REGIONE DEL VENETO
ULSS7 PEDEMONTANA
Via dei Lotti, n. 40
36061 Bassano del Grappa (VI)
Codice fiscale e partita IVA 00913430245

N. 2037 DEL 28/10/2022

DELIBERAZIONE
del

DIRETTORE GENERALE

Nominato con D.P.G.R. n. 26 del 26/02/2021

Coadiuvato dai sigg.:

DIRETTORE AMMINISTRATIVO	dott.ssa MICHELA CONTE
DIRETTORE SANITARIO	dr. ANTONIO DI CAPRIO
DIRETTORE DEI SERVIZI SOCIO – SANITARI	dott.ssa ALESSANDRA CORO'

OGGETTO: APPROVAZIONE ADDENDUM N. 1 AL CONTRATTO SOTTOSCRITTO CON LA SOCIETÀ NOVARTIS FARMA RELATIVO ALLO STUDIO CLINICO PROFIT DAL TITOLO " PROGRAMMA DI ESTENSIONE ROLL-OVER (REP) MULTICENTRICO, IN APERTO PER CARATTERIZZARE LA SICUREZZA E LA TOLLERABILITÀ DI IPTACOPAN (LNP023) IN PAZIENTI CON EMOGLOBINURIA PAROSSISTICA NOTTURNA (EPN) CHE ABBIANO COMPLETATO GLI STUDI DI FASE 2 E 3 IN PNH CON IPTACOPAN".

IL DIRETTORE GENERALE
DELL'AZIENDA ULSS 7 PEDEMONTANA
dott. Carlo Bramezza

Proponente: UOC AFFARI GENERALI
Anno Proposta: 2022 Numero Proposta: 2177/22

Il Dirigente, Direttore dell'UOC Affari Generali nonché Responsabile del procedimento, attesta che la presente proposta di deliberazione è stata regolarmente istruita nel rispetto della vigente normativa nazionale, regionale e regolamentare: f.to Paola Dalla Zuanna

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Il Direttore dell'U.O.C. Affari Generali relaziona quanto segue.

Premesso che:

- con deliberazione n. 1477 del 05.08.2022 è stato approvato il Regolamento aziendale sulla gestione delle sperimentazioni cliniche profit e no-profit, comprensivo anche della regolamentazione dei fondi per la gestione della ricerca con determinazione delle quote dei fondi stessi e fissazione dei criteri per l'attribuzione dei compensi;
- con deliberazione n. 1684 del 09.09.2022 sono stati aggiornati i componenti del Nucleo per la Ricerca Clinica Aziendale (N.R.C.) ai sensi della DGRV n. 2174 del 23.12.2016.

Rilevato che :

- con deliberazione n. 1958 del 12.11.2021 è stato autorizzato lo studio clinico profit internazionale dal titolo "*Programma di estensione roll-over (REP) multicentrico, in aperto per caratterizzare la sicurezza e la tollerabilità di iptacopan (LNP023) in pazienti con Emoglobinuria Parossistica Notturna (EPN) che abbiano completato gli studi di fase 2 e 3 in PNH con Iptacopan"* e sottoscritto il relativo contratto con la Società Novartis Farma;
- lo studio di cui sopra è attualmente in corso presso l'U.O.C. di Oncoematologia del P.O. di Bassano, il cui Sperimentatore Responsabile è il dr. Eros Di Bona, Direttore della struttura citata;
- l'attività di sperimentazione in questione, con promotore commerciale, è svolta dal personale sanitario al di fuori del normale orario istituzionale.
- l'introito totale per paziente arruolato, qualora tutte le fasi siano rispettate, corrisponde ad € 7.100,00+ I.V.A., per un totale di circa 3 pazienti per Centro; per ulteriori dettagli si rinvia all'addendum allegato alla presente proposta:

SCHEDA STUDIO

Titolo	Approvazione addendum n. 1 al Contratto sottoscritto con la società Novartis Farma relativo allo studio clinico profit dal titolo *" Programma di estensione roll-over (REP) multicentrico, in aperto per caratterizzare la sicurezza e la tollerabilità di iptacopan (LNP023) in pazienti con Emoglobinuria Parossistica Notturna (EPN) che abbiano completato gli studi di fase 2 e 3 in PNH con Iptacopan"*
Struttura interessata	U.O.C. Oncoematologia del P.O. Bassano
Sperimentatore principale	Dr. Eros Di Bona - Direttore dell'U.O.C. di Oncoematologia P.O. Bassano
Protocollo	CLNP023C12001B
EudraCT	2020-004385-19
Sperimentazione	68/21
Promotore	Novartis Farma S.p.A

Dato atto che:

- in data 13/07/2021, nota ns. prot. 62963 del 27.07.2021, la Società Novartis Farma ha presentato

al Comitato Etico per le sperimentazioni Cliniche della Provincia di Vicenza (CESC) richiesta di approvazione dell'Emendamento "*001 del 13.07.2021 (IB di LNP023 Ed.8) – Appendice 9 del 13.07.2021*" alla sperimentazione;

- il CESC di Vicenza ha espresso parere favorevole in ordine all'emendamento "*001 del 13.07.2021 (IB di LNP023 Ed.8) – Appendice 9 del 13.07.2021"* in occasione della seduta del 12.10.2021, nota ns. prot n. 88326 del 25.10.2021;
- la principale modifica introdotta con l'emendamento di cui sopra consiste nell'aggiornamento dell'investigator's Brochure di LNP023 Edizione 8 del 24.03.2021 come segue:
  - sostituzione del codice del farmaco LNP023 con la nuova denominazione INN, Iptacopan
  - aggiunte due nuove indicazioni in studio: la nefrite da lupus (LN) e la degenerazione maculare legata all'età precoce e intermedia (e/iAMD)
  - aggiornate le sezioni relative agli studi clinici con nuovi protocolli per le indicazioni già in studio: PNH, IgAN, Ahus
  - aggiunti i risultati preliminari di studi di tossicità giovanile in giovani cani.
  - inserito come nuovo rischio potenziale di sicurezza "la mineralizzazione dell'aorta con aumento di peso del cuore".
- in data 10.01.2022, nota ns. prot. 2624 del 13.01.2022, la Società Novartis Farma ha presentato al CESC di Vicenza richiesta di approvazione dell'ulteriore Emendamento "003 del 10.01.2022 (emendamento 2 al protocollo) – Appendice 9 del 10.01.2022" alla sperimentazione;
- il CESC di Vicenza ha espresso parere favorevole in ordine all'emendamento "003 del 10.01.2022 (emendamento 2 al protocollo) – Appendice 9 del 10.01.2022" in occasione della seduta del 12.04.2022, nota ns. prot. 40974 del 05.05.2022.
- le principali modifiche del nuovo emendamento riguardano:
  - l'aggiornamento del protocollo - v. 02 del 22.10.2021 - e della relativa sinossi
  - l'aggiornamento dell'informativa e del consenso per lo studio
  - la rivalutazione del budget dello studio come segue:
    - € 150,00 per ciascuna trasfusione di globuli rossi (trasfusione RBC) qualora si rendesse necessaria durante il corso dello studio
    - € 200,00 per ciascuna visita non programmata che si rendesse necessaria durante il corso dello studio.
- per tali aspetti si è reso necessario modificare l'allegato A2 del Contratto in essere con la Società Novartis Farma mediante apposito Addendum n. 1 al Contratto e aggiornare il protocollo - v. 02 del 22.10.2021 - allegati entrambi alla presente proposta di deliberazione.

Tutto ciò premesso, si propone di approvare il protocollo aggiornato – v. 02 del 22.10.2021 - e l'Addendum n.1 al Contratto in essere con la Società Novartis Farma SpA per lo studio profit dal titolo:*" Programma di estensione roll-over (REP) multicentrico, in aperto per caratterizzare la sicurezza e la tollerabilità di iptacopan (LNP023) in pazienti con Emoglobinuria Parossistica Notturna (EPN) che abbiano completato gli studi di fase 2 e 3 in PNH con Iptacopan"*, in corso presso l'U.O.C. di Oncoematologia del P.O. Bassano, entrambi allegati alla presente proposta di deliberazione per farne parte integrante e sostanziale

IL DIRETTORE GENERALE

Vista la relazione e la proposta del Responsabile del procedimento;

Dato atto che il responsabile del Servizio competente ha attestato l'avvenuta regolare istruttoria

della pratica, in ordine alla compatibilità con la vigente legislazione statale, regionale e regolamentare;

Visti:

- il decreto ministeriale 15/07/1997;
- la circolare del Ministero della Salute 02/09/2002 n. 6;
- il D.lgs 24/06/2003, n. 211;
- il decreto ministeriale 17/12/2004;
- la DGRV 28/12/2006, n. 4430;
- il decreto ministeriale 12/05/2006;
- il D.lgs 6/11/2007, n. 200;
- il decreto ministeriale 21/12/2007;
- la determinazione AIFA 20/03/2008;
- la DRGV 07/10/2008, n. 2855;
- la Legge 08/11/2012, n. 189 – Decreto Balduzzi;
- il decreto del Ministero della Salute 08/02/2013;
- la DRGV 28/06/2013 n. 1066;
- il D.M. 30/11/2021

Acquisito il parere favorevole del Direttore Amministrativo, Sanitario e dei Servizi Socio-Sanitari, per quanto di rispettiva competenza

DELIBERA

1. di prendere atto dei pareri favorevoli espressi dal Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza (CESC) in ordine agli emendamenti sostanziali di cui in premessa per lo studio clinico profit dal titolo " *Programma di estensione roll-over (REP) multicentrico, in aperto per caratterizzare la sicurezza e la tollerabilità di iptacopan (LNP023) in pazienti con Emoglobinuria Parossistica Notturna (EPN) che abbiano completato gli studi di fase 2 e 3 in PNH con Iptacopan"*;
2. di autorizzare gli emendamenti sostanziali relativi allo studio clinico " *Programma di estensione roll-over (REP) multicentrico, in aperto per caratterizzare la sicurezza e la tollerabilità di iptacopan (LNP023) in pazienti con Emoglobinuria Parossistica Notturna (EPN) che abbiano completato gli studi di fase 2 e 3 in PNH con Iptacopan"*;
3. di approvare il protocollo di studio aggiornato - v. 02 del 22.10.2021 - allegato al presente atto per farne parte integrante e sostanziale;
4. di approvare l'addendum n. 1 al Contratto, precedentemente stipulato tra la Società Novartis Farma e l'Azienda ULSS 7 Pedemontana, relativo alla sperimentazione clinica profit di cui sopra, il cui sperimentatore principale è il dr. Eros Di Bona – Direttore dell'U.O.C. di Oncoematologia del P.O. di Bassano, allegato al presente atto per farne parte integrante e sostanziale;
5. di precisare che le modifiche al Contratto in essere riguardano in particolar modo l'allegato A2 , che riguardano importi aggiuntivi come di seguito riportato:
   - € 150,00 per ciascuna trasfusione di globuli rossi (trasfusione RBC) qualora si rendesse necessaria durante il corso dello studio
   - € 200,00 per ciascuna visita non programmata che si rendesse necessaria durante il corso dello studio;
6. di precisare che restano fermi e invariati tutti gli altri termini e condizioni di cui al Contratto approvato con deliberazione n. 1958 del 12.11.2021;

7. di dare atto che il presente provvedimento è soggetto a pubblicazione ai sensi dell'art. 23, lettera d) del D.L.vo 14 marzo 2013 n. 33;

8. di dare atto che la presente deliberazione viene pubblicata all'albo del sito istituzionale dell'Azienda per 10 gg. continuativi, inviata contestualmente al Collegio Sindacale e diventa esecutiva il giorno stesso della sua pubblicazione come da norma regolamentare approvata con deliberazione n. 1386 del 22/07/2022.

NOVARTIS

Novartis Research and Development

LNP023 (Iptacopan)

Clinical Trial Protocol CLNP023C12001B

An open label, multicenter roll-over extension program (REP) to characterize the long-term safety and tolerability of iptacopan (LNP023) in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who have completed PNH Phase 2 and Phase 3 studies with iptacopan.

Document type:	Amended Protocol Version
EUDRACT number:	2020-004385-19
Version number:	02 (Clean)
Clinical Trial Phase:	IIIb
Release date:	22-Oct-2021

Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Alternative Pathway
App	Application
aPTT	Activated Partial Thromboplastin Time
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
BTH	Breakthrough Hemolysis
BUN	Blood Urea Nitrogen
C3	Complement Component 3
C3G	Complement 3 Glomerulopathy
CD	Cluster of Differentiation
CDP	Clinical Development Plan
CFR	Code of Federal Regulations
CK	Creatinine Kinase
cm	Centimeters
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
CO_2	carbon dioxide
CP	Classical Pathway
CRF	Case Report/Record Form (paper or electronic)
CT	Computerized Tomography
CTT	Clinical Trial Team
CV	Coefficient of Variation
CYP	Cytochrome P 450
DDE	Direct Data Entry
DMC	Data Monitoring Committee
EC	Ethics Committees
ECG	Electrocardiogram
EDC	Electronic Data Capture
EORTC	European Organization for Research and Treatment of Cancer
eSAE	Electronic Serious Adverse Event
EOS	End of Study
ER	Emergency Room
ESAs	Erythropoiesis-Stimulating Agents
eSAE	Electronic Serious Adverse Event
EU	European Union
EUDRACT	European Union Drug Regulating Authorities Clinical Trials
EVH	Extravascular Hemolysis
FACIT	Functional Assessment of Chronic Illness Therapy

FACIT-F	FACIT Fatigue Scale
FB	Factor B
Fc	Fragment Crystallizable region
FDA	Food and Drug Administration
FIH	First in Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GPI	Glycophosphatidylinositol
HIF-PHI	Hypoxia-inducible factor prolyl hydroxylase inhibitors
HRQoL	Health-Related Quality of Life
HRU	Healthcare Resources Utilization
hsCRP	High-Sensitivity C-Reactive Protein
IA	Interim Analysis
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
IgA	Immunoglobulin A
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
IVH	Intravascular Hemolysis
Kg	Kilogram
LDH	Lactate Dehydrogenase
MAVE	Major Adverse Vascular Events
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
ml	Milliliter(s)
MRI	Magnetic Resonance Imaging
ms	Milliseconds
NO	Nitric Oxide
NTI	Narrow Therapeutic Index
NYHA	New York Heart Association
OATP	Organic Anion Transporter Protein
ORN	Off-site Research Nurse
P-gp	P-glycoprotein
PD	Pharmacodynamic(s)
PGIS	Patient Global Impression of Severity of Fatigue
PIGA	Phosphatidylinositol N-Acetylglucosaminyltransferase Subunit A
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Hemoglobinuria

PRO	Patient Reported Outcomes
PT	Prothrombin Time
QMS	Quality Management System
QoL	Quality of Life
RBC	Red Blood Cell(s)
REP	Roll-over Extension Program
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Query
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Transfusion Avoidance
UK	United Kingdom
ULN	Upper Limit of Normal
US	Ultra Sound
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 200 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
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study

Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
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 02 (22 October 2021)

Short summary of the amendment rationale and major changes

The purpose of this amendment is to provide more clarity to when the patients will transition from the various parent studies, and to update the treatment discontinuation section in case of confirmed pregnancy as well as the liver event table in line with the parent Phase 3 protocols. In addition this opportunity was used to align the protocol with standardized language and procedures used in iptacopan Phase 3 studies across the PNH program, especially for the information for concomitant and prohibited medication and to implement editorial changes for clarity and consistency in the protocol.

Major revisions are made:

Section 2.1: To update language for intercurrent events

Section 3: To define the end of treatment in the parent studies and to replace study design figure to incorporate the changes in the definition of end of treatment and to change the phrase ‘patient card’ to ‘Participant Safety Card’ as per update to Section 6.2.2.

Section 4.5: To add recent juvenile animal toxicity findings and simplified pre-clinical safety findings, to be aligned with the latest iptacopan IB v.8. To change the phrase ‘patient card’ to ‘Participant Safety Card’ as per update to Section 6.2.2.

Section 5.2: To remove exclusion criteria #1 in order to avoid redundancy.

Section 6.2.1 and Section 6.2.2: To update and align the concomitant, permitted medication section with program harmonized language/Phase III parent study protocols for drug-drug interactions (Permeability glycoprotein (P-gp) substrates, specifically for DOACs, and added dabigatran as prohibited medication) and to remove recommendations related to corticosteroids, anticoagulants, iron supplements, vitamin B12, and folic acid on stable dose prior to screening as specified in the parent protocols.

Section 8: To update the Assessment Table 8.1 with addition of inclusion/exclusion criteria, correct errors, apply consistency in assessments during study visits and add clarification about EOS and EOT.

Text related to the management of iptacopan interruption and follow-up has been deleted. Clarification that patients need to visit the site for an unscheduled visit in case of any sign and symptoms of PNH, breakthrough hemolysis or the requirement of blood transfusion and the required analysis and treatment for those symptoms should be done has been added to the phone call section.

Section 8.1: Clarified that screening can be performed from 30 days prior to the enrollment visit up to the day of enrollment in this study.

Section 8.2: To update language around collection of demographic data considering country specific regulations, to add scientific rationale for the collection of these data as specified by health authorities and to remove PNH clone size required for inclusion as medical history.

Section 8.4.1: hsCRP added to Chemistry category. Type I added to High-Sensitivity flow cytometry category.

Section 8.6: To remove "RBC Transfusion" from Table 8-5 and to add, "Type I, II and III RBCs and PNH clone size in WBCs to High-sensitivity flow cytometry.

Section 9.1.1: To align recommendation on action to be taken for participants who become pregnant during the study to be consistent with Phase III parent study protocols. Section on discontinuation of treatment added for clarity.

Section 10.1.3 : Expanded on the instructions to report SAEs within 24 hours to also include 'immediately, without undue delay, under no circumstances later than' 24 hours.

Section 10.1.4: To add that pregnancy reporting should be done on a "Pharmacovigilance Pregnancy Form".

Section 10.2.2: To add that significant safety findings (e.g., SUSAR) from this study will be shared with the program level DMC.

Section 12.4.3: To update the details for a while on treatment policy

Section 12.5: To update the handling of transfusions for analysis

Section 16.2: Consolidated Table 16-1 and Table 16-2 into Table 16-1 in Appendix 2 for liver events/trigger definitions in PNH and follow up requirements for clarity.

Other changes are mostly editorial as mentioned below to provide more clarity or details:

- Inclusion of International Nonproprietary Name (INN) for LNP023 – iptacopan in parenthesis on the first page and in the Introduction section.
- Minor edits to align text and update applicable sections with the Phase III parent protocols as below:
  - Section 6.6.2: Bacterial removed from the title of the section and change from "Patient card" to " Participant safety card"
  - Section 6.7.1.1: To add clarification that unused medication should be returned at every in-clinic visit in the "Handling of study treatment section".
  - Section 7: 'Home nursing' changed to 'off-site nursing' in this section and throughout the document. 'Pandemic' changed to 'public health emergency'.
- Section 8.5.1: Patient experience interview section. Update of Protocol summary in line with the protocol.
- Update of List of abbreviations and reference sections.
- Correction of typographic errors throughout the document

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. 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.

Amendment 01 (20 July 2021)

Short summary of the amendment rationale

This amendment is implemented to clarify and align the wording related to the timing of roll over of patients from the core studies to this study. Patients are eligible to roll over into this study after they have completed the treatment phase, without undergoing tapering or down titration of iptacopan (LNP023), in the respective core studies to allow for continuous and uninterrupted treatment.

No changes needed to the Informed Consent.

Protocol summary

Protocol number	CLNP023C12001B
Full Title	An open label, multicenter roll-over extension program (REP) to characterize the long-term safety and tolerability of iptacopan (LNP023) in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who have completed PNH Phase II and Phase III studies with iptacopan
Brief title	Long-term safety and tolerability of iptacopan in patients with Paroxysmal Nocturnal Hemoglobinuria
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the long-term safety, tolerability and efficacy of iptacopan in patients with PNH and to provide access to patients who have completed the treatment extension period (without tapering down) of the Phase 2 and Phase 3 trials and derived benefit from iptacopan treatment.
Primary Objective(s)	The primary clinical question of interest is to evaluate the long-term safety and tolerability of iptacopan monotherapy in participants with PNH who have completed the treatment extension period (without tapering down) of the previous Phase II and III clinical studies with iptacopan
Secondary Objectives	The secondary clinical questions of interest are: To evaluate the clinical benefit of iptacopan in maintaining sustained hemoglobin levels ≥ 12 g/dL, in the absence of red blood cell transfusion To evaluate the clinical benefit of iptacopan in maintaining transfusion avoidance (TA) defined as the proportion of participants who remain free from transfusions To evaluate the clinical benefit of iptacopan by assessing the rates of breakthrough hemolysis (BTH) and of Major Adverse Vascular Events (MAVE)
Study design	This study is an open-label, single arm, multicenter, roll-over extension study to characterize long-term safety, tolerability and efficacy of iptacopan and to provide access to iptacopan to patients with PNH who have completed the treatment extension period (without tapering down) of the Novartis-sponsored Phase II or III studies with iptacopan
Study population	The study will enroll patients who have been diagnosed with PNH and have completed the treatment extension period (without tapering down) of Phase II iptacopan studies CLNP023X2201, CLNP023X2204 or Period 4 of CLFG316X2201 (switching from LFG316 to iptacopan) or Phase III iptacopan studies (CLNP023C12302 and CLNP023C12301). Approximately 165 study participants will be enrolled in the study.
Key Inclusion criteria	• Male and female participants ≥ 18 years of age with a diagnosis of PNH who completed the treatment extension period (without tapering down) of Phase II iptacopan studies (CLNP023X2204, CLNP023X2201)or Period 4 of CLFG316X2201 or Phase III (CLNP023C12302 and CLNP023C12301) clinical studies at the time point of enrollment visit in this roll over extension. • Prior vaccinations against *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* infections should be up to date (i.e., any boosters required administered according to local regulations). • Per investigator's clinical judgement, the patient may benefit from continued treatment with iptacopan and has been clinically stable on iptacopan monotherapy for at least 3 months.
Key Exclusion criteria	• Any comorbidity or medical condition (including but not limited to any active systemic bacterial, viral or fungal infection or malignancy) that in the opinion of the investigator could put the subject at increased risk or potentially confound study data.. • History of recurrent invasive infections caused by encapsulated organisms, such as Neisseria meningitidis, Streptococcus pneumoniae or Haemophilus influenzae.

	• Female participants who are pregnant or breastfeeding, or intending to conceive during the course of the study. • Women of childbearing 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 investigational drug.
Study treatment	iptacopan (LNP023)
Treatment of interest	Participants will be receiving open label oral iptacopan 200 mg b.i.d monotherapy
Efficacy assessments	• Hemoglobin, reticulocytes, LDH and other PNH-related signs and symptoms laboratory parameters • Red blood cell transfusions • Breakthrough hemolysis • Major Adverse Vascular Events (MAVE)
Key safety assessments	• Laboratory evaluations in blood and urine • Adverse event monitoring • Electrocardiogram (ECG) • Coagulation panel/thrombosis
Other assessments	An assessment of patient-reported outcomes is planned in this trial using EORTC QLQ-C30, EQ-5D-5L, FACIT-Fatigue and PGIS
Data analysis	The primary and secondary analyses will use the safety set that includes all participants who received at least one dose of study treatment. The Aalen-Johansen estimator will be used to derive the estimator defined in the estimand section. Other safety outcomes will be presented descriptively. The following endpoints will be used to assess the long-term clinical benefit of iptacopan in patients with PNH: 1 Response defined as maintaining sustained hemoglobin levels ≥ 12 g/dL in the absence of transfusions evaluated over yearly follow up intervals 2 Absence of administration of packed-red blood cell transfusions evaluated over yearly follow up intervals 3 Occurrences of breakthrough hemolysis and of Major Adverse Vascular Events (MAVE) occurring evaluated over yearly follow up interval Descriptive statistics of hemoglobin levels, transfusion avoidance, breakthrough hemolysis and Major Adverse Vascular Events (MAVE) will be provided by visit/time and cohort. The clinical benefit of iptacopan in maintaining sustained hemoglobin levels ≥ 12 g/dL, in the absence of red blood cell transfusion and in maintaining transfusion avoidance (TA) defined as the proportion of participants who remain free from transfusions will be evaluated by a logistic regression model. The covariates include sex, age (categorical), indicator variable of hemoglobin above 12 g/dL at enrollment and cohort indicator. The proportion of responders will be derived from the estimated probabilities derived from the model fit as the mean of the individual logistic regression model predictions, together with 95% confidence intervals, where the standard error will be derived by the bootstrap method. The estimation of rates of breakthrough hemolysis (BTH) of Major Adverse Vascular Events (MAVE) will be carried out using negative binomial models.
Key words	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 (IVH), 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-acetyl glucosaminyl transferase subunit A (PIGA) gene (Brodsky 2014). Consequently, PNH blood cells lack 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 cell lysis.

The clinical spectrum of PNH varies and signs and symptoms include anemia, thrombosis, smooth muscle dystonia, fatigue, hemoglobinuria, chronic kidney disease and pulmonary hypertension. The clinical presentation is driven by uncontrolled complement activation on CD55 and CD59 deficient PNH type RBCs culminating with hemolysis and the release of free hemoglobin, and platelet activation (Hill et al 2013). Hemolysis results in release of intracellular hemoglobin and lactate dehydrogenase (LDH) into 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 morbidity and mortality in patients with PNH and can occur at any site; although venous is more common (80–85%), it can also be arterial (15–20%) (Hillmen et al 2007).

Eculizumab and ravulizumab (engineered from eculizumab by 4 amino acid substitutions in the complementarity-determining and Fc regions resulting in a significantly prolonged half-life and dosing interval) are approved anti-C5 antibody therapies for the treatment of PNH and the current standard of care (SoC) where available. The introduction of eculizumab has significantly reduced the thromboembolic risk of PNH patients improving morbidity and mortality and largely improved the quality of life (QoL) of PNH patients.

Although the anti-C5 antibody therapy is generally effective in treating intravascular hemolysis, there remains a high unmet medical need for PNH. Different authors reported heterogeneous hematological response with eculizumab and a substantial proportion of patients not achieving normal or near normal hemoglobin levels (Risitano et al 2009, Hill et al 2010, DeZern et al 2013, McKinley et al 2017). The residual anemia in eculizumab treated PNH patients is attributed to C3-mediated extravascular hemolysis. The progressive deposition of C3 fragments on PNH erythrocytes eventually leads to chronic extravascular hemolysis (Risitano and Marotta 2018).

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

Iptacopan (LNP023) is a novel, oral, small molecular weight compound that inhibits factor B (FB). FB is a key protease of the complement alternative pathway (AP). Inhibition of FB with oral iptacopan has the potential to prevent both intra- and extravascular hemolysis, and therefore, offer therapeutic benefits over and above the current SoC. Additionally, the oral route of administration offers patients an advantage compared to the intravenous route of administration of current SoC.

Two Phase II studies with iptacopan are ongoing which provide evidence of iptacopan's effect on inhibiting both intra- and extravascular hemolysis. In the CLNP023X2201 Phase II study, PNH patients with signs of active hemolysis and anemia despite optimal eculizumab therapy were enrolled and treated with iptacopan at a dose of 200 mg b.i.d (cohort 1) concomitantly with the approved SoC. At the planned interim analysis (IA) of 10 participants completing 13 weeks of combined treatment, the results demonstrate clinical benefits that included:

- LDH reduction, normalization of hemoglobin in the majority of patients in the absence of red blood cell transfusions, and control of extravascular hemolysis (reduction of bilirubin, reticulocytes and increase in haptoglobin).
- Reduced C3 deposition and prolonged survival of PNH type red blood cells.
- Sustained inhibition of the complement alternative pathway and profound and sustained reduction of Fragment Bb.

The protocol included the option of modifying or discontinuing eculizumab treatment after 6 months of add-on treatment with iptacopan. At the time of the IA, 5 out of 10 participants have discontinued eculizumab treatment and continued with iptacopan monotherapy for up to two months with no signs of breakthrough hemolysis and transfusion independence.

The second ongoing Phase II study, CLNP023X2204, enrolled anti-C5 treatment-naïve PNH patients with signs of active hemolysis. Participants were treated with iptacopan monotherapy in two cohorts with forced titration after 4 weeks (from 25 to 100 mg; and from 50 to 200 mg). A planned IA was conducted when 7 of the 8 participants completed 8 weeks of treatment (4 weeks on lower dose and 4 weeks on higher dose). The preliminary results with iptacopan monotherapy showed:

- LDH reduction in all patients, hemoglobin increases in the majority of patients in absence of red blood cell transfusions, and normalization of intra- and extravascular hemolysis (increase in haptoglobin and decrease in reticulocytes and bilirubin).
- As expected with iptacopan monotherapy there was no C3-fragment deposition on PNH type RBCs but an increase in PNH clone size, indicating prolonged survival of PNH type RBCs.

For further details on the Phase II studies, please refer to the Investigator Brochure. CLNP023C12302, a Phase III study in PNH patients with residual anemia despite anti-C5 therapy will assess the efficacy and safety of iptacopan compared to current SoC for demonstration of superior efficacy of iptacopan. A second Phase III study CLNP023C12301 will assess the efficacy and safety of iptacopan in patients naive to complement inhibition.

To ensure continuous treatment of PNH patients upon completion of the Phase II and Phase III studies with iptacopan and to collect long-term safety, tolerability and efficacy data, patients will be offered the opportunity to enroll in this open-label roll-over extension study and receive open-label treatment of 200 mg iptacopan b.i.d. PNH patients resistant to eculizumab are

currently completing a Phase II study (CLFG316X2201) with a Novartis anti-C5 monoclonal antibody LFG316. Within this study, patients will be offered to switch from LFG316 to iptacopan since the development of LFG316 was terminated. Novartis considers iptacopan to be a suitable treatment option for eculizumab resistant PNH patients who participated in this study and offers rolling-over these patients after having switched from LFG316 to iptacopan into this study.

In summary, this study will provide continued access to iptacopan for participants from the PNH Phase II and III studies through 3 years post last patient first visit (LPFV) of the roll-over-extension study or until iptacopan becomes commercially available in the respective country, whichever is shorter. It is noteworthy to mention that this roll-over extension study will run in parallel to the Phase II (CLNP023X2201 and CLNP023X2204) and Phase III (CLNP023C12301 and CLNP023C12302) studies.

1.2 Purpose

The purpose of this roll-over extension study is to evaluate the long-term safety, tolerability and efficacy of iptacopan in patients with PNH and to provide access to patients who have completed the treatment extension period (without tapering down) Phase II (CLNP023X2201 and CLNP023X2204) and Phase III(CLNP023C12301 and CLNP023C12302) trials and derived benefit from iptacopan treatment.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the long-term safety and tolerability of iptacopan monotherapy in participants who have completed the treatment extension period (without tapering down) of the previous Phase II and III clinical studies with iptacopan	• Safety evaluations including but not limited to adverse events/serious adverse events, safety laboratory parameters, vital signs, etc., through End of Study visit
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the clinical benefit of iptacopan in maintaining sustained hemoglobin levels ≥ 12 g/dL, in the absence of red blood cell transfusion	• Response defined as maintaining sustained hemoglobin levels ≥ 12 g/dL in the absence of transfusions evaluated over yearly follow up intervals
• To evaluate the clinical benefit of iptacopan in maintaining transfusion avoidance (TA) defined as the proportion of participants who remain free from transfusions	• Absence of administration of packed-red blood cell transfusions evaluated over yearly follow up intervals
• To evaluate the clinical benefit of iptacopan by assessing the rates of breakthrough hemolysis (BTH) and of Major Adverse Vascular Events (MAVE)	• Occurrences of breakthrough hemolysis and of Major Adverse Vascular Events • (MAVE) occurring evaluated over yearly follow up intervals
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To evaluate the clinical benefit of iptacopan by long term monitoring of Health Care Resources Utilization (HRU)	• Rates of hospitalizations, and emergency room visits over yearly follow up intervals

Objective(s)	Endpoint(s)
• To assess the long-term effect of iptacopan in participant-reported overall fatigue severity and health-related quality of life	• Change from Day 1 in participant-reported outcomes scores for FACIT-Fatigue, PGIS, EORTC QLQ-C30, and EQ-5D-5L evaluated over yearly follow up intervals
• To further assess the participants' experience with the study medication from previous studies	• Participants responses to a semi-structured 'Patient Experience Interview' designed to further elicit the patient experience with the study medication
• To assess the long-term effect of iptacopan on PNH clone size in RBCs and White Blood Cells (WBC)	• PNH clone size in red blood cells (percentage of Type I, II and Type III RBCs) and in WBCs (granulocytes/monocytes) collected between Day 1 and End of Study (EOS) visit

2.1 Primary estimands

The purpose of the trial is to provide post trial access to treatment with iptacopan and, as a reflection of this, the main clinical question is the evaluation of the long-term safety and tolerability of iptacopan in PNH participants who have completed the treatment extension period (without tapering down) of previous Phase II and III clinical studies with iptacopan , with the safety endpoints including adverse events/serious adverse events, safety laboratory parameters, vital signs, through End of Study visit. The definition of an estimand using the totality of safety data is impractical, however, it is useful to apply the estimand framework and focus on Adverse Events (AE) of special interest. The clinical question that may be addressed is what is the probability of experiencing AEs of special interest in all participants when under iptacopan treatment?

The justification of this primary estimand is that it will capture long-term safety and tolerability of study drug using clinically relevant safety evaluations collected in this study.

The primary estimand is described by the following attributes:

- Population: PNH-patients who have completed the treatment extension period (without tapering down) of previous Phase II and III clinical studies with iptacopan and have been clinically stable on iptacopan monotherapy for at least 3 months. Further details about the population are provided in Section 5.
- Treatment of interest: the investigational treatment iptacopan 200 mg b.i.d. Further details about the investigational treatment are provided in Section 6.
- Intercurrent events: Discontinuation from treatment or discontinuation from study will be handled with while on treatment policy. Dosing events such as altering the frequency of study medication intake and transfusions will be handled with a treatment policy approach, meaning that participants will be considered as effectively continuing with the study treatment regardless of the occurrence of these events.
- The summary measure: the probability of AEs of special interest during study follow up estimated by the cumulative incidence function.

2.2 Secondary estimands

The population associated with the secondary estimands is the same as for the primary estimands. The proposed approach in the case of transfusions will be described in the endpoints

definition, while breakthrough hemolysis events, and MAVEs will be handled with a treatment policy strategy.

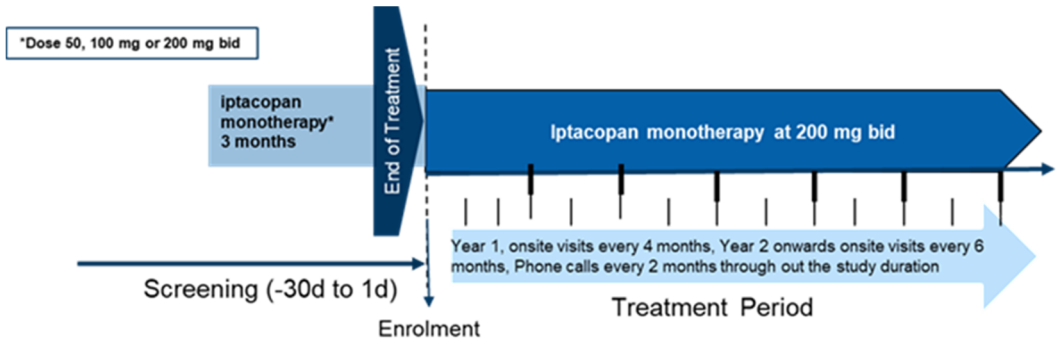
The secondary estimands are defined by the evaluation of treatment effects on the following endpoints and summary measures:

- Proportion of participants responders maintaining hemoglobin level ≥ 12 g/dL, in the absence of transfusions at yearly follow up intervals. The summary measure is the probability of being a responder, estimated as proportion on iptacopan treatment in the studied population.
- Proportion of participants (responders) not receiving any transfusions during the yearly follow up (Transfusion Avoidance). The summary measure is the proportion of study participants.
- Rates of Major Adverse Vascular Events (MAVE) occurring at yearly follow up intervals. The summary measure is occurrences per year.

3 Study design

Study CLNP023C12001B is a Phase IIIB, open-label, single arm, multicenter, roll-over extension study to characterize long-term safety, tolerability and efficacy of iptacopan and to provide access to iptacopan to patients with PNH who have completed the treatment extension period in a Novartis-sponsored Phase II or Phase III studies (without tapering down) with iptacopan (see Figure 3-1 below). For patients rolling over from the LFG316 study, patients will be switched to iptacopan in the previous study for at least 3 months so that they will be eligible for this study.

Figure 3-1 Study design



Approximately 165 study participants will be enrolled in the study.All participants must provide written informed consent prior to start of any study-related activities in this roll-over trial.

The participant may be enrolled in the CLNP023C12001B study after confirmation of eligibility. It is foreseen that all eligible participants will enter the study at the latest on the day of End of treatment (EOT) of the preceding study. For the purpose of this study protocol and throughout the document, the end of treatment (without tapering down) in the preceding study refers to:

- last treatment visit in the treatment extension period of CLNP023X2201 and CLNP023X2204

- last day in treatment (extension) period 4 in CLFG316X2201
- last day in the treatment extension period in CLNP023C12302 and CLNP023C12301

To ensure a seamless roll-over and continued access to iptacopan, it is recommended that after signing the study Informed Consent Form (ICF), the screening visit be scheduled between 30 days prior to the EOT up to the same day as EOT of the parent study. Inclusion and exclusion criteria will be assessed to verify the participants' eligibility for enrollment into the study.

The assessments obtained at the EOT of the parent study, and those required for this study, will not be repeated at the **screening/enrollment** visit. Assessments obtained at the screening/enrollment visit will represent the baseline for the study. The baseline value is defined to be the last assessment at or prior to study treatment. If any of the assessments required for this study are not included as part of the parent study's EOT, assessments will be done as per Table 8-1. These data will be used to fulfill the screening/enrollment baseline data collection.

If the participant fails screening for any reason, the participant can be re-screened once as described in Section 8.1.

Laboratory assessments will be conducted by a central laboratory. Safety assessment will include, but not be limited to, safety laboratory tests, vital signs (including body temperature), ECG, concomitant medication changes/updates and adverse events (AEs). Efficacy assessments will include assessment of hemoglobin and LDH as part of the safety lab assessments, requirement for and units of pRBC transfusion, occurrence of breakthrough hemolysis and MAVE. During the scheduled visits (every 4 months in the first year and every 6 months from second year and beyond) at the clinic, participants will complete the ePRO, FACIT-Fatigue and PGIS, and every 12 months the EORTC QLQ C-30 and EQ5D.

The onsite visit frequency will be every 4 months in the first year and every 6 months from 2nd year and beyond, with follow-up phone calls every two months to collect a set of information to bridge the time between the scheduled visits while profiting from the participants more accurate reporting about recent events/changes. Please, refer to Section 8 for details.

Vaccinations need to be verified as current against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. These vaccinations should have been administered for the parent studies and will not be required unless a booster is needed (per vaccine labeling and local guidelines) or if there is concern about loss of protection. Vaccines should cover as many serotypes as possible (including meningococcal serotypes A, C, Y, W-135 and B). To minimize participants burden the use of multivalent vaccines is recommended, as locally available and per local guidelines and regulations (e.g., quadrivalent vaccine for *N. meningitidis* which covers serotypes A, C, Y and W-135 and Pneumovax-23 which covers 23 *S. pneumoniae* serotypes). For the vaccination type and booster requirements use local guidelines, and locally available vaccines (and refer to the package insert of those, or local guidelines).

Because of the known risk of infections caused by encapsulated bacteria in patients treated with complement inhibitors, particularly infections caused by *Neisseria meningitidis*, all participants will be provided with a Participant Safety Card (See Section 6.6.2). 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.

The study will provide iptacopan at a dose of 200 mg b.i.d to participants until

- participant no longer derives benefit from iptacopan according to the investigator, or
- the benefit-risk profile of the product in PNH is no longer positive, or
- the product becomes commercially available in a specific country following product launch and subsequent reimbursement for PNH, where applicable, or
- if a marketing application or reimbursement of an investigational product is rejected/not pursued in a region/country for the indication under study, or
- 3 years after LPFV

whichever is sooner.

For this study, End of Treatment (EOT)/ End of study (EOS) is defined as the point/time of last study treatment administration and when the participant completes the final study evaluation.

Following product launch and subsequent reimbursement in the country of residence, where applicable, the participant will be directed by the treating physician to receive the product through typical commercial channels locally. In case approval is not obtained in a country, the participant will be switched to the local SoC (either anti-C5 antibody therapy, if available, or locally available supportive care).

4 Rationale

4.1 Rationale for study design

This is a multi-center, roll-over extension program for PNH patients who have completed the treatment extension period (without tapering down) of the prior Phase II and III studies with iptacopan and are judged by their study investigator to derive benefit from iptacopan treatment. The study will enable collection of long-term safety, tolerability, and efficacy data of iptacopan. The open-label design is appropriate to provide participants the opportunity to gain access to treatment with iptacopan until marketing authorizations are received and the drug product becomes commercially available and/or is reimbursed in the country according to local rules for post-trial access of the participant's residence. The study is currently planned to run for 3 years after LPFV.

4.2 Rationale for dose/regimen and duration of treatment

The iptacopan dose of 200 mg b.i.d. as continuous treatment has been selected for this study primarily based on the available efficacy and safety data obtained at the time of IAs from the two ongoing Phase II PNH studies and is supported by PKPD modeling results. Furthermore, the dose of 200 mg b.i.d is the dose chosen for the two Phase III studies and hence the expected dose to be commercialized should iptacopan be approved.

In the CLNP023X2201 study, two iptacopan doses were assessed in patients with active hemolysis despite treatment with eculizumab. Iptacopan at a dose of 200 mg b.i.d. was administered to 10 PNH participants (cohort 1) and at a dose of 50 mg b.i.d. to 6 PNH

participants (cohort 2). An 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.

In the CLNP023X2204 study, four iptacopan doses were assessed in anti-C5 antibody treatment naive patients. Study participants received iptacopan monotherapy with sequential dose increments at Week 4 from 25 mg b.i.d. to 100 mg b.i.d (sequence 1) or 50 mg b.i.d. to 200 mg b.i.d. (sequence 2). IA was conducted after 13 participants were randomized and completed Week 8 visit assessments.

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

Participants treated with iptacopan 200 mg b.i.d. (as add-on to eculizumab) had clinical benefits not achieved with eculizumab including control of IVH demonstrated by LDH reduction, control of EVH demonstrated by reduction of bilirubin, reticulocytes and increase in haptoglobin resulting in normalization of hemoglobin in the majority of participants in the absence of red blood cell transfusions. The hematological response participants achieved with iptacopan 200 mg b.i.d. add-on therapy was maintained with iptacopan monotherapy during the extension period when eculizumab treatment was discontinued in 5/10 participants (at the time of the IA) who continued with iptacopan monotherapy. Following the IA, two additional participants discontinued eculizumab treatment. C3 deposition was fully reversed by addition of iptacopan at a dose of 200 mg b.i.d. and survival of PNH red blood cells prolonged further supporting control of EVH by iptacopan at a dose of 200 mg b.i.d. There was sustained inhibition of the complement alternative pathway and profound and sustained reduction of Fragment Bb demonstrating target engagement.

Participants receiving iptacopan monotherapy showed that iptacopan at dose levels ≥ 25 mg b.i.d. had LDH reduction of more than 60% from baseline in all participants and early transfusion-free hemoglobin increase in the majority of participants. Other hemolysis relevant laboratory values indicated that iptacopan administered as monotherapy controls both intra- (LDH reduction) and extravascular hemolysis (decrease of reticulocytes and bilirubin, increase in haptoglobin).

Preliminary information from cohort 2 in CLNP023X2201 suggests that the 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 dose of 200 mg b.i.d (add-on treatment to eculizumab).

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

The exposure-response model developed with data from the First In Human (FIH) study with iptacopan in healthy volunteers predicts that a dose of about 200 mg b.i.d. would be needed to achieve > 90% inhibition of the alternative pathway (Wieslab assay) in > 70% of subjects. Given the risk of (breakthrough) 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 latest iptacopan IB.

The duration is chosen to allow the study participants to receive treatment until the drug becomes available for the participant which is approximately 36 months after the LPFV.

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

Not applicable

4.4 Purpose and timing of interim analyses/design adaptations

In order to provide long term safety and efficacy data interim reports of data maybe produced as required while the study is ongoing.

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 iptacopan IB (Section 15). The safety results from the CLNP023X2201 study (PNH patients treated with eculizumab) as well as CLNP023X2204 study (anti-C5 treatment-naïve PNH patients) are summarized in the IB (Section 15). Iptacopan at a dose of 200 mg b.i.d. has been safe and well tolerated in these studies.

Appropriate eligibility criteria, as well as study specific stopping rules for the investigational drug with guidance to ensure continued treatment of PNH are included in this protocol. Recommended guidelines for monitoring and management of infections are provided in Section 6.6.2. The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures by participants, including vaccinations prior to starting study treatment, close monitoring and appropriate risk mitigation strategies. This study does not involve any risks regarding study procedures (e.g. no invasive research procedures). One theoretical risk 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.

Iptacopan did not show any mutagenic, teratogenic or genotoxic potential in a 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 childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

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

- Increase of hemoglobin to normal/near normal values in the absence of red blood cell transfusions

- Control of extravascular hemolysis
- Reduction of LDH

It is expected that the improved hematological response upon iptacopan treatment will translate into improved quality of life, most importantly an improvement in fatigue. More details about the preliminary results of the Phase II studies can be found in Section 1.1 and the IB.

The main potential safety risk for complement inhibitors is infections, particularly those caused by encapsulated bacteria. To date, no increased risk of infections has been reported in preclinical studies with iptacopan and one infection caused by encapsulated bacteria has been reported in clinical trials.

Translational research has shown that the serological response to meningococcal infection is maintained during AP blockade but that it is markedly reduced after blockade of the classical pathway (CP) with C5-blockers like eculizumab. Serum bactericidal activity studies of serum from vaccinated patients against meningococci showed that C5 inhibitors block killing of meningococci, whereas AP inhibitors have less inhibitory effect on meningococcal killing (Konar and Granoff 2017). Vaccination is therefore predicted to be an effective mitigation strategy to reduce the risk for individuals treated with iptacopan. Participants will be vaccinated against meningococcal, pneumococcal and *H. influenzae* infections according to local guidelines and vaccine 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 these symptoms. The investigator will employ clinical judgement to determine an appropriate course of treatment. Antibiotic treatment should be started immediately for infections caused by encapsulated bacteria, with action taken with study medication considered on a case-by-case basis. Recommended guidelines for monitoring and management of infections (including COVID-19) are provided in Section 6.6.2.

Other safety risks are based on preclinical data, with no relevant findings in clinical studies performed to date. There are potential risks of testicular effects, bone marrow toxicity with severe anemia, aorta mineralization and increased heart weight (seen only in very young dogs and not in adult dogs or adult other species) and thyroid changes. The preclinical findings are described in more detail in the IB.

In addition, 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 was well tolerated. Overall, no deaths or Serious Adverse Events (SAE) were reported, no imbalances from placebo in rates of AEs in the first in human study and no AEs which led to study drug discontinuation. Similarly, data from the two ongoing Phase 2 studies in patients with PNH (29 participants exposed to iptacopan) and studies carried out in complement-driven renal disease (IgA nephropathy study, in which 32 participants were exposed to iptacopan for 3 months at various dose levels up to 200 mg b.i.d. in Part 1 and 55 patients have been exposed up to 6 months in Part 2; and the C3G study, in which more than 27 participants were exposed to iptacopan for up to 3 months at various dose levels up to 200 mg b.i.d.) confirmed that the safety profile was favorable and supported continuation of development.

In summary, the benefit risk relationship for iptacopan 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 patients who have been diagnosed with PNH and have completed the treatment extension period of (without tapering down) of the Phase II studies CLNP023X2201, CLNP023X2204, or Period 4 of CLFG316X2201 (switching from LFG316 to iptacopan) or Phase III iptacopan studies (CLNP023C12302 and CLNP023C12301).

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any study specific assessment is performed.
2. Male and female participants ≥ 18 years of age with a diagnosis of PNH who have completed the treatment extension period (without tapering down) of Phase II iptacopan studies (CLNP023X2204, CLNP023X2201), Period 4 of CLFG316X2201 or Phase III (CLNP023C12302 and CLNP023C12301) clinical studies at the time point of enrollment visit in this roll over extension.
3. Prior vaccinations against *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* infections should be up to date (i.e. any boosters required administered according to local regulations).
4. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
5. Per investigator's clinical judgement, the patient may benefit from continued treatment with iptacopan and has been clinically stable on iptacopan monotherapy for at least 3 months.

5.2 Exclusion criteria

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

1. .
2. Any comorbidity or medical condition (including but not limited to any active systemic bacterial, viral or fungal infection or malignancy) that, in the opinion of the investigator, could put the subject at increased risk or potentially confound study data
3. History of recurrent invasive infections caused by encapsulated organisms, such as *Neisseria meningitidis, Streptococcus pneumoniae* or *Haemophilus influenzae*.
4. Female participants who are pregnant or breastfeeding or intending to conceive during the course of the study.
5. Women of childbearing 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 investigational drug. Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/ vaginal suppository
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

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

6. Concomitant treatment with any complement inhibitor (eg, eculizumab, ravulizumab) and those listed in Section 6.2.2.
7. History of hypersensitivity to iptacopan or its excipients or to drugs of similar chemical classes.
8. History of hematopoietic stem cell transplantation
9. Known or suspected hereditary complement deficiency

6 Treatment

Participants will be receiving open label oral iptacopan (LNP023) 200 mg b.i.d monotherapy.

6.1 Study treatment

Participants will take 200 mg iptacopan (LNP023) b.i.d. monotherapy after rolling over in this extension study.

6.1.1 Investigational and control drugs

In this study, the "study treatment" includes only the investigational drug, iptacopan (LNP023).

Table 6-1 Investigational Drug

Investigational Drug	Pharmaceutical dosage form	Route of administration	Supply type
iptacopan (LNP023), 200 mg	Hard gelatin capsule	Oral use	Open label, participant specific kits
iptacopan (LNP023), 10* mg	Hard gelatin capsule	Oral use	Open label, participant specific kits
* used only during tapering down of iptacopan (LNP023) dose, see Section 9.1.1			

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.1.3 Supply of study treatment

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

6.1.4 Treatment arms/group

All participants will be assigned at visit Day1 (Enrollment) to iptacopan (LNP023) 200 mg b.i.d, as this is a single arm open label study.

6.1.5 Treatment duration

The planned duration of treatment with iptacopan (LNP023) is approximately 36 months after the LPFV or until the product launch and/or subsequent reimbursement (where applicable). Where reimbursement is not possible in a country, iptacopan (LNP023) will be provided to Novartis trial participants until the product is launched in that country.

Participants who have taken part in the Phase II or III studies and may derive clinical benefit from the continued treatment with iptacopan (LNP023) based on the investigator's evaluation will receive post-trial access and enroll in this roll-over extension study. This means the provision of treatment is available to trial participants following their completion of the treatment extension period of the parent trial. Treatment with iptacopan (LNP023) will be provided until one of the following conditions is met: participant no longer derives clinical benefit per investigator's clinical judgement, investigator discontinues participant's treatment, the Phase III studies do not show positive benefit/ risk profile, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy 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. 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

During the study, it is recommended to adjust the dose and/or discontinue dosing of erythropoiesis-stimulating agents (ESAs)and/or hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) based on participant's hemoglobin level as per local guidelines and practice. As a general guidance, it is recommended to reduce the ESA and/or HIF-PHI dose by 50% if hemoglobin is ≥12 g/dL and/or to stop ESA dosing if hemoglobin is ≥13 g/dL. Use particular caution in participants with coexisting cardiovascular disease, stroke and chronic kidney disease.

Iptacopan has been shown to have a weak inhibition potential for the liver uptake transporter OATP1B1. Calculation revealed that the exposure (AUC) of respective sensitive substrates may be increased by <1.5 fold. Although the expected effect on the exposure of respective co-medications is small and may not be clinically relevant, it is recommended to combine 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, the direct oral anti-coagulation drugs apixaban, rivaroxaban and edoxaban which are P-gp substrates should be used with caution. For edoxaban a staggered dosing (see below) is recommended, in particular for participants with impaired kidney function.

For narrow therapeutic index (NTI) immunosuppressants (e.g., cyclosporine, sirolimus, tacrolimus on a stable dose) which are substrates for the efflux transporter P-gp with no alternative treatment available a staggered dosing approach is recommended. This can be accomplished by administering the respective comedication **>3hrs following oral** (LNP023) **iptacopan administration**. Alternatively, compounds with a shorter Tmax of around < 2 hours (i.e., fast absorption) can be given **>1hr prior to oral** (LNP023) **iptacopan administration**. 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 patients receiving immunosuppressants (stable dose) 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 (LNP023) administration.

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. 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.

Table 6-2 Prohibited Medications

Medication	Action
Live Vaccination	Prohibited for the entire study treatment duration
Gemfibrozil, a potent inhibitor of metabolizing enzymes CYP2C8, UGT1A and liver uptake transporter OATP1B1	Gemfibrozil must be stopped 48 hours before first iptacopan dose until end of iptacopan treatment and replaced with another appropriate medication used for that indication.
Strong CYP2C8 inhibitors (e.g Clopidogrel)	Comedication must be stopped 7 days before the first iptacopan dose untill the end of iptacopan treatment and replaced by another appropriate medication used for that indication.
Sensitive/ narrow therapeutic index P-gp substrates (e.g. digoxin, quinidine, paclitaxel, fentanyl, phenytoin)	Comedication must be interrupted 48 hours before the first iptacopan dose. If no alternative treatment is available, a staggered dosing approach is recommended (refer to Section 6.2.1.1)
Anticoagulant drug dabigatran which is a P-gp substrate	Comedication must be interrupted 48 hours before the first iptacopan dose. Should not be used in combination with iptacopan and replaced with another appropriate medication used for that indication as a staggered dosing is also not recommended.

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 BTH requiring rescue medication in the opinion of the investigator, rescue medication is allowed and should be managed by the investigator 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. Given the fact that patients will be enrolling into the study from one of four other studies, participants will be given a new Participant No. for this roll over extension study.

A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No. Additional details regarding rescreening are provided in Section 8.1.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study; participants will receive single arm open label iptacopan 200 mg b.i.d.

An Interactive Response Technology (IRT) System will be used to enroll participants into the study and dispense study drug. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT system will prompt the investigator to enter the participant's Participant No. into the system and then assign a uniquely numbered medication kit for the first iptacopan treatment to be dispensed to the participant on Day 1. The IRT will be used to assign additional uniquely numbered medication kits at all designated treatment dispensing visits of the trial.

6.4 Treatment blinding

Treatment is not blinded to participants, investigator staff, persons performing the assessments, and the clinical trial team (CTT).

6.5 Dose escalation and dose modification

Iptacopan will be administered at 200 mg b.i.d. and there are no dose adjustments planned. Please refer to Section 9.1.1 and Section 6.7.2 for recommended procedures if iptacopan is to be permanently discontinued.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

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

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

Participants on iptacopan 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 treatments dispensed and returned must be recorded in the Drug Accountability Log

6.6.2 Recommended treatment of adverse events

Infections

All study 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 serious bacterial infection, participants should be immediately considered for emergency evaluation and empirically treated with an appropriate antibiotic course. In case of any severe infection (bacterial or non-bacterial including COVID-19), 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).

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 serious bacterial infection and to contact the investigator or local physician immediately in case of suspicion of infection, in which case antibiotic treatment should be started as soon as possible.

6.7 Preparation and dispensation

Each study site will be supplied with iptacopan (LNP023) in packaging as described under investigational and control drugs section.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of 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 4 (in the first treatment year) and 6 (from the second treatment year and beyond)-months 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.

Implementation will need to be discussed with Novartis.

The dispatch of study drug from the study site to the subject's home/preferred address is allowed providing the following is met

1. adherence to labelled storage conditions during transportation
2. communication with the subject that allows the shipment and receipt of the study drug
3. compliance with Good Clinical Practice (GCP)

If the option of study drug home delivery is utilized then the investigator/site staff will confirm the participant's well-being and perform the required protocol assessments. Upon delivery, the study drug will be verified as received in good condition and within the acceptable temperature range. All records of shipments, receipt, returns, and drug accountability will be maintained by the study site in compliance with GCP.

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 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 and additional treatment

6.7.1.1 Handling of study treatment

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

6.7.1.2 Handling of additional treatment

NA

6.7.2 Instruction for prescribing and taking study treatment

Participants should take iptacopan (LNP023) at the dose of 200 mg twice per day (in the morning and in the evening) at approximately the same times each day and ideally with 12-hours interval between morning and evening dosing. Iptacopan (LNP023)10 mg should be provided as tapering down medication in case of discontinuation. For tapering down, participant should take three capsules in the evenings for 7 days, and one capsule a day in the evenings for 7 further days.

Table 6-3 Iptacopan (LNP023) dose and treatment schedule

Dose level	Posology	iptacopan (LNP023) dose strength
200 mg b.i.d.	1 capsule twice daily	200 mg
10 mg b.i.d*	3 capsules daily for 7 days then1 capsule daily for 7 days	10 mg
*Tapering down in case of discontinuation		

Participants should be instructed to swallow capsules whole and not to chew or open them. Each dose should be taken with a glass of water, and irrespective of food intake.

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 usual daily dosing. That dose should be omitted and the subject should continue treatment with the next scheduled dose.

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

On study visit days, the participants should not take that day's morning dose until instructed by the site staff following the completion of all study assessments. All kits of study treatment assigned by the IRT will be recorded in the IRT system.

7 Informed consent procedures

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

If applicable, in cases where the participants' 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 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 International Council for Harmonization of Technical Requirements for

Pharmaceuticals for Human Use (ICH) GCP guidelines E6 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 prevails 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:
- As applicable, Pregnancy Outcomes Reporting Consent for female subjects or the female partners of any male subjects who took study treatment.
- Informed Consent Form for Optional off-site research nursing visits during a Public Health Emergency

Women of childbearing 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.

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

Participants might be asked to complete an interview /questionnaire to provide feedback on their clinical trial experience in the core studies.

8 Visit schedule and assessments

For scheduled site-visits (every 4 months in the first year and every 6 months on following years)

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

Unless specified 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) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

For participants who permanently discontinue iptacopan, the Investigator should refer to Section 9.1.1 for details on the recommended procedures.

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, and for sites not participating in Off-site Research Nursing (ORN) visits (Section 8.6), 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 phone-visits (every 2 months between site-visits)

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

The investigator site's personnel will call the participant as outlined in Table 8-1 or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

In case of any sign and symptoms of PNH, breakthrough hemolysis or the requirement of blood transfusion an unscheduled visit should be scheduled and the required analysis and treatment such as blood transfusion for those symptoms should be done.

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment 1st year**							**Treatment 2nd year and beyond**		**Study Completion**
Visit Name	**Screening**	**Enrollment**	**Mon-2 (Phone call)**	**Mon-4 (onsite visit)**	**Mon-6 (Phone call)**	**Mon-8 (onsite visit)**	**Mon-10 (phone call)**	**Mon-12 (onsite Visit)**	**Month 2,4,8,10 (Phone call)**	**Month 6,12 (onsite visit)**	**EOT/EOS[5]**
Months	**-1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 to 58**	**18 to 54**	**60**
Days	**-30 to 1**	**1**	**60**	**120**	**180**	**240**	**300**	**360**	**420 to 1740**	**540 to 1620**	**1800**
Informed consent	X										
Inclusion/Exclusion criteria	X	X									
Demography	X										
Medical history/current medical conditions	X										
Vaccination[1]	X			X		X		X		In each treatment year only on the onsite visits every 6 months	X
Physical Examination	S	S						S		In each treatment year only during the on-site visits and every 12 months	S
Blood Pressure and Pulse Rate	X	X		X		X		X		In each treatment year only on the onsite visits every 6 months	X
Body Height	X										
Body Weight	X	X		X		X		X		In each treatment year only on the onsite visits every 6 months	X

Period	**Screening**	**Treatment 1st year**							**Treatment 2nd year and beyond**		**Study Completion**
Visit Name	**Screening**	**Enrollment**	**Mon-2 (Phone call)**	**Mon-4 (onsite visit)**	**Mon-6 (Phone call)**	**Mon-8 (onsite visit)**	**Mon-10 (phone call)**	**Mon-12 (onsite Visit)**	**Month 2,4,8,10 (Phone call)**	**Month 6,12 (onsite visit)**	**EOT/EOS[5]**
Months	**-1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 to 58**	**18 to 54**	**60**
Days	**-30 to 1**	**1**	**60**	**120**	**180**	**240**	**300**	**360**	**420 to 1740**	**540 to 1620**	**1800**
Body Temperature	X	X		X		X		X		In each treatment year only on the onsite visits every 6 months	X
Pregnancy and assessments of fertility[2]	X	X		X		X		X		In each treatment year only on the onsite visits every 6 months	X
Clinical Chemistry	X			X		X		X		X	X
Urine analysis (dip stick)	X			X		X		X		In each treatment year only on the onsite visits every 6 months	X
Hematology	X			X		X		X		X	X
Coagulation	X			X		X		X		X	X
Breakthrough hemolysis	X								X	In each treatment year on all visits	X
High-sensitivity flow cytometry		X						X		In each treatment year only during the on-site visits and every 12 months	X
PNH-related sign and symptoms	X	X	X	X	X	X	X	X	X	In each treatment year on all visits	X
RBC transfusion	X									In each treatment year on all visits	

Period	**Screening**	**Treatment 1st year**							**Treatment 2nd year and beyond**		**Study Completion**
Visit Name	**Screening**	**Enrollment**	**Mon-2 (Phone call)**	**Mon-4 (onsite visit)**	**Mon-6 (Phone call)**	**Mon-8 (onsite visit)**	**Mon-10 (phone call)**	**Mon-12 (onsite Visit)**	**Month 2,4,8,10 (Phone call)**	**Month 6,12 (onsite visit)**	**EOT/EOS[5]**
Months	**-1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 to 58**	**18 to 54**	**60**
Days	**-30 to 1**	**1**	**60**	**120**	**180**	**240**	**300**	**360**	**420 to 1740**	**540 to 1620**	**1800**
Electrocardiogram (ECG)	X			X				X		In each treatment year only during the on-site visits and every 12 months	X
Adverse Events	X								X	In each treatment year on all visits	X
Major Adverse Vascular events		X	X	X	X	X	X	X	X	In each treatment year on all visits	X
Concomitant medications	X								X	In each treatment year on all visits	
Patient Experience Interview[3]		X									
Patient reported outcomes[4]		X		X		X		X		In each treatment year only on the onsite visits every 6 months	X
ER visits/ hospitalization	X	X	X	X	X	X	X	X	X	In each treatment year on all visits	X
Surgical and medical procedures	X	X	X	X	X	X	X	X	X	In each treatment year on all visits	X
IRT	X	X		X		X		X		In each treatment year only on the onsite visits every 6 months	X

Period	**Screening**	**Treatment 1st year**							**Treatment 2nd year and beyond**		**Study Completion**
Visit Name	**Screening**	**Enrollment**	**Mon-2 (Phone call)**	**Mon-4 (onsite visit)**	**Mon-6 (Phone call)**	**Mon-8 (onsite visit)**	**Mon-10 (phone call)**	**Mon-12 (onsite Visit)**	**Month 2,4,8,10 (Phone call)**	**Month 6,12 (onsite visit)**	**EOT/EOS[5]**
Months	**-1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 to 58**	**18 to 54**	**60**
Days	**-30 to 1**	**1**	**60**	**120**	**180**	**240**	**300**	**360**	**420 to 1740**	**540 to 1620**	**1800**
Drug dispensation		X		X		X		X		In each treatment year only on the onsite visits every 6 months	
Study completion information											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] Vaccination depends on the level of immunization of each single participant and the need for vaccination or booster injections as needed. Participants who need a booster prior to the next site visit will be called to the site for the booster administration.
[2] Pregnancy serum test at screening and pregnancy urine test or pregnancy serum test at each onsite visit according to the local requirements. Additional pregnancy testing might be performed if requested by local requirements
[3] Patient Experience Interview will be administered at Extension Day 1. This is optional for patients to give their feedback on their experience of the study treatment in the previous study.
[4] PROs include the FACIT-Fatigue and Patient Global Impression of Severity of Fatigue (PGIS), which will be completed by participants at Extension Day 1, every onsite visit and end of study; EORTC QLQ C-30 and EQ-5D-5L will be completed by participants at Extension Day 1, every Month 12 visit and end of study.
[5] For patients not able to continue iptacopan treatment due to unavailability in their country at the EOS visit, EOS will be after completing recommended procedures defined in Section 9.1.1

8.1 Screening

Screening

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

The screening visit will be performed as per the assessment schedule (between 30 days prior to the enrollment and up to the day of EOT of the parent study). The assessments obtained at the EOT of the parent study, which are required for this study, will become part of the **screening/enrollment** visit and the participant may be enrolled in the CLNP023C12001B study after confirmation of eligibility. If any protocol required assessments for this study are not included as part of the parent study's EOT, assessments will be completed/samples collected as per Table 8-1 and analyzed by the central laboratory. This data will be used to fulfill the screening/enrollment baseline data collection.

Rescreening participants

Participants who fail screening can be re-screened one additional time after screen failing. However treatment continuity is key and rescreening must occur within 30 days prior to and up to the day of EOT of the parent study. A new participant ID number should be used for re-screening and the participant must be re-consented prior to performing any screening assessments. All required screening assessments must be performed for participants being rescreened.

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

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

Any SAEs occurring after the participant has provided informed consent and until the time the participant is deemed a Screen Failure, or 30 days after the last dose of study medication in the parent study, whichever is later, must be reported to Novartis.

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 for all participants. Participant race/ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Medical history/current medical conditions will include: date for diagnosis of PNH (and age or disease duration will be derived up to the date of screening); vaccination history; MAVE history (dates and type); the packed-RBC transfusion received in the 6 months prior to enrollment; 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 concomitant therapy Section 6.2.1) taken prior to Screening will be recorded in the CRFs.

Prior study participation (study code) will also be included in the eCRF.

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

8.3.1 Hemoglobin, transfusion avoidance, and other PNH-related assessments

Blood samples for hematology and clinical chemistry will be collected according to Table 8-1 for the Treatment period. The following laboratory parameters will also be assessed: Hemoglobin**,** haptoglobin, reticulocyte count (as a marker for intravascular hemolysis) bilirubin, LDH, RBCs, PNH clone size (RBC/WBC).

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 red blood cell transfusion will be monitored continuously throughout the study.

Transfusion criteria below are provided as a general guide for the study investigator and investigators should apply their judgement regarding the decision for transfusion:

- Hemoglobin level ≤ 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 red blood cell transfusion administered as well as the signs and/or symptoms if applicable will be recorded in the CRFs. Symptoms typically associated with or precipitating the need of transfusion are listed below:

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

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

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

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

8.3.3 Breakthrough hemolysis

The occurrence of breakthrough hemolysis will be monitored continuously during throughout the study.

The criteria for clinical breakthrough is defined in Table 8-2 below if either one of the two clinical criteria is demonstrated, in presence of the laboratory evidence of intravascular hemolysis and should be reported in the 'Breakthrough hemolysis' CRF page in addition to the AE CRF 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 8-2), is defined as subclinical breakthrough hemolysis, and should **not** be reported in the 'Breakthrough hemolysis' CRF page.

Table 8-2 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

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

8.3.4 Major Adverse Vascular Events (MAVEs)

Assessments of MAVEs occur according to Table 8-1 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

8.3.5 PNH-related signs and symptoms

PNHs signs and symptoms will be collected according to Table 8-1. 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.

8.3.6 Appropriateness of efficacy assessments

The efficacy assessments including laboratory parameters hemoglobin (to determine the degree of anemia), LDH (as a marker for intravascular hemolysis), reticulocyte count, bilirubin and haptoglobin (as markers for extravascular hemolysis), and the need of red blood cell transfusions are important parameters for assessing treatment response in PNH. In fact, hemoglobin, and 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 symptoms 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, Kulasekararaj et al 2019, Ueda et al 2018). It has support for its validity in general populations (Yellen et al 1997, Webster et al 2003) and content validity has been supported specifically in PNH patients (Weitz et al 2012).

8.4 Safety

Safety assessments are specified below (Table 8-3) with the assessment schedules (Table 8-1) 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, that limits or prevents on-site study visits, and for sites not participating in Off-site Research Nursing (ORN) visits (see Section 8.6), regular phone or virtual calls may occur (as per scheduled visits) for safety monitoring and discussion of the participant´s health status until it is feasible for the participant to visit the site again.

For details on AE collection and reporting, refer to Section 10.1.

Table 8-3 Assessments and specifications

Assessments	Specifications
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 that meet the definition of an adverse event and are made after signing informed consent must be recorded as an adverse event.
Vital signs	Vital signs include BP and pulse measurements. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured with an appropriately sized cuff. If the value reported is out of range, repeat sitting measurements will be made 5 - 10 minute later and the second measurement will be used/entered in the CRFs.
Height and weight	Height in centimeters (cm) is collected at Screening only; body weight (to the nearest 0.1 kilogram (kg) assessed in indoor clothing, but without shoes) will be measured as specified in Table 8-1
Body temperature	The same route (temporal, tympanic, or axillary) and modality (temporal scanner, tympanic probe, thermometer) should be used for ongoing participant observations, as to allow for accurate temperature trend evaluation.

8.4.1 Laboratory evaluations

Unless specified in the table below (Table 8-4), 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) collection site may be used.

Clinically notable laboratory findings are defined in Section 16.1

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Table 8-4 Laboratory tests

Test Category	Test Name
Hematology	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
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma glutamyl transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, eGFR, 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
Urinalysis/urine dipstick assessment	Dipstick measurements for protein, bilirubin, blood, glucose, ketones, nitrites, pH, specific gravity and urobilinogen, and WBC/leukocytes will be performed at the site's local laboratory. If dipstick measurement results are positive (abnormal), results will be captured in the eCRF. Microscopy must be assessed locally following an abnormal dipstick test.
Coagulation/markers of thrombosis	Prothrombin time (PT), INR, activated partial thromboplastin time (aPTT), D-dimer, and fibrinogen
Pregnancy test	Serum / Urine pregnancy test , performed locally
High-sensitivity flow cytometry	Type I, II and Type III erythrocytes and PNH clone size in WBCs (granulocytes/monocytes)).

8.4.2 Electrocardiogram (ECG)

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

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

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

Single 12-lead ECGs are to be collected with ECG machines available at the site. Each ECG tracing must be labeled with study number, subject number, date and time, and filed in the study site source documents Investigator should document clinical evaluation in source. The ECG results collected are entered into the appropriate eCRF pages.

For any ECGs with participant safety concerns (please refer to Section 16.1 for notable abnormalities), two additional ECGs must be performed as soon as possible and within the same day 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.

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 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 (or serum pregnancy test where urinary pregnancy tests are not available) will be performed. Local pregnancy test and associated results will not be collected on CRF.

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

Assessments of fertility

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

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

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

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

8.4.4 Coagulation / markers of thrombosis

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

8.4.5 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 with encapsulated bacteria will be closely monitored throughout the study. Participant vigilance for early signs and symptoms of infection is required and supported by providing appropriate tools (Participant Safety Card) to enhance awareness and vigilance.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

The participant should be made aware that completed measure(s) are not reviewed by the investigator/ study personnel.

To further understand the participants' symptoms, functioning, and overall well-being, and their changes during the study, four patient reported outcomes (PRO) questionnaires will be used in this study:

- FACIT-Fatigue
- EORTC QLQ-C30
- EQ-5D-5L
- Patient Global Impression of Severity of fatigue (PGIS)

The PROs will be completed by participants, on an electronic PRO device (ePRO), before any other procedure or assessment at the screening and visits. Detailed instructions describing administrative procedures of the PROs including participant completion via ePRO will be provided to the sites.

The questionnaires should be completed in the language in which the respondent is most familiar. The participant should be given sufficient space and time to complete the questions.

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

Brief descriptions of each questionnaire are given in the sections below.

FACIT-Fatigue

The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. It will be used to assess patient-reported fatigue. FACIT-Fatigue is one of many different FACIT scales part of a collection of Health-Related Quality of Life (HRQoL) questionnaires referred to as the FACIT Measurement System (Webster et al 2003, Yellen et al 1997). The use of the FACIT-Fatigue 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-Fatigue 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 8.5.2.

EORTC QLQ-C30

The EORTC QLQ-C30 was selected for inclusion in the study as it is responsive to clinical status and changes over time. It is also widely recognized as a clinically relevant and reliable measure for assessing HRQoL, function, and symptoms (Aaronson et al 1993, Fayers et al 2002). The EORTC QLQ-C30 consists of 30 questions, which are incorporated into five functional domains (physical, role, cognitive, emotional, and social domains); a global health status/global quality of life scale; three symptom scales (fatigue, pain, nausea and vomiting scales); and six single items that assess additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and the perceived financial burden of treatment.

EQ-5D-5L

The EQ-5D-5L is a widely used questionnaire designed to assess health status in adults. The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Participants rate each of these items from 1 of the 5 levels: no problems, slight problems, moderate problems, severe problems, or unable to/extreme. A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best imaginable health state" and 0 represents the "worst imaginable health state." Respondents are asked to rate their current health by placing a mark along this continuum (Rabin and de Charro 2001; EuroQol Research Foundation. EQ-5D-5L User Guide 2019).

Patient Global Impression of Severity (PGIS)

A Patient Global Impression of Severity of fatigue symptoms will be used to understand the overall severity of fatigue experienced and the clinical meaningfulness of treatment effects experienced during this study. It contains one question to which the participant indicates their fatigue severity by selecting one of five response options: no symptoms, mild, moderate, severe, and very severe.

Patient Experience Interview

Participants in the study will have experienced the study medication and may have feedback that has not been asked or elicited through standardized PRO questionnaires. Qualitative patient feedback on the meaningfulness of changes in disease experience (i.e. changes in signs, symptoms, and quality of life impacts associated with PNH) during the clinical studies is of increasing interest to regulatory bodies and patient communities, interested in the value of new medications, and is discussed in Food and Drug Administration's (FDA) latest Patient Focused Drug Development Guidance (FDA 2020). The Patient Experience Interview as part of this study will explore the participant's experience with the previous study medications, including their satisfaction and preferences, with approximately 10 questions in a representative sample of patients.

All interviews will be conducted by researchers who are trained in qualitative interviewing techniques to ensure the quality of the interview and data protection. During each interview, interviewers will follow a semi-structured interview guide. This guide is not intended as a script to be followed verbatim but rather will be referenced during interviews to ensure that relevant and complete information related to the research question is collected in as spontaneous manner as possible. The training of the interviewers and the open-ended approach ensures that study participants are not unduly biased and that the language study participants use to describe their experiences is elicited organically (Staunton et al 2019). Interviews will be conducted over the phone or via teleconference software, last approximately 30-minutes, and will be audio-recorded and qualitatively analyzed. The interviews will be audio-recorded and qualitatively analyzed. The interviews will be optional and will be conducted according to the local regulatory allowance for conduction of these type of interviews.

8.5.2 Other Assessments

Health Care Resources Utilization (HRU)

Occurrence of hospitalizations, and emergency room visits at screening visit and between Day 1 and EOS visit will be collected in the CRFs.

8.6 Off-site research nursing (ORN) visits in the event of Public health emergency as declared by local or regional authorities

At the Investigator's discretion and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered alternative methods of providing continuing care such as phone calls, virtual contacts (e.g. teleconsult) or visits by site staff/Off-site Research Nurse (ORN) to the participant´s off-site location depending on local regulations and capabilities, which can replace on-site study visits, for the duration of the COVID-19 pandemic period/ other public health emergency disruptions until it is safe for the participant to visit the site again. 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 ORN and ultimately decided by the Investigator. The off-site visit will be offered in certain countries and sites and may replace on-site visits if Sponsor, Investigator and local regulations and conditions allow.

Participants, that the Investigator identifies as suitable benefiting from off-site visits, must provide a separate consent in the optional Off-site Research Nursing Informed Consent. The participants should discuss with the Investigator whether an on-site or off-site visit is more appropriate.

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

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 be enrolled and have completed Enrollment Visit (Day 1).
- If a participant has begun off-site visits and s/he suffers either (1) a severe AE or SAE (possibly related to study medication), and/or (2) any concurrent medical conditions which, in the opinion of the Investigator, could cause unacceptable safety risk, then the participant must resume the on-site visits. The participant may resume the off-site visits when, based on the Investigator's judgement, there are no further safety risks for the participant.

Table 8-5 List of the assessments to be performed during by off-site research nursing visit

Assessments*
Vaccination booster
Blood pressure and pulse rate
Body temperature
Breakthrough hemolysis event ***
PNH signs and symptoms

Adverse Events
Major Adverse Vascular Events
Concomitant medications
ER visits / hospitalization
Surgical and medical procedures
Study treatment administration
Blood samples to be collected **
Clinical Chemistry
Hematology
Coagulation/Markers of thrombosis
High-sensitivity flow cytometry Type I, II and III RBCs and PNH clone size in WBCs
*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. *** Reporting of BTH event requires consultation between ORN and investigator

8.6.1 Off-site research nursing (ORN) personnel

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

The ORN will perform the procedures which are listed in Table 8-5 as completely as possible at the visits specified in Assessment Schedule (Table 8-1). The ORN may collect and process laboratory samples, which are listed in Table 8-5 which will then be shipped to the appropriate Laboratory.

Data collected by ORN are provided to the Investigator for entry into the eCRF by the onsite study staff for the corresponding visit.

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 may occur when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

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

Study treatment must be discontinued under the following circumstances:

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

If a female trial participant becomes pregnant during the study, it is recommended to discontinue treatment with iptacopan. However, after an individual benefit-risk assessment by the investigator, iptacopan continuation may be considered in exceptional circumstances. Counseling should be provided to the participant regarding 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 which warrants immediately stopping iptacopan treatment, 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 and PNH clone size, increase in serum creatinine, thrombosis, and change in mental status. If serious hemolysis occurs, the Investigator should consider the following supportive treatments (and recording them in the appropriate CRF pages):

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

A visit one week after permanent discontinuation of 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), PNH clone size, dipstick urinalysis, PNH signs and symptoms and all adverse events. All data collected will be entered in the appropriate CRF page.

If treatment with iptacopan has to be discontinued, but it is not warranted to immediately discontinue iptacopan treatment, i.e. discontinuation due to participant/guardian decision or confirmed pregnancy, it is recommended to consider appropriate replacement therapy (including starting the anti-C5 antibody treatment if available) as judged by the investigator.

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, followed by
- 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 (i.e., end of the first week with 3x10 mg iptacopan treatment; and end of the second week with10 mg iptacopan treatment), and one week after the last iptacopan dose. The following assessments should be carried out: LDH, creatinine, hemoglobin, coagulation/thrombosis markers (PT/INR, aPTT, D-dimer, and fibrinogen), PNH clone size, dipstick urinalysis, PNH signs and symptoms 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.

Discontinuation of treatment may also occur at the end of the study (study completion). In case approval is not obtained in a country, the participant needs to be switched to the local SoC (either anti-C5 antibody therapy, if available, or locally available supportive care) and iptacopan tapering needs to be implemented

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 (refer to Section 9.1.1) 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 Study Completion 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.

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.

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

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

Action taken with study 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 for at least 7 days after the last dose of study medication.

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 Section 16.1.

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 the events (Note: If more stringent, local regulations regarding reporting timelines prevail). For screen failure patients, any SAEs occurring after the participant has provided informed consent and until the time the participant is deemed a Screen Failure, or 30 days after the last dose of study medication in the parent study, whichever is later, must be reported to Novartis. 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.

Any SAEs experienced by participants within 7 days following the last dose of study treatment should be reported in the study eCRF. All SAEs experienced after the 7 day period (follow-up) up to 30 days after EOS should be reported to the Novartis Safety office using a paper SAE form. Any SAEs experienced after 30 days after EOS should only be reported to the Novartis Safety office if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations, 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, under no circumstances later than 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail).

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

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 Novartis 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 (EC) in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

Pregnancies

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

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS) 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 of any pregnancy outcome. Any SAE experienced during pregnancy must be reported. Post-natal follow up should occur at 1, 3 and 12 months after delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

Treatment error type	Document in 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 (Section 16.2) for complete definitions of liver laboratory triggers.

For a participant exposed to study treatment, a liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are also outlined in Table 16-1 . Repeat liver chemistry tests (i.e. ALT, 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 the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), exposure to environmental chemical agents, alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease

These investigations can include based on investigator’s discretion:

- Imaging such as abdominal US, CT or MRI, as appropriate

- Considering gastroenterology or hepatology consultations.
- All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Data Monitoring Committee

There is a Data Monitoring Committee (DMC) functioning at the iptacopan program level and any significant safety findings (e.g. SUSARs) from this study will be shared with the DMC.

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source

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

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

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

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

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

11.2 Database management and quality control

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

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.

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 IIRT.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the data will be made available for data analysis. 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 Contract Research Organization (CRO) representative will review the protocol and data capture requirements (i.e. eSource Direct Data Entry (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 a centralized Novartis/delegated CRO 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 eCRFs 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

The final analysis will be conducted on all participant data at the time the trial ends. Interim reports may be produced during the study as detailed in Section 4.4.

For all analyses, cohort A refers to participants who were naive to complement inhibitor therapy, including anti-C5 antibody when iptacopan treatment was started in the parents studies, and cohort B refers to participants who had experienced complement inhibitor therapy, including anti-C5 antibody when iptacopan treatment was started in the parent studies. All analyses will be performed by cohort to account for differences in disease characteristics at the start of treatment with iptacopan before entering CLNP023C12001B.

In general, for all analyses, the baseline refers to the screening visit or the most recent assessment prior to enrolment in CLNP023C12001B.

Multiple uses of data through the study will be further specified in the Statistical Analysis Plan (SAP).

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

12.1 Analysis sets

The Safety Set includes all participants who received at least one dose of study treatment.

12.2 Participant demographics and other baseline characteristics

The Safety Set will be used for the analyses below.

Demographic and other baseline data will be listed and summarized descriptively for all participants and by cohort.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term for all participants and by cohort. Relevant medical history, current medical conditions, results of laboratory screens, and any other relevant information will be listed by participant and cohort.

12.3 Treatments

The Safety set will be used for the analyses below.

The duration of exposure in days to iptacopan will be summarized by means of descriptive statistics for all participants and by cohort.

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

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

The analysis of the long-term safety and tolerability of iptacopan has defined as the primary estimand the probability of AEs of special interest under long term treatment with iptacopan. In the analysis of Adverse Events of special interest, the probability of experiencing the events while-on-treatment with iptacopan will be estimated using the cumulative incidence function. In the case of competing risk events, the Aalen-Johansen estimator will be used to derive the estimator defined in the estimand section. In the case when no competing risk events were observed, a Kaplan-Meier estimator will be used to derive the estimates.

The crude rates and exposure adjusted incidence rates for AEs will be used to summarize the occurrence of adverse events. Specific patterns of interest will be summarized and displayed based on estimates obtained using piecewise discrete failure time analysis methods. The analysis of safety endpoints described below is supportive of the primary estimand.

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

For all safety analyses, the Safety Set will be used. The endpoints included are all relevant safety events and laboratory measurements, as well as vital signs.

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 addition, a separate summary for death including on-treatment and post treatment deaths will be provided. 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). All tables will be presented by cohort.

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) or the end of study visit, whichever occurs first.

Plots to visualize trends in longitudinal safety data may be created for all participants and by cohort.

Adverse events

All information obtained on AEs will be displayed by cohort and for all participants.

The number (and percentage) of participants with treatment emergent AEs (events started after the first dose of extension study medication or events present prior to start of extension study medication 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 AEs, death, serious AEs, and other significant AEs leading to discontinuation.

The number (and percentage) of participants with AEs and AEs of special interest (including but not limited to serious infections due to encapsulated bacteria) will be summarized. In addition, exposure-adjusted incidence rates will be calculated, as the number (and

percentage) of participants experiencing an AE within a fixed period of time, i.e. 1 year, 2 years, or appropriate intervals. The above analysis will be descriptive of the time course of AEs as well as of AEs of special interest. AEs of special interest will be summarized as cumulative incidence and as mean rates.

For incidence calculations (incidence fraction) a participant with multiple AEs within a primary system organ class will only be counted once towards the total of the primary system organ class.

Vital signs

Summary statistics will be provided by cohort and visit/time. Abnormalities will be summarized by cohort, and visit/time where normal ranges are available.

12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted according to Section 8.4.2. Summary statistics will be provided by cohort and visit/time. Abnormalities will be summarized by cohort, and visit/time.

Clinical laboratory evaluations

Laboratory data for participants with relevant abnormalities will be summarized by participant and visit/time relative to the start of study medication. Summary statistics will be provided by cohort and visit/time. Shift tables using the low/normal/high/(low and high) classification may be used to compare baseline to the worst on-treatment value.

12.4.2 Statistical model, hypothesis, and method of analysis

The statistical evaluations of all safety data will be descriptive. Hypothesis testing will not be performed.

12.4.3 Handling of remaining intercurrent events of primary estimand

Due to the nature of this long-term extension trial, participants who permanently discontinue study treatment will not continue study visits beyond the EOS. Hence, permanent treatment discontinuation is considered as an intercurrent event in the study. Given that the estimand will focus on the while-on-treatment risk, all available measurements of the participants up until 7 days after the date of the last actual administration of iptacopan, or EOS visit, whichever is longer will be used in the analyses.

12.4.4 Handling of missing values not related to intercurrent event

Missing data unrelated to intercurrent events may occur due to missed visits or missed assessment. In such cases, the missing observations will not be replaced, but participants will be considered to continue in the risk set and no further adjustments will be made to the analysis. Descriptive statistics will be based on all available measurements, but the denominator will be composed of those participants who continue in the study but for whom data are missing. The number of missing observations for each occassion will be reported.

12.4.5 Supportive analyses

Potential impact of a new wave of COVID-19 infections or Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster affecting measurements have been minimized through the measures proposed in Section 8.6. 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 or Public Health emergency related intercurrent events so that inference would still concern treatment effects in a world that is not in the midst of an extraordinary pandemic situation. The methodology for these estimands and additional sensitivity analyses for cases of missing data due to the impact of COVID-19 infections or Public Health emergency will be specified in detail in an amendment to the SAP developed in the event of renewed COVID-19 infection waves or Public Health emergency. 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 or Public Health emergency.

12.5 Analysis of secondary endpoints/estimands

The safety set will be used also for the following analyses.

The following endpoints will be used to assess the long-term clinical benefit of iptacopan in patients with PNH:

- Response defined as maintaining sustained hemoglobin levels greater than or equal to 12 g/dL in the absence of transfusions evaluated over yearly follow up intervals
- Absence of administration of packed-red blood cell transfusions evaluated over yearly follow up intervals
- Occurrences of breakthrough hemolysis and of Major Adverse Vascular Events (MAVE) occurring evaluated over yearly follow up interval

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. Statistical Analyses for the secondary endpoints will be detailed in the statistical analysis plan.

12.5.1 Patient reported outcomes

In this study the question addressed by the analysis of PRO instruments will be maintenance of any improvements in fatigue under long term treatment with iptacopan. The main instrument used is FACIT-Fatigue, and the determination of responder groups representing meaningful changes from a patient perspective will be supported by the use of the PGIS (Patient Global Impression of Severity) as an anchor instrument. Analyses supporting results from the Phase 3 studies will be further refined to provide a robust description of treatment outcomes as reflected in the patient reported outcomes.

Additionally, relevant changes in the subscales of the EORTC-QLQ-C30 that were previously identified as informative in Phase 3 studies will be analyzed. EQ-5D-5L results will be collected and analyzed appropriately to support Health Technology assessments.

12.6 Analysis of exploratory endpoints

Statistical analyses for the exploratory endpoints will be detailed in the statistical analysis plan.

12.7 Interim analyses

For interim reports as foreseen in Section 4.4 a Statistical Analysis Plan will be drafted that will cover the purpose of the interim analyses.

12.8 Sample size calculation

No formal statistical power calculations to determine sample size are performed for this study as the sample size depends on the number of participants who are enrolled/expected to enroll from the previous Phase 2 and 3 clinical studies with iptacopan. Approximately 165 participants are expected to be included in this trial.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

Novartis publication policy training materials will be provided to investigators during the investigator meetings for details on the Novartis publication policy including authorship criteria.

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

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16 Appendices

16.1 Appendix 1: Clinically notable ECG and renal function values

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 pre-dose baseline [msec]
- QTcF >500 or increase >60 compared to pre-dose 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.

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.

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

Table 16-1 Definition of trigger, 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 symptomsb • Report outcomec
> 3 × ULN and INR > 1.5 (in the absence of anticoagulation) If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	• Interrupt the study treatment (if possibly related to study treatment) • Hospitalize if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
> 5 to ≤ 8 × ULN If elevated at baseline: > 3 x baseline or > 300 U/L (whichever occurs first)	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality (investigate alternative etiologies)[a] • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
> 3 × ULN to ≤ 5 × ULN (accompanied by symptoms)[b] If elevated at baseline: > 2 x baseline	• Interrupt the study treatment (if possibly related to study treatment) • Hospitalize if clinically appropriate • Establish causality (investigate alternative etiologies)[a]	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion) • Monitor for symptoms[b]

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

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

[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.

Criteria	Actions required	Follow-up monitoring
TBL: total bilirubin; ULN: upper limit of normal		

ADDENDUM n. 1 AL CONTRATTO

PER SPERIMENTAZIONE CLINICA

"An open label, multicenter roll-over extension program (REP) to characterize the long-term safety and tolerability of iptacopan (LNP023) in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who have completed PNH Phase 2 and Phase 3 studies with iptacopan"

Codice Protocollo CLNP023C12001B

Numero EudraCT 2020-004385-19

TRA

L'**Azienda Sanitaria ULSS 7 Pedemontana** (d'ora innanzi denominata **"Azienda**"), con sede legale in Via dei Lotti, 40 - 36061 Bassano del Grappa (VI) - C.F. e P. IVA 00913430245 in persona del Legale Rappresentante, Dott. Carlo Bramezza, in qualità di Direttore Generale

E

La Società **NOVARTIS FARMA S.p.A.,** Codice Fiscale N. 07195130153, Partita IVA N. 02385200122, con sede in Viale Luigi Sturzo, 43 – 20154 – Milano (MI) - nelle persone dei procuratori Dott. Marco Girani e Dott.ssa Donatella Albanesi, come tali uniti di idonei poteri (di seguito per brevità "**Società**")

PREMESSO CHE

- la Società in data 02.12.2021 ha stipulato con l'Azienda ULSS 7 Pedemontana la Convenzione relativa alla Sperimentazione

Clinica dal titolo “An open label, multicenter roll-over extension program (REP) to characterize the long-term safety and tolerability of iptacopan (LNP023) in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who have completed PNH Phase 2 and Phase 3 studies with iptacopan” Protocollo CLNP023C12001B, Codice Identificativo 2020-004385-19 (di seguito “**Protocollo**”), in corso presso dell’U.O.C. di Oncoematologia dell’Azienda ULSS 7 Pedemontana, sotto la responsabilità del Dr. Eros Di Bona (Sperimentatore Principale);

- a seguito di una rivalutazione del budget dello studio, la Società si impegna a corrispondere all’Azienda degli importi aggiuntivi;
- a fronte di quanto sopra si rende pertanto necessario modificare l’allegato A2 del contratto in essere.

Le premesse fanno parte integrante del presente Addendum.

SI CONVIENE E SI STIPULA QUANTO SEGUE:

L’allegato A2 devono intendersi modificato come di seguito riportato **in grassetto.**

A2. Oneri e compensi

Compenso a paziente incluso nello studio: € 7.100,00 + I.V.A.

L’importo per singolo paziente che non abbia completato l’intero ciclo di visite sarà determinato in base al numero di visite effettuate, ovvero:

Screening	€ 650,00 + I.V.A.
Randomization	€ 500,00 + I.V.A.
M2 - Telefonata	€ 50,00 + I.V.A.
M4	€ 400,00 + I.V.A.

M6 - Telefonata	€ 50,00 + I.V.A.
M8	€ 400,00 + I.V.A.
M10 - Telefonata	€ 50,00 + I.V.A.
M12	€ 500,00 + I.V.A.
M14 - Telefonata	€ 50,00 + I.V.A.
M16 - Telefonata	€ 50,00 + I.V.A.
M18	€ 400,00 + I.V.A.
M20 - Telefonata	€ 50,00 + I.V.A.
M22 - Telefonata	€ 50,00 + I.V.A.
M24	€ 500,00 + I.V.A.
M26 - Telefonata	€ 50,00 + I.V.A.
M28 - Telefonata	€ 50,00 + I.V.A.
M30	€ 400,00 + I.V.A.
M32 - Telefonata	€ 50,00 + I.V.A.
M34 - Telefonata	€ 50,00 + I.V.A.
M36	€ 500,00 + I.V.A.
M38 - Telefonata	€ 50,00 + I.V.A.
M40 - Telefonata	€ 50,00 + I.V.A.
M42	€ 400,00 + I.V.A.
M44 - Telefonata	€ 50,00 + I.V.A.
M46 - Telefonata	€ 50,00 + I.V.A.
M48	€ 500,00 + I.V.A.
M50 - Telefonata	€ 50,00 + I.V.A.
M52 - Telefonata	€ 50,00 + I.V.A.
M54	€ 400,00 + I.V.A.
M56 - Telefonata	€ 50,00 + I.V.A.
M58 - Telefonata	€ 50,00 + I.V.A.
M60 - EoS	€ 600,00 + I.V.A.

Inoltre, la Società si impegna a corrispondere i seguenti importi aggiuntivi:

- **€ 150,00 per ciascuna trasfusione di globuli rossi (trasfusione RBC) che si rendesse necessaria durante il corso dello studio;**

- **€ 200,00 per ciascuna visita non programmata che si rendesse necessaria durante il corso dello studio;**

…OMISSIS…

Poiché le attività sono state nel contempo già svolte per i pazienti già inclusi nella Sperimentazione, alla sottoscrizione del presente Addendum la Società provvederà a corrispondere all'Azienda gli importi aggiuntivi relativi alle visite effettuate sino a quel momento.

Rimane ben inteso che tutte le clausole della Convenzione, non modificate e/o integrate dal presente Addendum 1 mantengono la loro piena validità ed efficacia.

Il presente Addendum n. I viene sottoscritto con firma digitale dal Rappresentante Legale dell'Azienda e dai Procuratori della Società ai sensi dell'art. 24 del D. Lgs. 82/2005, giusta la previsione di cui all'art. 15, comma 2bis della Legge n. 241/1990, come aggiunto dall'art. 6, D.L. 18/10/2012, n. 179, convertito in Legge 17/12/2012 n. 22.

L'imposta di bollo sull'originale informatico di cui all'art. 2 della Tabella Allegato A – tariffa parte I del DPR n. 642/1972 è a carico della Società ed è assolta da quest'ultima in modo virtuale ai sensi dell'art. 15 del D.P.R. n. 642/1972 e successive modificazioni, come da autorizzazione Agenzia delle Entrate n.69 del 14.12.2007; l'eventuale registrazione in caso d'uso sarà a carico della Parte interessata.

Fermo il resto.

Letto, confermato e sottoscritto.

Origgio lì, _____

Per la Società

I Procuratori

Dott. Marco Girani

_____

Dott.ssa Donatella Albanesi

_____

Bassano del Grappa, li __/__/_____

Per l' Azienda ULSS 7 Pedemontana
Il Rappresentante Legale

Dott. Carlo Bramezza

Firma _____