LNP023 (iptacopan) dose – see Section 9.1.1 for details

6.1.2 Additional study treatments

No other treatment beyond iptacopan are included in this trial.

6.1.3 Treatment arms/group

This is a single arm study; all participants will receive iptacopan at a dose of 200 mg orally b.i.d.

6.1.4 Treatment duration

The planned duration of the Core treatment period is 24 weeks. If a participant's study treatment is discontinued for any reason, every effort must be made to continue with the study assessments up to Week 24.

An Extension treatment period of 24 weeks is offered to participants who complete the Core treatment period. In the event a participant's study treatment is discontinued during the Extension treatment period for any reason, and if possible, participants should continue with the study assessments up to Week 48.

Please refer to Section 9.1.1 for recommendations for participants who discontinue iptacopan for any reason during the Core or Extension treatment period.

Participants who complete this trial and continue to derive clinical benefit from the treatment based on the investigator's evaluation may join the Rollover extension program (REP).

6.2 Other treatment(s)

6.2.1 Concomitant therapy

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

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

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

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

Systemic corticosteroids are allowed to be used for hematological conditions if on stable dose (less than 0.25 mg/kg/d) at least 4 weeks before Screening. During the study, the dose should not be changed during the Core treatment period (up to Day 168 Visit). During the extension treatment period, the dose of systemic corticosteroids can be adjusted based on participant's condition and local guidelines.

Iptacopan has been shown to have a weak inhibition potential for the liver uptake transporter Organic Anion-transporting Polypeptide 1B1 (OATP1B1). Calculation revealed that the exposure (area under the curve (AUC)) of respective sensitive substrates may be increased by <1.5 fold. Although the expected effect on the exposure of respective co-medications is small and may not be clinically relevant, it is recommended to combine iptacopan with sensitive OATP1B1 substrates or those having a narrow therapeutic index (NTI) with caution or apply a staggered dosing (see below). A list of OATP1B1 substrates to be used with caution will be provided to the investigators.

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

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

6.2.2 Prohibited medication

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

- Any other complement inhibitors, including anti-C5 antibody, are prohibited for the entire study treatment. If anti-C5 antibody is started, the patient should permanently discontinue iptacopan.
- Live vaccines are prohibited for the entire study treatment duration.
- Preclinical studies have shown that systemic disposition of iptacopan is primarily mediated by metabolic clearance, predominantly by CYP2C8 and to a smaller extent by direct glucuronidation. In addition, some contribution from direct renal (approximately 20%) and

direct biliary excretion (around 5 to 10%) is anticipated. iptacopan is also a substrate for the organic anion-transporting polypeptide (OATP) hepatic uptake transporter (see above). To ensure participant safety, co-medications that inhibit multiple disposition mechanisms of iptacopan (e.g. Gemfibrozil) are prohibited. The same applies to strong CYP2C8 inhibitors (main clearance pathway) such as clopidogrel.

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

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

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

6.2.3 Rescue medication

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

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

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

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

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study.

All eligible participants will be assigned medication kits via Interactive Response Technology (IRT). The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a unique medication number for the first package of study treatment (iptacopan) to be dispensed to the participant.

6.4 Treatment blinding

Treatment will be open to participants, Novartis Clinical Trial Team (CTT), the investigator staffs and persons performing the assessments. The CTT will have access to standard reports of patient profiles and other listings necessary to fulfill data review. There will be an Independent Statistician and an Independent Programmer who will provide analyses of safety data for the review of the members of the DMC at periodic intervals.

6.5 Dose escalation and dose modification

Iptacopan will be administered at a dose of 200 mg b.i.d. Dose adjustments and/or interruptions are not planned.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by explaining that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

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

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

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

6.6.2 Recommended treatment of adverse events

The participants and treating staff need to be instructed to be vigilant for any clinical signs of bacterial infections (e.g., malaise, chills, fever, nausea, photophobia, generalized muscle and joint pain) and to measure the body temperature at minimum at the times of symptoms of presumed infection. Participants will be instructed to contact the study physician immediately

in case of suspicion of infection or elevated body temperature (> 38.3°C by oral or tympanic method) for a 'phone directed triage.

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

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

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

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

LNP023 (Iptacopan) Participant Safety Card

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

6.7 Preparation and dispensation

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

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

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

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

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the

participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment

6.7.1.1 Handling of study treatment

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

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

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

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

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

6.7.2 Instruction for prescribing and taking study treatment

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

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

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

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

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

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

7 Informed consent procedures

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

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

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

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH Good Clinical Practice (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 participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Heath Authority.

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

The following informed consents are included in this study:

- Main study consent, which also included:
  - An additional signature page for participants moving to Extension treatment period
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
  - A subsection that requires a separate signature for the ‘Optional Consent for Patient Interview’
- Informed Consent Optional for genetic research

- Informed Consent Form for Optional Home Nursing visits during a pandemic
- Informed Consent Form for Optional Off-site Research Nursing (ORN) visits for Week 2 and/or Week 6 visits
- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

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

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

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

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

8 Visit schedule and assessments

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

Except for obtaining the 2 hour post-dose PK sample, all assessments should be performed prior to dose administration the day of visits.

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

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

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

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

The home nursing visits will be carried out by a third-party vendor centrally sourced by the Sponsor that can provide qualified research nurses who will perform study assessments under the oversight of the Investigator. The qualified nurses will be under delegation of the

investigator. The investigator will retain accountability for participant's oversight and all medical decisions (i.e. protocol specified medical procedures, AE/SAE assessment and reporting, changes in medication, etc.).

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster or in special circumstances, that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by 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. For more details refer to Section 8.6.

Participants who prematurely discontinue iptacopan treatment for any reason during the Core treatment period should continue in the study up to Week 24 visit, completing all scheduled visits assessments. Please, refer to Section 9.1.1 for details on the recommended procedures to follow in case of permanent discontinuation.

Participants who prematurely discontinue iptacopan treatment during the Extension treatment period of the study for any reason, and if possible, should continue in the study up to the Week 48 visit completing all scheduled visit assessments. The same guidance for managing iptacopan permanent discontinuation as in the Core treatment period applies (Section 9.1.1).

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

Table 8-1 Assessment schedule – Core treatment period

Period	Screening		Core treatment period											
Visit Name	**Screening**	**Hb /LDH confirm.**	**Day 1**	**Day 7**	**Day 14**	**Day 28**	**Day 42**	**Day 56**	**Day 84**	**Day 112**	**Day 126**	**Day 140**	**Day 154**	**Day 168[7]**
Visit Numbers	**1**	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**
Days	**-56 to -1**	**-56 to -1**	**1**	**7 ±1**	**14 ±1**	**28 ±1**	**42 ±3**	**56 ±3**	**84 ±3**	**112 ±3**	**126 ±3**	**140 ±3**	**154 ±3**	**168 ±3**
Weeks	**-8 to -1**	**-8 to -1**	**1**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**18**	**20**	**22**	**24**
Informed consent	X													S
Eligibility criteria	X	X												
Demography	X													
Medical history/current medical conditions	X													
Vaccination[1]	X													
Alcohol and Smoking history	X													
Hepatitis B, C and HIV screen	X													
Physical examination	S		S			S								S
Blood pressure and pulse rate	X		X	X	X	X	X	X	X	X	X	X	X	X
Body height	X													
Body weight	X													X
Body temperature	X		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (serum)	S													
Pregnancy test (urine)			S						S					S
Clinical Chemistry (full)	X		X					X		X				X
Clinical Chemistry (abbreviated)		X(LDH only)		X	X	X	X		X		X	X	X	
Hematology (full)[2]	X	X (Hb only)	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation/Markers of thrombosis	X		X			X		X	X	X		X		X

Period	**Screening**		**Core treatment period**											
Visit Name	**Screening**	**Hb /LDH confirm.**	**Day 1**	**Day 7**	**Day 14**	**Day 28**	**Day 42**	**Day 56**	**Day 84**	**Day 112**	**Day 126**	**Day 140**	**Day 154**	**Day 168[7]**
Visit Numbers	**1**	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**
Days	**-56 to -1**	**-56 to -1**	**1**	**7 ±1**	**14 ±1**	**28 ±1**	**42 ±3**	**56 ±3**	**84 ±3**	**112 ±3**	**126 ±3**	**140 ±3**	**154 ±3**	**168 ±3**
Weeks	**-8 to -1**	**-8 to -1**	**1**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**18**	**20**	**22**	**24**
Panel of hormones blood samples	X		X			X		X	X	X		X		X
[redacted]														
PK blood collection[3]				X		X			X					X
DNA sample collection (optional)[4]			X											
Urinalysis	X		X			X		X	X	X		X		X
Urine Albumin/Creatinine ratio			X						X					X
Breakthrough hemolysis	X													
MAVE	X													
[redacted]														
RBC transfusion	X													
12-lead Electrocardiogram (ECG)	X		X						X					X
Adverse Events	X													
Concomitant medications	X													
[redacted]														
Surgical and medical procedures	X													
Patient reported outcomes		X[5]	X	X[6]	X		X		X		X	X	X	X
[redacted]														
Iptacopan DAR			X											
Disposition		X												

X - Assessment to be recorded in the clinical database or received electronically from a vendor
S - Assessment to be recorded in the source documentation only

[1] It is recommended to administer vaccines at least 2 weeks prior to initiation of iptacopan. However, administration of these vaccines less than 2 weeks prior to start of iptacopan or up to 2 weeks (up to Day 14) after iptacopan initiation, is at the discretion of the investigator. If iptacopan treatment is started less than 2 weeks post-vaccination or before a specific vaccination is given, participant must be given prophylactic antibiotic at the start of iptacopan and for at least 2 weeks after vaccination.

[2] Local reticulocytes testing can be performed at the same time as the central testing during the Screening period. In the event that the absolute reticulocytes count as assessed by the central laboratory during the Screening period is below the protocol defined threshold (absolute reticulocytes <100x109/L) and only in this scenario, the results from the local lab testing can be used to determine participant's eligibility.

[3] PK samples will be taken pre-dose and approximately 2h post-dose.

[4] If the DNA sample is not taken at Day 1 visit, it can be taken at any visit thereafter.

[5] First PRO completion should occur at a screening visit prior to Day 1 and before any other assessment at that visit.

[6] Only FACIT-Fatigue [redacted] will be carried out on Day 7.

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

[redacted]

Table 8-2 Assessment Schedule - Extension treatment period

Period	Extension treatment Period					
Visit Name	**Day 196**	**Day 224**	**Day 252**	**Day 280**	**Day 308**	**Day336/EOS**
Visit Numbers	**201**	**202**	**203**	**204**	**205**	**9999[1]**
Days	**196 ± 5**	**224 ± 5**	**252 ± 5**	**280 ± 5**	**308 ± 5**	**336 ± 5**
Weeks	**28**	**32**	**36**	**40**	**44**	**48**
Blood pressure and pulse rate	X	X	X	X	X	X
Physical examination						S
Body weight						X
Body temperature	X	X	X	X	X	X
Pregnancy test(urine)						S
Clinical Chemistry (full)		X				X
Clinical Chemistry (abbreviated)	X		X	X	X	
Hematology (full)	X	X	X	X	X	X
Coagulation/markers of thrombosis	X	X	X	X	X	X
Panel of hormones blood samples	X	X		X		X
[redacted]						
Urinalysis	X	X	X	X	X	X
Urine Albumin/Creatinine ratio			X			X
Breakthrough hemolysis	X					
MAVE	X					
[redacted]						
RBC transfusion	X					
12-lead Electrocardiogram (ECG)						X
Adverse Events	X					
Concomitant medications	X					
[redacted]						
Surgical and medical procedures	X					
Patient reported outcomes	X	X	X	X	X	X

Period	Extension treatment Period					
Visit Name	**Day 196**	**Day 224**	**Day 252**	**Day 280**	**Day 308**	**Day336/EOS**
Visit Numbers	**201**	**202**	**203**	**204**	**205**	**9999[1]**
Days	**196 ± 5**	**224 ± 5**	**252 ± 5**	**280 ± 5**	**308 ± 5**	**336 ± 5**
Weeks	**28**	**32**	**36**	**40**	**44**	**48**
Iptacopan DAR	X					
Disposition	X					

X - Assessment to be recorded in the clinical database or received electronically from a vendor

S - Assessment to be recorded in the source documentation only

Chemistry abbreviated: LDH, Albumin, ALT, aspartate aminotransferase (AST), GGT, estimated glomerular filtration rate (eGFR), hs-C-reactive protein, Serum creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN)/Urea, Ferritin

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

8.1 Screening

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

Rescreening participants

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

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

8.1.1 Information to be collected on screening failures

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

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

8.1.2 Hemoglobin and LDH assessments and transfusion during Screening

During the Screening period, mean hemoglobin < 10 g/dL and LDH >1.5 ULN will be determined by central laboratory assessments prior to starting study treatment evaluated by two measurements (hemoglobin mean < 10 g/dL; both LDH values >1.5 ×ULN), two to eight weeks apart; or by one hemoglobin measurement (<10 g/dL) from the first assessment for patients receiving a pRBC transfusion after the first assessment.

Transfusion administered based on hemoglobin during the Screening period

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

If a participant receives a packed-RBC transfusion following the first assessment carried out for the Screening visit (Hb value < 10 g/dL by central laboratory), he/she will be eligible without an additional hemoglobin assessment by the central laboratory.

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

8.1.3 Absolute reticulocytes count during Screening

The absolute reticulocytes count will be measured at Screening to determine eligibility with regards to exclusion criterion # 6. Due to the kinetics of maturation of reticulocytes into mature red blood cells and turnaround time from reticulocytes sample collection and analysis by central laboratory, local reticulocytes testing can be performed at the same time as the central testing during the Screening period. In the event that the absolute reticulocytes count as assessed by the central laboratory during the Screening period is below the protocol defined threshold (absolute reticulocytes $<100x10^9$/L) and only in this scenario, the results from the local lab testing can be used to determine participant's eligibility. The results of the local laboratory values (including reference ranges) should be included in the eCRF to document eligibility.

8.2 Participant demographics/other baseline characteristics

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

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

Relevant medical history/current medical conditions will include: date for diagnosis of PNH (and age for diagnosis and disease duration will be derived up to the date of screening), vaccination history, and MAVE history (dates and type). In addition, the number of transfusions and unit numbers of packed-RBC will be collected for the 12 months preceding Screening. For participants in China, historical data on hemoglobin, LDH and absolute reticulocyte count (ARC) laboratory values will be retrospectively collected for the 6 months preceding Screening.

Relevant medical history, smoking and alcohol history will also be collected.

Prior concomitant medications (including vitamins, herbal preparations, over the counter medications, and those medications highlighted in the entry criteria) **and procedures** (any therapeutic intervention including surgery, biopsies, or non-pharmacological therapy) taken prior to Screening will be recorded in the CRFs. Medications for the treatment of PNH preceding screening will be collected in the CRF.

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

8.3 Efficacy

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

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

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

The following laboratory parameters will be assessed: Hemoglobin, [redacted] reticulocyte count, [redacted], LDH, RBCs, [redacted]

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

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

8.3.2 Red blood cell transfusion

The need for administration of RBC transfusion will be monitored continuously during the Core treatment period.

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

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

- Hemoglobin level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and/or symptoms of sufficient severity to warrant a transfusion
- Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), regardless of presence of clinical signs and/or symptoms

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

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

[redacted]

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

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

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

8.3.3 Breakthrough hemolysis

The occurrence of BTH will be monitored continuously during the Core treatment period.

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

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

Table 8-3 Breakthrough hemolysis definition

	Clinical criteria		Laboratory criteria
	Hemoglobin levels	**Signs or symptoms**	**LDH level**
Clinical breakthrough*	Decrease equal to or more than 2 g/dL (compared to the latest assessment, or within 15 days)	Gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs & symptoms	> 1.5-times ULN and increased as compared to the last 2 assessments
Subclinical breakthrough	Decrease less than 2 g/dL (compared to the latest assessment, or within 15 days)	No clinical signs or symptoms, except moderate hemoglobinuria	> 1.5-times ULN and increased as compared to the last 2 assessments

LDH: lactate dehydrogenase; ULN: Upper Limit of Normal;

*The breakthrough is defined clinical if either one of the two clinical criteria is demonstrated, in presence of laboratory evidence of intravascular hemolysis (LDH level)

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

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

8.3.4 Patient Reported Outcomes (PRO) - FACIT-Fatigue

The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. It will be used to assess patient-reported fatigue. FACIT-Fatigue is one of many different FACIT scales part of a collection of health-related quality of life (HRQoL) questionnaires referred to as the FACIT Measurement System (Yellen et al 1997, Webster et al 2003). The use of the FACIT-F in PNH patients has been reported in several publications and is sensitive to changes in disease status, allowing demonstration of statistically significant and clinically meaningful results (Brodsky et al 2008, Ueda et al 2018, Kulasekararaj et al 2019). All FACIT scales are scored so that a high score is better. As each of the 13 items of the FACIT-F Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best. For additional Patient Reported Outcomes (PROs) assessed in the study, please refer to Section 8.5.1.

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

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

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

Detailed instructions describing administrative procedures of the PROs including participant completion via ePRO will be provided to the sites.

8.3.5 PNH-related signs & symptoms

Paroxysmal nocturnal hemoglobinurias (PNHs) signs and symptoms will be collected according to Table 8-1 for the Core treatment period. The investigator (or designee) will record the presence of the following signs and symptoms:

- Reddish or cola-colored urine especially in the morning / or hemoglobinuria
- Feeling weak or tired
- Shortness of breath / dyspnea
- Dysphagia / difficulty swallowing
- Chest pain
- Abdominal / belly pain
- Erectile dysfunction / impotency

These signs and symptoms of PNH will be reported in the CRF at each visit.

During the extension treatment period, PNHs signs and symptoms will be collected according to Table 8-2.

8.3.6 Major Adverse Vascular Events (MAVEs)

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

- Acute peripheral vascular occlusion
- Amputation (non-traumatic; nondiabetic)
- Cerebral arterial occlusion/cerebrovascular accident
- Cerebral venous occlusion
- Dermal thrombosis
- Gangrene (non-traumatic; nondiabetic)
- Hepatic/portal vein thrombosis (Budd‐Chiari syndrome)
- Mesenteric/visceral arterial thrombosis or infarction
- Mesenteric/visceral vein thrombosis or infarction
- Myocardial infarction
- Pulmonary embolus

- Renal arterial thrombosis
- Renal vein thrombosis
- Thrombophlebitis / deep vein thrombosis
- Transient ischemic attack
- Unstable angina
- Other, please specify

8.3.7 Appropriateness of efficacy assessments

The efficacy assessments including laboratory parameters hemoglobin (to determine the degree of anemia), LDH (as marker for intravascular hemolysis), reticulocytes, [redacted] are important parameters for assessing treatment response in PNH. In fact, hemoglobin, the need of RBC transfusions are the determining parameters for classifying treatment response to complement inhibitor therapy with LDH and reticulocytes as ancillary parameters (Risitano et al 2019). Breakthrough hemolysis is a phenomenon reported with eculizumab and also ravulizumab, therefore is part of the efficacy assessments for iptacopan, a new complement inhibitor, in this study. As thromboembolism is the leading cause of mortality in patients with PNH (Hill et al 2013), it is important to assess MAVE for iptacopan treatment in PNH patients. The majority of these efficacy assessments have been used in the eculizumab and ravulizumab registrations studies and will provide clinically relevant results for PNH.

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

8.4 Safety

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, or in special circumstances that limits or prevents on-site study visits, regular phone or virtual calls may occur (as per scheduled visits) for safety monitoring and discussion of the participant´s health status until it is feasible for the participant to visit the site again.

For details on AE collection and reporting, refer to Section 10.

Table 8-4 Assessments and specifications

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

8.4.1 Laboratory evaluations

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

If participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) may be used as defined in Table 8-7.

Clinically notable laboratory findings are defined in Appendix 1.

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

Table 8-5 Laboratory tests

Test Category	Test Name
Hematology - full list	Hematocrit, total Hemoglobin, Mean corpuscular hemoglobin, Haptoglobin, Reticulocytes counts, Red blood cells (RBC) count, RBC distribution width, RBC mean corpuscular volume, White blood cell (WBC) count with differentials and Platelet count

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

8.4.2 Electrocardiogram (ECG)

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

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

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

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

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

8.4.3 Pregnancy and assessments of fertility

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

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

The participant should inform the investigator if they believe they might be pregnant. Please refer to Section 9.1.1 on recommendations for iptacopan therapy in case of a pregnancy.

Assessments of fertility

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

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

- 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 testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Coagulation panel/thrombosis

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

8.4.5 Reproductive and thyroid hormones monitoring

The assessments indicated below will be done in all participants as per the Assessment schedules in Table 8-1 and Table 8-2.

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

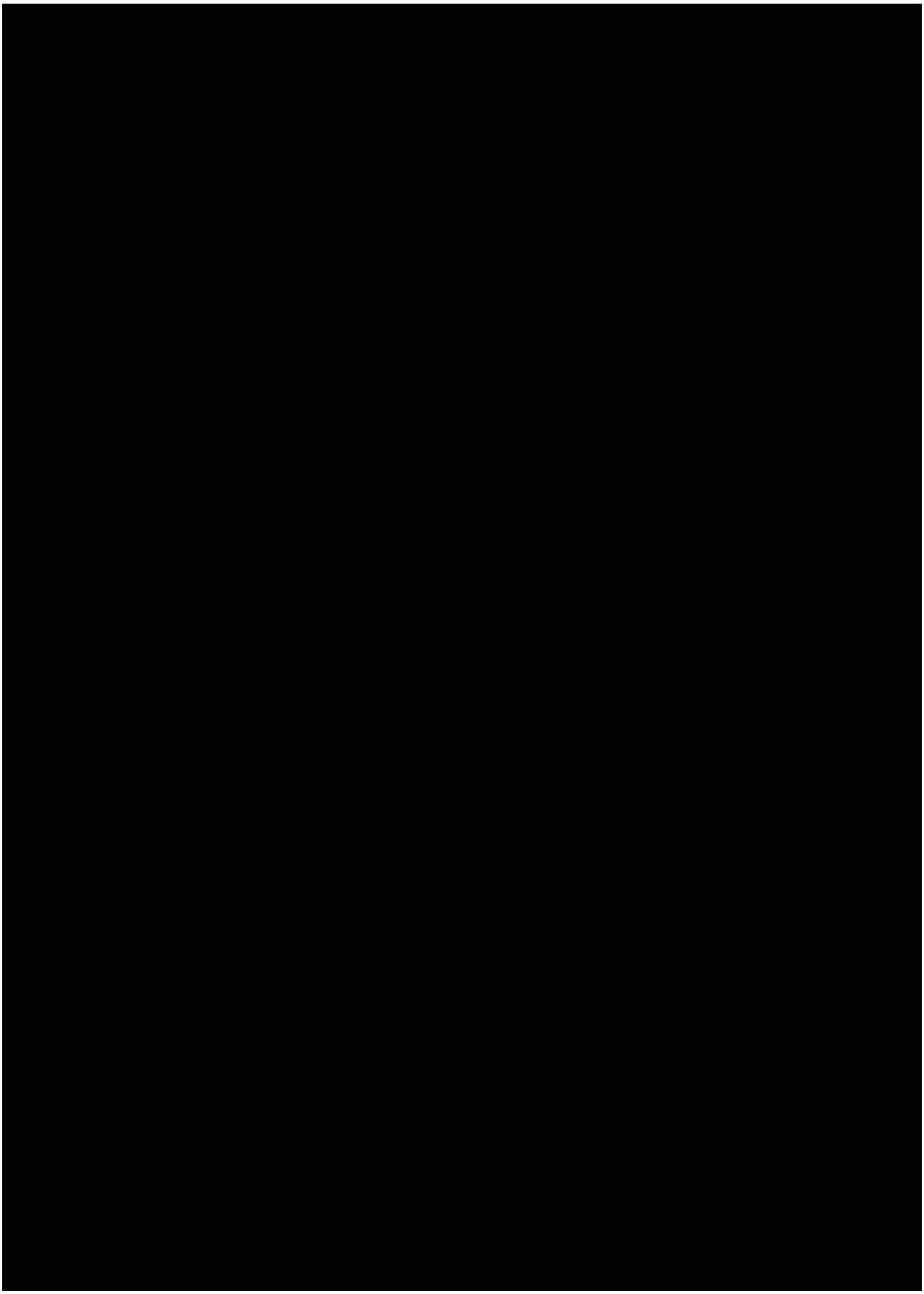
8.4.6 Urine albumin creatinine ratio (UACR)

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

8.4.7 Appropriateness of safety measurements

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

8.5 Additional assessments



8.5.2 Pharmacokinetics

PK samples will be collected at the visits defined in the assessment schedule (Table 8-1) and as highlighted below.

In the event of a pandemic or in special circumstances that limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible, and in case that an ORN visits are planned at that site (see Section 8.6), the collection of samples may be modified by Novartis and will be communicated to the Investigator.

The first sample of the day must be collected in the morning and immediately prior to taking the first daily iptacopan dose (pre-dose). The Investigator should remind the participant prior to the visit that during that specific visit the iptacopan morning dose will be administered at the site after collection of the blood sample.

There is a second sample collected approximately 2 hours after dose administration. The Investigator should also remind the participants of the requirement for a second sample collection. Investigator should encourage participants to report vomiting that occurs within 5h after dosing as this need to be captured in the dedicated eCRF page.

Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

Table 8-6 PK blood log

Period	Visit Name	Days	Weeks	Time	PK blood collection		
					Size (mL)	Dose ref.ID	Sample No.
Treatment Phase	Day 7	7	1	pre-dose	2	101	201
				2h post-dose	2	101	202
	Day 28	28	4	pre-dose	2	104	203
				2h post-dose	2	104	204
	Day 84	84	12	pre-dose	2	112	205
				2h post-dose	2	112	206
	Day 168	168	24	pre-dose	2	124	207
				2h post-dose	2	124	208
Unplanned	Unplanned				2		1001+

Pharmacokinetic (PK) samples will be obtained and evaluated in all participants taking iptacopan. [redacted]

Iptacopan will be determined in human plasma by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 1.0 ng/mL. Metabolites (as needed) may be determined as appropriate, but those analysis will be reported outside of the clinical study report (CSR).

Concentrations will be expressed in mass per volume units (ng/mL) and will refer to the free base. PK parameters to be determined are Cmax and Ctrough.

Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

8.5.3 DNA sampling

The study includes an optional genetic research component which requires an informed consent signature if the participant agrees to participate. Sample will be collected, on Day 1 as indicated in Table 8-1. If DNA sample is not taken at Day 1 visit, it can be taken at any visit thereafter. The purpose of genetic research may be to identify inherited genetic factors which may (1) be related to the causes and consequences of PNH, its pathophysiology and associated comorbidities, (2) predict response to treatment with iptacopan, (3) predict genetic predisposition to side effects. The goal is to better understand the safety and treatment effect of iptacopan, or to learn more about human diseases, or to help develop ways to detect, monitor and treat diseases.

[redacted]

Laboratory manuals will be provided with detailed information on sample collection, handling, and shipment.

8.6 Off-site visits

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

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

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

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

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

Conditions to enable off-site visits

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

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

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

Off-site research nursing (ORN) personnel

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

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

The ORN may collect and process Laboratory samples according to Table 8-7, which will then be shipped to the Central Laboratory. However if results of these sample collected at ORN are obtained from the local laboratory then results need to be entered in the appropriate local laboratory CRF pages.

Assessment will be performed following the timing indicated in the assessment schedule (Table 8-1 and Table 8-2), but will be limited to those included in Table 8-7.

Table 8-7 List of the assessments to be performed during off-site research nursing visit

Assessment list to be performed during ORN
Assessments*
Vaccination booster
Blood pressure and pulse rate
Body temperature
Breakthrough hemolysis event
[redacted]
Adverse Events
Major Adverse Vascular Events
Concomitant medications
[redacted]
Surgical and medical procedures
Records of questionnaire completion
Study treatment administration / Checking availability
Blood samples to be collected**
Clinical Chemistry
Hematology
Coagulation/Markers of thrombosis
Panel of hormones blood samples
[redacted]
Iptacopan pharmacokinetic sample***

* Data collected are entered in the study CRF pages for the corresponding visit.

** Results obtained from the local laboratory are entered in the appropriate local laboratory CRF pages.

***Iptacopan pharmacokinetic samples will be collected during the ORN visits only when more details on feasibility (e.g. stability at ambient temperature) are available and the approach has been fully validated. Details will be included in the manual provided by the ORN service provider.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

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

Study treatment must be discontinued under the following circumstances:

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

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

If treatment with iptacopan has to be discontinued immediately, i.e. because of a significant safety risk, appropriate replacement therapy must be offered to participants based on investigator’s judgment and local availability (including starting anti-C5 antibody treatment if available).

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

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

A visit one week after permanent discontinuation of iptacopan should occur for the following assessments: LDH, creatinine, hemoglobin, coagulation/thrombosis markers (Prothrombin time

(PT)/INR, activated partial thromboplastin time (aPTT), D-dimer, and fibrinogen), [redacted] dipstick urinalysis, [redacted] and all adverse events. All data collected will be entered in the appropriate CRF page.

If treatment with iptacopan is discontinued prematurely but it is not warranted to immediately discontinue iptacopan treatment, e.g., discontinuation due to participant/guardian decision, it is recommended to consider appropriate replacement therapy based on investigator's judgment and local availability (including starting anti-C5 antibody treatment if available). In addition, it should be considered to taper down iptacopan over a period of 14 days, as follows:

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

The investigator should consider the proposed monitoring and supportive treatments listed above in case serious hemolysis occurs. For iptacopan tapering, weekly visits are recommended until one week after last iptacopan dose for the following assessments: LDH, creatinine, hemoglobin, coagulation/thrombosis markers (PT/INR, aPTT, D-dimer, and fibrinogen), [redacted] dipstick urinalysis, [redacted] and all adverse events. All data collected will be entered in the appropriate CRF page.

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' Section 9.1.2).

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

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

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

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

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

- New / concomitant treatments
- Safety laboratory assessments
- Adverse Events / Serious Adverse Events

All dose changes must be recorded on the appropriate CRF. The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

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

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

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

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

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

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

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

- Discontinuation of study drug development

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

9.2 Study completion and post-study treatment

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

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

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

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

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

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

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

1. The severity grade

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

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

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

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

6. Its outcome

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

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

Adverse event monitoring should be continued at least until 7 days after the last dose of study medication, or until the first day of dosing in the REP.

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

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

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

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

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

10.1.1.1 Adverse events of special interest

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

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

- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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

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

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

10.1.3 SAE reporting

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

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

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

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

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

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

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the stopping of investigational drug should be considered as described in Section 9.1.1, and the trial participant must be asked to read and sign the pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the study informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up for 12 months after the birth to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS) on a Pharmacovigilance Pregnancy Form. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must also be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

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

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

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

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), exposure to environmental chemical agents, alcohol use, recreational drug use, and special diets.
  - Exclusion of underlying liver disease

These investigations can include based on investigator's discretion:

- Imaging such as abdominal US, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), as appropriate

- Considering gastroenterology or hepatology consultations.

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

10.2.2 Data Monitoring Committee

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

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

10.2.3 Steering Committee

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

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

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

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

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis at the end of the Core treatment period. Before this, IRT information will also be made available to the Independent Statistician and Independent Programmer for carrying out analyses for the periodic safety review of data by the DMC. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/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 participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis/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 participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical

information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

12 Data analysis and statistical methods

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

An additional CSR will be produced when the last participant has completed the last visit in the Extension treatment period, and the final study database has been locked.

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

12.1 Analysis sets

The Enrolled Set comprises all participants enrolled in the study.

The Full Analysis Set (FAS) comprises all participants with confirmed eligibility to whom study treatment has been assigned. This will be the data set used for analysis of all efficacy endpoints.

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment they received, where treatment received is defined as the assigned treatment if the participant took at least one dose of that treatment.

The analysis set including the complete follow up of participants up to the completion of the Extension treatment period will be defined in the corresponding statistical analysis plan (SAP).

12.2 Participant demographics and other baseline characteristics

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

Categorical data will be presented as frequencies and percentages. The summary statistics shown for continuous data will be mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum.

12.3 Treatments

The Safety set will be used for the analyses of exposure to iptacopan described below.

The duration of exposure (in days) to iptacopan as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

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.

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

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

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

The primary endpoint related to increase in Hb will define a participant as a responder if

- The change from baseline in hemoglobin is ≥ 2 g/dL on three out of four measurements taken at the visits occurring in last six weeks (from Day 126 to Day 168) of the Core treatment period, and
- The participant has not required (i.e. not received and not met the criteria for administration as per Section 8.3.2) any packed-red blood cells transfusions between Day 14 and Day 168.
- The baseline hemoglobin will be the mean of the two measurements confirming the hemoglobin entry criterion in participants who do not receive a transfusion between the first and second confirmatory measurements. In participants who receive a transfusion after the first confirmatory measurement, the baseline will be the first measurement.

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

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis of the primary endpoint will be a logistic regression to estimate the response probability. The covariates include sex, age (categorical), an indicator variable of baseline hemoglobin above 8 g/dL and an indicator of transfusion dependence at enrollment.

This means that the proportion of responders will be derived from the estimated marginal probabilities derived from the model fit as the mean of the individual logistic regression model predictions, together with the 95% confidence intervals (CI), where the standard error will be derived by the bootstrap method.

The primary analysis of primary endpoint is the assessment of the proportion of patients reaching the status of responder. The lower bound of the two-sided 95% confidence interval of the response rate obtained from primary analysis will be compared to a threshold of 15%. Lower

bound of the two-sided 95% confidence interval ≥ 15% is sufficient for demonstration that iptacopan improves hematological response in PNH patients with hemolysis and anemia in the absence of transfusions. The derivation of the threshold is explained in Section 12.8.1.

12.4.3 Handling of remaining intercurrent events of primary estimand

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

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

12.4.4 Handling of missing values not related to the intercurrent event

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

Missing hemoglobin data due to withdrawal from study in the event that a participant did not have a prior RBC transfusion, will be imputed based on pattern mixture models which aims to be consistent with the inclusion of hemoglobin data under the treatment policy strategy following all other intercurrent events. For participants with intermittent missing data during study follow up where reasons for missingness are assumed to be unrelated to response or compliance status, their missing data will be handled with a missing at random approach and imputed consequently. The full specification will be provided in the SAP.

12.4.5 Sensitivity analyses for primary endpoint/estimand

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

12.4.6 Supplementary analysis

A supplementary estimand considering the use of rescue therapy (as defined in Section 6.2.3) under intercurrent event as treatment failure, for the purpose of efficacy assessment, will be performed. The supplementary estimand will have the same population, treatment of interest, summary measure as the primary estimand in Section 2.1. For this analysis, transfusions will be considered treatment failures whereas discontinuations of study medication for any reason will be handled with treatment policy strategy.

12.4.7 Supportive analyses

The estimation of proportions described above will be further displayed for subgroup categories defined by previous transfusion dependence, length of time since diagnosis, prior supportive therapy (e.g. steroids, androgens etc.), age categories, sex, and baseline hemoglobin.

Other supportive analyses

Potential impact of a new wave of COVID-19 infections affecting measurements have been minimized through the measures proposed in Section 8. Other impact that at this stage cannot be excluded such as withdrawal from study follow up due to infection which would require dealing with such events as additional intercurrent events. This would define additional estimands, possibly primary and secondary estimands all of which would deal with the COVID-19 related intercurrent events so that inference would still concern treatment effects in a world that is not in the midst of an extraordinary pandemic situation. The methodology for the analyses targeting these estimands and additional sensitivity analyses for cases of missing data due to the impact of COVID-19 infections will be specified in detail in an amendment to the SAP developed in the event of renewed COVID-19 infection waves. Decisions on handling of possible increases in background risks impacting study endpoints will also take into consideration relevant epidemiological information on local incidence of COVID-19 infections.

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Handling of RBC transfusions will depend on the endpoint and this is described below. In the case of discontinuation of study medication, breakthrough hemolysis, or MAVEs, these are intercurrent events which are expected to be reflected in the endpoints, hence the treatment policy strategy will be applied.

The proportion of participants achieving sustained hemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions will be evaluated by means of standardized marginal proportions.

Transfusion avoidance will be evaluated as the proportion of participants not requiring (i.e. not received and not met the criteria for administration as per Section 8.3.2) any transfusion between Day 14 and Day 168, and the estimation will be evaluated by means of standardized marginal proportions derived similarly to the estimation applied to the primary estimand.

Change from baseline in hemoglobin levels is estimated under the hypothetical situation in which participants would not have received transfusions on iptacopan treatment. This will be accomplished by the use of imputed values based on a normal distribution whose mean is restricted to a range consistent with not having received an RBC transfusion and the within visit covariance matrix will borrow from the observed within participant covariance matrix, to replace hemoglobin values following a transfusion. The model for the estimation is a repeated measures model with an unstructured covariance structure, and including visit and baseline hemoglobin levels and the interaction between visit and baseline levels. Additional covariates will be age (categorical), sex and transfusion dependency. The treatment estimates will be computed as the mean changes corresponding to the average of hemoglobin levels measured in the last 6 weeks of treatment (that is the visits occurring between Day 126 and Day 168).

Changes from baseline in scores of fatigue using the FACIT-Fatigue questionnaire will be derived from a longitudinal repeated measures model including test scores collected as all visits. The baseline is defined as the mean of levels obtained pre-treatment (Screening visit) and Day 1 value. The estimation will be an average of treatment estimates derived for visits occurring

between Day 126 and Day 168. Main effects will be transfusion dependency and interaction terms will be the same as those used to compare changes in hemoglobin.

The estimation of the change from baseline in reticulocyte counts will be derived from a longitudinal repeated measures model including data collected throughout the study and where baseline is defined as the value on Day 1. In this model, transfusion dependency, baseline covariates as well as interaction terms will be the same as for changes in hemoglobin. The estimation will use the average of model derived estimates obtained at visits occurring between Day 126 and Day 168.

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

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

The estimation of rates of breakthrough hemolysis (BTH) will be carried out using a negative binomial model. Transfusion dependency and covariates will be included similarly as for the other endpoints.

In all estimations based on a longitudinal model, missing data will be imputed multiple times under a model that considers the reasons for missingness. The imputed datasets will be used in the estimation of the longitudinal model. For the analysis of change from baseline Hb and/or where missing data are imputed, the model comparisons will be derived using Rubin's combination rules.

12.5.2 Safety endpoints

The analysis set used for all safety analyses will be the safety set (SAF). All tables will be presented. The complete details of all safety summaries will be provided in the SAP. The following mentions safety outcomes of interest and provides a non-exhaustive description of principles to be followed in the preparation of outputs.

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

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

Adverse events

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

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

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

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to discontinuation of study medication, and for iptacopan tapering if this is followed prior to complete study dose discontinuation.

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

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

Vital signs

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

12-lead ECG

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

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

Summary statistics will be provided by visit/time.

Clinical laboratory evaluations

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

[redacted]

12.5.4 Patient reported outcomes

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

In this study, the question addressed by the analysis of PRO measurements is whether treatment with iptacopan improves patient-reported fatigue symptoms as measured by the FACIT-Fatigue and this analysis is a secondary endpoint described with the secondary endpoints/estimands. This section briefly describes supportive analyses of FACIT-Fatigue as well as supportive analyses using a secondary clinical outcome instrument.

[redacted]

Further, responder analyses derived from changes in FACIT-Fatigue will be performed. Response is defined as at least a 5-point improvement in the FACIT-Fatigue total score from baseline at a patient-level. Given the greater variability at the patient-level, a 5-point change is recommended as a meaningful important difference.

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

[redacted]

Descriptive statistics and displays by visit will be produced.

[redacted]

12.7 Interim analyses

Safety data will be monitored by an independent DMC, and analyses to the effect of this evaluation will be performed during the course of the study with the frequency to be determined in the Charter. Access to a limited number of efficacy measurements by the DMC will be

provided solely for the purpose of evaluating benefit of treatment with iptacopan against any risk. The DMC will function under a charter to be finalized prior to the first patient screening. The Charter will include guidelines for communication concerning safety of participants between the DMC and the sponsor representative to ensure that these are in keeping with the sensitive nature of the open label trial and do not introduce bias. The analyses to be provided to the DMC will also be specified in the appendix to the Charter.

Interim reports of the safety data may be produced as mentioned in Section 4.4. [redacted] The interim reports will not consider inferences based on efficacy.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size is calculated based on the half-width (the margin of error in the estimate) of a 2-sided 95% confidence interval for the proportion of participants reaching the status of responder (primary endpoint). The proposed sample size of 40 participants is sufficient to achieve a target absolute margin of error not larger than 0.155.

The different scenarios of observed response rate and its 95% confidence intervals are shown in Table 12-1.

Table 12-1 Precision of response rate with N = 40

Sample Size	Observed Response Rate	Unadjusted 95% Confidence Interval
40	30%	(15.8%, 44.2%)
40	40%	(24.8%, 55.2%)
40	50%	(34.5%, 65.5%)
40	60%	(44.8%, 75.2%)

The lower bound of the two-sided 95% confidence interval of the response rate obtained from the primary analysis will be compared to a threshold of 15% and exceeding the threshold is sufficient for demonstration that iptacopan improves hematological response in PNH patients with hemolysis and anemia in the absence of transfusions.

For the sample size of 40 participants, given the observed proportion of responders is 40%, there is 96.4% probability that the lower bound of the 2-sided 95% confidence interval (CI) will exclude a threshold of 15%.

Derivation of the 15% threshold

The threshold of 15% is derived by indirectly estimating hemoglobin response in two studies with eculizumab: Study ALXN1210-PNH-301 (Ultomiris CHMP Assessment Report 2019, Brodsky et al 2021) that included a treatment naive population and the first eculizumab pivotal study, TRIUMPH (Hillmen et al 2006, Dmytrijuk et al 2008) that was conducted in a more severe population of transfusion dependent patients before the availability of eculizumab as SoC for PNH. The treatment periods for both historical studies were 26 weeks.

The patient-level hemoglobin data were not available for these historical studies, and hence direct estimation of the proportion of patients who achieved hemoglobin increases from baseline ≥ 2 g/dL in the absence of transfusions was not feasible. However, an indirect approach through simulation indicates that the probability of being a responder (defined as change of hemoglobin ≥ 2 g/dL regardless of transfusions) is 14.7% (95% CI: 5.0% - 21.1%) for ALXN1210-PNH-301 and is 4.49% (95% CI: 0.5% - 11.0%) for TRIUMPH. The difference in estimated probability of being a responder between ALXN1210-PNH-301 and TRIUMPH is likely due to the difference in populations, with the TRIUMPH population consisting of all transfusion dependent patients, while ALXN1210-PNH-301 included less severe patients due to availability of SoC.

Please note these estimates (14.7% and 4.49%) actually overestimate the hematological effect for eculizumab in the studies because the hemoglobin levels correspond to all patients at Week 26 including those who have received transfusions during treatment.

The 15% threshold is chosen to be above the estimated hemoglobin increases regardless of transfusions in both historical studies, and exceeding this threshold is sufficient for demonstration that iptacopan improves hematological response in PNH patients with hemolysis and anemia in the absence of transfusions. R® software was used for the calculations (R Core 2017). Further details about simulation approach will be provided in Statistical Analysis Plan.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in European Union Drug Regulatory Authorities Clinical Trial (EudraCT). In

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

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

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

15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

Renal alert values

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

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

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

ECG alert values

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

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

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

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

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

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

Criteria	Actions required	Follow-up monitoring
	• Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	
Any AE potentially indicative of a liver toxicity[d]	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	Investigator discretion

[a] Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

[b]Severe fatigue, malaise (general), abdominal pain (right upper quadrant), nausea, vomiting or rash with eosinophilia

[c]Resolved = return to Day 1 values; Condition unchanged = stable values at three subsequent monitoring visits at least 2 weeks apart; Condition deteriorated = values worsen or liver transplantation; and Fatal.

[d]These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms.

ALP: alkaline phosphatase; GLDH: glutamate dehydrogenase TBL: total bilirubin; ULN: upper limit of normal