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Clinical Trial Protocol Title:

A multicenter, single arm, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who have Hb≥10 g/dL in response to anti-C5 antibody and switch to iptacopan

Clinical Trial Protocol Number: CLNP023C12303 / NCT05630001

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Brief Title: A multicenter, single arm, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who have Hb≥10 g/dL in response to anti-C5 antibody and switch to iptacopan

Study Phase: IIIb

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Sponsor Name: Novartis

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Amendment 02 (12-December-2023)

Amendment Rationale

This amendment aims to revise the protocol based on new information in line with the annual Investigator's Brochure update and to include updates related to the Auxiliary Medicinal Products (AxMPs) and their safety reporting in line with the changes required under EU Clinical Trial Regulation (EU-CTR) No 536/2014.

Main changes in this amendment:

Section 2.2, Section 2.3, Section 4.1, Section 4.3: Updated risks as per IB v10 and updated status of phase 2 and 3 studies in PNH. Added results from completed hepatic impairment and results from CLNP023X2201, CLNP023X2204 and QTc study.

Section 4.1 and Section 6.4.1: Based on updates in IB v10, added requirement of sample collection for bacterial cultures in suspicion/confirmation of infection, added guidance to treat infections and recommendations for treatment interruptions and recommencement as per investigator's clinical assessment of benefit and risk.

Section 5.1: Updated inclusion criteria 3 to 3a: clarified stable regimen of previous anti-C5 antibody treatment should be as per the locally approved label.

Section 6.8.2.1: Removed the OATP1B1/1B3 and P-gp inhibitors as prohibited medications and permitted concomitant medications requiring caution and/or action based on results from completed drug-drug interaction (DDI) study.

Section 8.6, Section 8.6.1 to Section 8.6.3: Causality assessment and reporting of AE and SAEs related to AxMPs added.

Section 8.6.3 and Table 10-1: Expedited reporting of potential Hy's Law cases added.

Other changes to the protocol:

Table 1-1:

- Updated footnote 1: Guidance for conducting ETD visit, footnote 4: Urinalysis dipstick assessment results will be recorded in eCRF and footnote 13: for collection of cultures in case of bacterial infection.
- Added footnote 14: Defined time window for patient interview.

Section 7.1: Removed discontinuation of study treatment in case of use of prohibited medication.

Section 8.2: Clarified data collection of "eligible" participants

Section 8.4.4: Changed "WBC/leukocytes" to "leukocyte esterase" as a test name and aligned with Table 1-1.

Section 8.6.6: Removed sentence about infections caused by encapsulated bacteria as an AESIs

Section 10.1.2: Added new abbreviations.

Section 11: Added references

Other changes to align with latest Novartis protocol template were performed to:

Table 6-1: Updated formatting

Section 6.2.1: Added storage conditions of study treatment can be found on the IMP bottle label.

Section 6.3.2: Added clarification that treatment blinding is not applicable as this is an open label study.

Section 6.7.1: Updated language for study treatment errors

Section 7.5: Added indication (PNH) to reasons of early termination.

Section 8.6.4: Updated language for pregnancy follow-up and reporting.

Section 10.2.2: Definitions of AxMP added and definition for Investigational medicinal product is updated.

Other relevant sections in the protocol are updated for consistency and clarity in relation to updates made in above mentioned sections. Also, observed typos and formatting errors were corrected.

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

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

The changes herein are also reflected in the Informed Consent.

Amendment 01 (23 February 2023)

Amendment Rationale

The main rationale of this amendment is to define the time limit for the historical PNH clone size results for eligibility, without which patients with a PNH clone size of below 10% could be included. The limit of 12 months before screening to get this data is reasonably sufficient to have a PNH clone size of similar amount at time of screening. Additionally, the optional interim analyses are removed.

Major revisions are made to:

Section 3: Added a secondary objective to assess the effect of iptacopan on transfusion avoidance defined as the proportion of participants who remain free from transfusions and added a corresponding endpoint evaluating absence of administration of packed RBC transfusions between Day 1 and Day 168 (no change in data collection strategy).

Section 4.6 and Section 9.8: Optional Interim Analyses are removed.

Section 5.1: Inclusion criterion #2: Updated to define a limit of 12 months prior to Screening visit 1 for use of the PNH clone size test results from historical data to determine eligibility.

Other changes to the protocol are:

Section 2.2: Updated based on available results of APPLY-PNH study.

Section 4.3.1: Auxiliary Medicinal Product (AxMP) defined as per EU CTR.

Section 6.2.3: Updated instructions for dosing of iptacopan in the event of vomiting.

Section 6.7: Clarified that in case of missed iptacopan dose or vomiting within 4 hours of previous dose, a single dose of iptacopan taken will not be considered as an overdose to reduce the risk to participants of hemolysis.

Section 8.6.4: Aligned with standard template language

Section 7.1: Clarified that permanent treatment discontinuation is when study treatment is discontinued before EoS visit/Day 168 visit.

Section 9.3.3 and Section 9.3.4: Clarified imputation strategies.

Section 9.4.1: Added back-up methods for secondary endpoints in case of non-convergence of regression models.

Table 1-1:

- Added a Urinalysis assessment timepoint at D168
- Added vaping as an option in smoking history.
- Updated Surgical procedures to Surgical and medical procedures, added a timepoint at screening visit 2

Other relevant sections in the protocol are updated for consistency and clarity in relation to updates made in above mentioned sections. Also, observed typos and formatting errors were corrected.

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

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.

1 Protocol summary

1.1 Summary

This is a multicenter, single-arm, open label trial, with iptacopan treatment for 24 weeks in adult PNH patients. Eligible participants must have a mean Hb ≥10 g/dL in response to a stable regimen with anti-C5 for at least 6 months and must be transfusion free for the same period. This study is comprised of two periods:

- A **Screening period** lasting up to 8 weeks.

Baseline for primary and key secondary objectives is defined as the mean of three Hb assessments conducted at central laboratory: two during screening and the third on Day 1 before starting treatment.

Baseline for all other objectives is defined as Day 1 or, in case of missing data on Day 1, any previous assessment done during Screening.

- A 24-week open-label, iptacopan **Treatment period**.

A total of approximately 50 participants will be enrolled in the trial. All participants must provide written informed consent prior to start of any study-related activities.

The study design is shown in the schematic in Section 1.2.

Screening

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

Participants will be asked to review and sign the ICF prior to starting the screening assessments. After signing the ICF, inclusion and exclusion criteria will be assessed to verify participants' eligibility for enrollment into the study at screening visit 1. If patient meets eligibility criteria during screening visit 1, screening visit 2 will be performed to confirm hemoglobin as per inclusion criterion 4 and vaccination status as per inclusion criteria 5 and 6. This will be followed by the visit's assessment as outlined in Table 1-1, as applicable.

By signing the ICFs, the participants will provide access to the following medical records for the last 6 to 12 months prior to Screening:

- Date and result of PNH WBC clone size performed in the 12 months prior to screening.
- Hb levels, MAVEs and anti-C5 antibody regimen reported in the past 6 months
- the number of transfusions and unit numbers of packed-RBC received in the past 12 months.

Participants must be vaccinated as outlined in Section 5.1 Inclusion criteria. Vaccines should cover as many serotypes as possible (including meningococcal serotypes A, C, Y, W-135 and B). To minimize participant burden, the use of multivalent vaccines is recommended as locally available and 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).

If eligibility criteria are not met due to any assessment, the participant should be considered as having failed the screening and does not proceed to treatment period. In the case where a safety laboratory value at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once, before participant is considered to have failed screening. The participant can be rescreened as described in detail in Section 5.3.

Treatment period

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

Refer to Section 6.8.1 which provides details about the protocol-specific guidelines for participants who need to receive a packed-RBC transfusion during the treatment period.

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

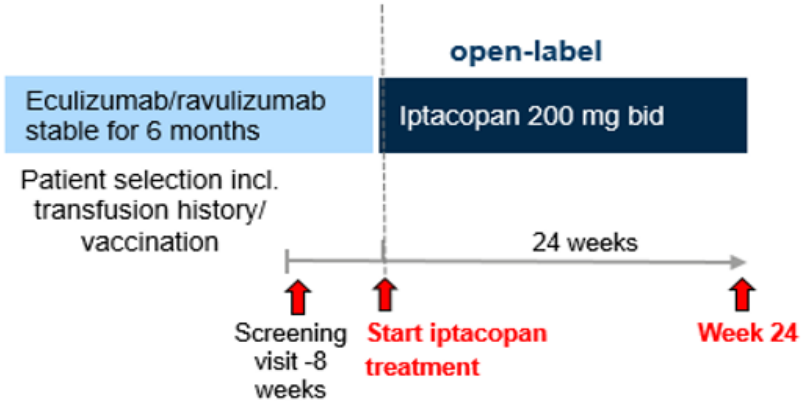
For participants who permanently discontinue iptacopan administration, close monitoring and treatment proposals are indicated in Section 7.1. Every effort must be made to keep participants in the study to complete all visits and assessments up to Day 168 visit. The treatment period will end with the completion of the Day 168 visit assessments.

After completion of the treatment period, participants who complete this trial while still receiving iptacopan and who continue to derive clinical benefit from the treatment based on the Investigator's evaluation will be able to join the Roll-over extension program (REP; CLNP023C12001B), which will provide access to iptacopan and enable long-term safety monitoring.

For participants not agreeing to continue in the REP after completing Day 168 visit, they may follow the recommended procedures defined in Section 7.1.

1.2 Schema

Figure 1-1 Study design



1.3 Schedule of activities (SoA)

The SoA lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. If one visit is postponed or brought forward, it should not result in the next visit being postponed or brought forward. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants, that the Investigator identifies as suitable for off-site visits, must provide informed consent (i.e., signature on the optional consent for activities that may be done outside of the study site, in the study informed consent form). The participants are under no obligation to participate in off-site visits, as they can decide to continue with on-site visits at the study site. Participants may have Off-Site Healthcare Professional (OHP) available to them for the second screening visit, Day 14/21, Day 28, Day 56, Day 112, Day 126, Day 140 and Day 154. The off-site visits will be carried out by a third-party vendor centrally sourced by the Sponsor that can provide qualified research nurses who will perform study assessments under the oversight of the Investigator, as per Section 8.11. The qualified nurses will be under the delegation of the Investigator. The Investigator will retain accountability for participant's oversight and all medical decisions (i.e. protocol specified medical procedures, AE/SAE assessment and reporting, changes in medication, etc.).

Participants who discontinue from study treatment are to complete the early treatment discontinuation (ETD) visit as soon as possible and attend the follow-up visits as indicated in the SoA.

Participants who discontinue from study should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product must be reconciled, and the

adverse events and concomitant medications not previously reported must be recorded on the CRF.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-1 Assessment Schedule

Period	**Screening**		**Treatment Period**											**Follow-up**	
Visit Name	**Visit 1**	**Visit 2**	**Visit 101**	**Visit 102**	**Visit 103**	**Visit 104**	**Visit 105**	**Visit 106**	**Visit 107**	**Visit 108**	**Visit 109**	**Visit 110**	**ETD/EoS[1]**	**Follow-up 1**	**Follow-up 2**
Days	**-56 to -8**	**-49 to -2**	**1**	**7 ±1**	**14±3 or 21±3**	**28 ±3**	**56 ±3**	**84 ±3**	**112 ±3**	**126 ±3**	**140 ±3**	**154 ±3**	**168 ±3**	**ETD + 7 days**	**ETD + 14 days**
Weeks	**-8 to -2**	**-7 to -1**	**1**	**1**	**2 or 3**	**4**	**8**	**12**	**16**	**18**	**20**	**22**	**24**	**-**	**-**
Informed consent	X														
Inclusion / Exclusion criteria	X	X[2]	X[2]												
Demography	X														
Medical history/current medical conditions	X														
Vaccination	X	X													
Smoking/vaping history	X														
Alcohol history	X														
Hepatitis screen	X														
HIV screen	X														
Physical Examination	S		S					S					S		
Body Height	X														
Body Weight	X							X					X		
Blood Pressure and Pulse Rate	X		X	X	X	X	X	X	X	X	X	X	X		
Body Temperature	X	X	X	X	X	X	X	X	X	X	X	X	X		
Electrocardiogram (ECG)	X												X		

Period	Screening		Treatment Period											Follow-up	
Visit Name	Visit 1	Visit 2	Visit 101	Visit 102	Visit 103	Visit 104	Visit 105	Visit 106	Visit 107	Visit 108	Visit 109	Visit 110	ETD/EoS[1]	Follow-up 1	Follow-up 2
Days	-56 to -8	-49 to -2	1	7 ±1	14±3 or 21±3	28 ±3	56 ±3	84 ±3	112 ±3	126 ±3	140 ±3	154 ±3	168 ±3	ETD + 7 days	ETD + 14 days
Pregnancy and assessments of fertility[3]	S												S		
Urinalysis[4]	X		X	X	X	X	X	X	X	X	X	X	X		
Clinical Chemistry (full)	X		X					X					X		
Clinical Chemistry (abbreviated) [5]				X	X	X	X		X	X	X	X		X	X
Hematology	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X		X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]			[redacted]			[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]
[redacted]				[redacted]				[redacted]						[redacted]	[redacted]
[redacted]				[redacted]		[redacted]		[redacted]					[redacted]		
[redacted]			X												
FACIT-Fatigue	X		X					X					X		
TSQM			X					X					X		
CCI [redacted]			[redacted]										[redacted]		
[redacted]													[redacted]		
PNH signs and symptoms			X	X	X	X	X	X	X	X	X	X	X	X	X
Breakthrough hemolysis[12]			X	X	X	X	X	X	X	X	X	X	X		

Period	Screening		Treatment Period											Follow-up	
Visit Name	Visit 1	Visit 2	Visit 101	Visit 102	Visit 103	Visit 104	Visit 105	Visit 106	Visit 107	Visit 108	Visit 109	Visit 110	ETD/EoS[1]	Follow-up 1	Follow-up 2
Days	-56 to -8	-49 to -2	1	7 ±1	14±3 or 21±3	28 ±3	56 ±3	84 ±3	112 ±3	126 ±3	140 ±3	154 ±3	168 ±3	ETD + 7 days	ETD + 14 days
MAVEs			X	X	X	X	X	X	X	X	X	X	X		
RBC transfusion			X	X	X	X	X	X	X	X	X	X	X		
Adverse Events[13]	X													X	X
Prior medications	X	X													
Concomitant medications			X	X	X	X	X	X	X	X	X	X	X		
Surgical and medical Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X		
Iptacopan			b.i.d.												
Iptacopan kit dispensing			X			X	X	X	X		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] In case of permanent treatment discontinuation, ETD (Early Treatment Discontinuation) assessments and follow-up visits must be performed, refer to Section 7.1. Patient should also continue with study visits as originally planned and complete EoS at Day 168. If Follow-up visits correspond to standard visits in the Treatment period, any additional assessment defined for those standard visits (e.g. PROs) should also be completed. ETD visit should be performed as soon as possible after the permanent treatment discontinuation.
[2] Inclusion criteria 4, 5 and 6, exclusion criteria 2, 7, 8 will be checked at this visit.
[3] Serum test at screening; urine test at ETD
[4] Dipstick measurements for protein, bilirubin, blood, glucose, ketones, nitrites, pH, specific gravity, urobilinogen, and leukocyte esterase will be performed at the site's local laboratory. Results from dipstick measurement will be captured in the eCRF. Microscopy must be assessed locally following an abnormal dipstick test and results captured in the eCRF.
[5] LDH, ALT, AST, ALP, GGT, eGFR, hs-CRP, Serum creatinine, Total bilirubin and fractions, CK, Total cholesterol, LDL, HDL, Triglycerides
[6] Only hemoglobin will be assessed at Screening visit 2
[redacted]

Period	Screening		Treatment Period											Follow-up	
Visit Name	Visit 1	Visit 2	Visit 101	Visit 102	Visit 103	Visit 104	Visit 105	Visit 106	Visit 107	Visit 108	Visit 109	Visit 110	ETD/EoS[1]	Follow-up 1	Follow-up 2
Days	-56 to -8	-49 to -2	1	7 ±1	14±3 or 21±3	28 ±3	56 ±3	84 ±3	112 ±3	126 ±3	140 ±3	154 ±3	168 ±3	ETD + 7 days	ETD + 14 days
CCI [redacted]															

[12] in case of a suspected event of BTH between scheduled visits, an unplanned visit should be conducted. The Investigator should also collect a sample for the central laboratory assessment of Hb, LDH and Bilirubin (total and fractions), biomarkers (including CCI [redacted]) and PK, whenever possible.
[13] BTH and MAVEs during screening and follow-up period are to be collected in the AE page. In patients with a suspicion of or confirmed bacterial infection, cultures should be taken and treatment, including appropriate antibiotics, should be considered as per investigator's clinical judgement.

CCI [redacted]

2 Introduction

2.1 Study rationale

The purpose of this trial is to assess efficacy and safety of iptacopan in a population of PNH patients who have Hb ≥10 g/dL in response to anti-C5 standard of care treatment (SoC, eculizumab or ravulizumab) and switch to iptacopan. It will provide data in a population of PNH patients who were excluded from the iptacopan studies APPLY-PNH and APPOINT-PNH, but still represent a large component of PNH patients.

This trial intends to demonstrate non-inferiority to SoC treatment in patients who have achieved a good/major/complete hematological response to SoC, applying hematologic response categories reported by Risitano et al (2019) and to assess the effect on the change from baseline in Hb levels after 24 weeks of treatment with iptacopan 200 mg twice daily.

It also intends to demonstrate, as key secondary objective, superiority to SoC treatment.

The data generated will provide scientific evidence to switch from the SoC intra-venous (iv) infusion with anti-C5 antibody treatment (eculizumab/ravulizumab) to oral iptacopan treatment in these patients, while also providing information on patient's preference on administration route.

2.2 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 acetylglucosaminyltransferase subunit A (PIGA) gene. Consequently, PNH blood cells lack the glycophosphatidylinositol anchor protein and are deficient in the membrane-bound complement inhibitory proteins CD55 and CD59. As a result, PNH type red blood cells (RBCs) are attacked by complement leading to complement mediated lysis (Brodsky 2014).

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

Eculizumab and ravulizumab (engineered from eculizumab with prolonged dosing interval) are approved anti-C5 antibody therapies for the treatment of PNH and the current SoC where available. The introduction of eculizumab has significantly reduced the thromboembolic risk of

PNH patients improving morbidity and mortality and largely improved the quality of life (QoL) of PNH patients. Although the anti-C5 antibody treatment is generally effective in treating IVH, there remains a high unmet medical need for PNH. In the study of Risitano and colleagues, only about one third of patients treated with eculizumab achieved normal or near normal Hb levels (Hb ≥11 g/dL) without requiring RBC transfusions (Risitano et al 2009).

A classification of hematological response categories to complement inhibitor therapy has been proposed by the Severe Aplastic Anemia (SAA) Working Party of the European group for Bone Marrow Transplantation (EBMT) (Risitano et al (2019)). The classification using six categories has been applied to a large cohort of 93 PNH patients retrospectively (Debureaux et al 2019) after the first six months of treatment with eculizumab (n=80). It was observed that only 13% of patients achieved a complete or major response i.e. no transfusion with normal Hb ≥12 g/dL without (complete response) or with residual significant IVH / increased erythropoietic response (major response). 34% of patients achieved a good response (no transfusion with mild anemia (Hb ≥10 to <12 g/dL) with or without residual significant IVH and BMF ruled out) while the rest were patients with Hb <10 g/dL.

A simplified classification using four categories was applied to a large cohort of 160 PNH patients retrospectively (Debureaux et al 2021) with a median treatment duration of 5.8 years with eculizumab. It was observed that nearly 60% of patients achieved transfusion independent good (Hb 10-12 g/dL) or complete (no anemia) response in the first year of therapy. However they still suffered from extravascular hemolysis (EVH; 43% and 17% in patients with good response and complete response respectively), BTH (8% and 11% in patients with good response and complete response respectively) and other PNH symptoms.

The heterogeneous response to eculizumab or other anti-C5 antibody treatment can, in part, be explained through its mechanism of action inhibiting only the terminal part of the complement cascade. Therefore, deposition of C3 fragments on the cell surface of PNH type erythrocytes lacking CD55 is not impacted, rendering the cells susceptible to EVH. This is inconspicuous in untreated PNH patients, because signs and symptoms of IVH dominate. However, EVH eventually emerges once the therapeutic inhibition with anti-C5 agents prevents IVH. In fact, it can become the main mechanism of hemolysis in patients treated with eculizumab (Risitano et al 2009) and C3 mediated EVH represents an unmet medical need.

The PEGASUS trial showed that patients with Hb <10.5 g/dL who switched from anti-C5 to pegcetacoplan (anti-C3) had an improvement in hemoglobin, clinical and hematologic outcomes; these results support the additional benefit of a broad control over the complement cascade, which translate into reduction of IVH and EVH (Hillmen et al 2021).

Iptacopan (LNP023) is a novel, oral, small molecule 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 IVH and EVH, 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.

Final results from the completed Phase 2 PNH studies show that PNH patients treated with iptacopan, both as add-on therapy to eculizumab (CLNP023X2201) for at least 6 months followed by iptacopan monotherapy and as monotherapy (CLNP023X2204), have clinically relevant benefits as shown by a reduction in LDH levels and improvements in hemoglobin in

the absence of RBC transfusions in majority of the patients. Two Phase 3 studies with iptacopan are also completed, confirming the evidence of iptacopan's effect on inhibiting both IVH and EVH:

- APPLY-PNH was a Phase 3 study in PNH patients presenting with residual anemia (Hb <10 g/dL) despite treatment with anti-C5 antibody; this was a 24-week randomized, active comparator controlled, open-label study followed by a 24-week open-label treatment extension period. Results of the 24 Week randomized treatment period showed that both primary endpoints were achieved with iptacopan monotherapy, showing superiority vs. SoC; oral Iptacopan was significantly superior to anti-C5 in increasing Hb ≥2g/dL from baseline and a significant majority of patients achieved Hb ≥12 g/dL, via resolution of EVH and maintenance of IVH control. These hematological benefits were associated with transfusion independence in almost all patients and clinically meaningful improvements in patient-reported fatigue. Iptacopan monotherapy was well tolerated with a favorable safety profile (Peffault de Latour et al 2022)
- APPOINT-PNH was a single-arm, open label study to determine whether iptacopan is efficacious and safe for the treatment of PNH patients who are naive to complement inhibition therapy, including anti-C5 antibody. This study has a 24-week core treatment period followed by 24-week extension period. The study met the primary hematological response endpoint (increase in Hb ≥2g/dL from baseline). Results of the 24-week core treatment period showed that iptacopan monotherapy resulted in a clinically meaningful increase in Hb levels, with majority of patients achieving Hb levels of ≥ 12 g/dL, significantly reducing the need for RBC transfusions in nearly all patients. Iptacopan had a favorable safety profile and was well tolerated in PNH patients naïve to complement inhibitor therapy (Risitano et al 2023).

2.3 Benefit/Risk assessment

The risks associated with the use of iptacopan are those inferred by its pharmacology and the results of preclinical and clinical safety studies. The most relevant risks are described below and a complete description of preclinical and clinical safety findings is available in the iptacopan Investigator Brochure (IB).

Appropriate eligibility criteria, as well as study procedures, close clinical monitoring with appropriate risk mitigation strategies which may include a periodic review of safety data by an independent Data Monitoring Committee (DMC), guidance in case of serious hemolysis, clinical BTH or need for RBC transfusion and in case of treatment discontinuation to ensure continued treatment of PNH, are included in this protocol and will minimize risks for participants.

This study does not involve any risks regarding study procedures (e.g. no invasive research procedures).

One potential risk which is specific to PNH patients is the risk of serious hemolysis following discontinuation of treatment with iptacopan. The importance of compliance with treatment will be emphasized to patients and the risk of hemolysis following missed doses mentioned in the ICF. In case of permanent discontinuation of iptacopan, specific discontinuation procedures are outlined in Section 7.1.

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 child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study. No contraception requirements are needed for males participating in the trial. A negative pregnancy test is required to participate in this trial and pregnancy test will also be performed at the end of the study as described in Section 8.4.5. Refer to IB for complete information.

Infections caused by encapsulated bacteria are an important risk in patients treated with complement inhibitors. Refer to IB for updated information on infections with iptacopan.

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 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, Granoff 2017). In addition, more recent studies have confirmed this effect in meningococci (Ispasanie et al 2021) and shown that, although C5 inhibitors have no effect on host defence (opsonophagocytosis) against pneumococci, C3 inhibitors have a greater effect than inhibitors of Factor D or Factor B (Muri et al 2021). Vaccination is therefore predicted to be an effective mitigation strategy to reduce the risk for individuals treated with iptacopan. Participants are to be vaccinated against meningococcal, pneumococcal and *H. influenzae* infections according to local guidelines and availabilities, since these are all encapsulated bacteria. Publications on patients who are deficient in Factor B, report that they experienced recurrent *Streptococcus pneumoniae* and *Neisseria meningitidis* infections (Slade et al 2013, Gauthier et al 2021).

Participants will also be closely monitored for signs and symptoms of serious bacterialinfections (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. In patients with a suspicion of or confirmed bacterial infection, cultures should be taken and treatment, including appropriate antibiotics, should be considered as per investigator’s clinical judgement. The Investigator will employ clinical judgement to determine an appropriate course of treatment. Antibiotic treatment should be started immediately for infections caused by encapsulated bacteria, with action taken with study medication considered on a case-by-case basis. Recommended guidelines for monitoring and management of infections are provided in Section 6.4.1. For immunocompromised participants with a higher risk of infections, precautionary actions (e.g. prophylactic antibiotics) should be considered by the Investigator.

Other safety risks are based on preclinical data, with no relevant findings in clinical studies performed to date. These are classified as non-important potential risks of testicular effects and thyroid changes. The preclinical findings are described in more detail in the IB.

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

Preclinical thyroid effects have been observed; however, they were minimal and reversible. There have been no clinically relevant thyroid adverse events or changes in thyroid hormone levels in clinical trials to date.

Results from a hepatic impairment (HI) study (CLNP023A2105) showed that mild, moderate, severe HI had no impact on total iptacopan PK. No safety or tolerability concerns emerged from this study. A specific QTcF exposure response analysis was performed in healthy volunteers receiving single doses of iptacopan from 5 mg to 1200 mg. The QTcF exposure response analysis, including data from the study CLNP023X2101 and study CLNP023A2107, showed no effect of iptacopan on duration of QTcF at supratherapeutic dose up to 1200 mg.

In addition, safety results from completed healthy volunteer studies, two Phase 2 studies in patients with PNH, and Phase 2 studies carried out in complement-driven renal disease (IgA nephropathy and C3 glomerulopathy) confirm that the safety profile is favorable and support continuation of development. Refer to IB for complete information.

Based on the results from the 24 week randomized treatment period of APPLY-PNH (CLNP023C12302) and 24-week core treatment period of APPOINT-PNH (CLNP023C12301) (Section 2.2), the final results from the CLNP023X2201 study as well as CLNP023X2204 study (Section 4.3 for details), PNH patients randomized to iptacopan may have clinical benefits over and above the SoC including:

- Increase of Hb to normal/near normal values in the absence of RBC transfusions
- Control of EVH
- 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 results of the Phase 2 studies (CLNP023X2201 and CLNP023X2204) and completed Phase 3 studies (APPLY-PNH and APPOINT-PNH) can be found in the IB.

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

3 Objectives, endpoints, and estimands

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
•To demonstrate non-inferiority of iptacopan after switching from SoC (anti-C5) in Hb change from baseline.	• Change in Hb levels as mean of visits between Day 126 and Day 168 compared to baseline, defined as mean of Hb collected at screening (2 samples) and Day 1.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
•To demonstrate superiority of iptacopan after switching from SoC (anti-C5) in Hb change from baseline.	• Change in Hb levels as mean of visits between Day 126 and Day 168 compared to baseline, defined as mean of Hb collected at screening (2 samples) and Day 1.
•To assess the percentage of hematological responders to iptacopan treatment defined as Hb ≥12 g/dL in the absence of RBC transfusions	• Response defined as Hb ≥12 g/dL assessed between visits Day 126 and Day 168 in the absence of RBC transfusions, on three out of four measurements taken at the visits occurring in last six weeks
• To assess the effect of iptacopan on transfusion avoidance defined as the proportion of participants who remain free from transfusions	• Absence of administration of packed RBC transfusions between Day 1 and Day 168
• To assess the effect of iptacopan on markers of EVH and IVH.	• Change from baseline in ARC levels as mean of visits between Day 126 and Day 168 • Percentage change from baseline in LDH levels as mean of visits between Day 126 and Day 168
• To assess the patients' perceived differences in global satisfaction, effectiveness and convenience between baseline and Day 84 and Day 168 after switching from SoC (anti-C5) to iptacopan	• Difference in scores of the global satisfaction, effectiveness, and convenience domains of the Treatment Satisfaction Questionnaire for Medication (TSQM-9) between baseline and Day 84 and Day 168 assessed after switching from SoC (anti-C5) to iptacopan
• To assess changes in patient-reported fatigue from baseline to Day 84 and Day 168	• Change from baseline in patient-reported scores for FACIT-F collected at Day 84 and Day 168
• To assess the frequency of BTH rate through Day 168	• Occurrences of BTH reported between Day 1 and Day 168
• To assess the rates of Major Adverse Vascular Events (MAVEs including thrombosis) of iptacopan through Day 168	• Occurrences of MAVEs occurring between Day 1 and Day 168
• To assess the safety and tolerability of iptacopan	• Safety assessments (including adverse events/serious adverse events, safety laboratory parameters, vital signs etc.) between Day 1 and Day 168
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
•To assess the percentage of hematological responders defined as Hb ≥12 g/dL in absence of RBC transfusion, CCI [redacted]	• Response defined as Hb ≥12 g/dL assessed between visits Day 126 and Day 168 on three out of four measurements taken at the visits occurring in last six weeks CCI [redacted]
•To assess the effect of iptacopan treatment on CCI [redacted]	CCI [redacted] • CCI [redacted] collected between Day 1 and Day 168

Objective(s)	Endpoint(s)
• To assess the effects of iptacopan treatment in CCI	• CCI parameters CCI collected between Day 1 and Day 168
• To assess the effect of iptacopan treatment in CCI	• Change from baseline in CCI collected at Day 168. Participant responses to a CCI
• To assess CCI to iptacopan in the study population and CCI	• CCI iptacopan CCI • CCI
• To assess the effect of iptacopan treatment in the CCI	• Occurrence of CCI Day 1 and Day 168

3.1 Primary estimands

The primary clinical question is: what is the treatment effect of iptacopan after 24 weeks compared to baseline in PNH patients who have Hb ≥10 g/dL in response to stable regimen of anti-C5 antibody treatment, regardless of discontinuation of iptacopan and occurrence of BTH or MAVEs?

The attributes of the primary estimand are:

- Population: PNH Patients ≥ 18 years on stable regimen of anti-C5 treatment and with Hb levels stable ≥10 g/dL, without any RBC transfusion in the past 6 months.
- Treatment of interest: the investigational treatment iptacopan at a dose of 200 mg b.i.d regardless of whether the patient discontinues treatment (treatment policy).
- Intercurrent events: discontinuations of study medication for any reason, BTH events, and MAVEs will be handled with a treatment policy strategy. RBCs will be handled using an hypothetical strategy, as if patient would not have received transfusions on iptacopan treatment.
- The summary measure: the average change from baseline in Hb and 95% CI

3.2 Secondary estimands

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

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

- Change from baseline in Hb levels as mean of visits between Day 126 and Day 168. Superiority will be concluded and objective will be considered met if the lower bound of the estimated two-sided 95% CI is greater than 0 g/dL. RBC transfusions will be handled

using a hypothetical strategy, as if patient would not have received transfusions on iptacopan treatment. The summary measure is the mean change from baseline in Hb.

- Response defined as Hb ≥12 g/dL assessed between visits Day 126 and Day 168 in the absence of RBC transfusions, on three out of four measurements taken at the visits occurring in last six weeks. The summary measure is the probability of being a responder or the proportion of responders if a logistic regression analysis is unfeasible.
- Absence of administration of packed-RBC transfusions between Day 1 and Day 168: proportion of participants not receiving any transfusions between Day 1 and Day 168 (transfusion avoidance). The summary measure is the probability of being a responder or the proportion of responders if a logistic regression analysis is unfeasible.
- Change from baseline in ARC levels as mean of visits between Day 126 and Day 168 where the strategy applied to transfusions is treatment policy. The summary measure is the mean change from baseline of ARC levels.
- Percent change from baseline in LDH between Day 126 and Day 168 where the strategy applied to transfusions is treatment policy. The summary measure is derived from the mean log transformed ratio to baseline in LDH between Day 126 and Day 168.
- Difference in scores of the global satisfaction, effectiveness and convenience domains of the TSQM-9 between baseline and Day 84 and Day 168 assessed after switching from SoC (anti-C5) to iptacopan. The summary measure is the mean difference in patient-reported scores (for each of the three TSQM-9 domains).
- Change from baseline in patient-reported scores for FACIT-F collected at Day 84 and Day 168. The summary measure is the mean change from baseline in patient-reported scores for FACIT-F.
- Rates of occurrences of BTH reported through Day 168. The summary measure is occurrences per year.
- Rates of occurrences of MAVEs occurring through Day 168. The summary measure is occurrences per year.

4 Study design

4.1 Overall design

This is a multicenter, single-arm, open label trial, with iptacopan treatment for 24 weeks in adult PNH patients. Eligible participants must have a mean Hb ≥10 g/dL in response to a stable regimen with anti-C5 for at least 6 months and must be transfusion free for the same period. This study is comprised of two periods:

- A **Screening period** lasting up to 8 weeks.

Baseline for primary and key secondary objectives is defined as the mean of three Hb assessments conducted at central laboratory: two during screening and the third on Day 1 before starting treatment.

Baseline for all other objectives is defined as Day 1 or, in case of missing data on Day 1, any previous assessment done during Screening.

- A 24-week open-label, iptacopan **Treatment period**.

A total of approximately 50 participants will be enrolled in the trial. All participants must provide written informed consent prior to start of any study-related activities.

The study design is shown in the schematic in Section 1.2.

Screening

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

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

By signing the ICFs, the participants will provide access to the following medical records for the last 6 to 12 months prior to Screening:

- Date and result of PNH WBC clone size test performed in the 12 months prior to screening
- Hb levels, MAVEs and anti-C5 antibody regimen reported in the past 6 months
- the number of transfusions and unit numbers of packed-RBC received in the past 12 months.

Participants must be vaccinated as outlined in Section 5.1 Inclusion criteria. Vaccines should cover as many serotypes as possible (including meningococcal serotypes A, C, Y, W-135 and B). To minimize participant burden, the use of multivalent vaccines is recommended as locally available and 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).

If eligibility criteria are not met due to any assessment, the participant should be considered as having failed the screening and does not proceed to treatment period. The participant can be rescreened as described in detail in Section 5.3.

Treatment period

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

Refer to Section 6.8.1 which provides details about the protocol-specific guidelines for participants who need to receive a packed-RBC transfusion during the treatment period.

Because of the known increased risk of infections with encapsulated bacteria, all participants will be provided with a Participant Safety Card. Participants will be instructed to be vigilant for any clinical sign of bacterial infections and to contact the Investigator or local physician immediately in case of suspicion of infection and start antibiotic treatment as soon as possible. In patients with suspicion or confirmation of bacterial infection, bacterial cultures should be taken.

For participants who permanently discontinue iptacopan administration, close monitoring and treatment proposals are indicated in Section 7.1. Every effort must be made to keep participants in the study to complete all visits and assessments up to Day 168 visit. The treatment period will end with the completion of the Day 168 visit assessments.

After completion of the treatment period, participants who complete this trial while still receiving iptacopan and who continue to derive clinical benefit from the treatment based on the Investigator's evaluation will be able to join the Roll-over extension program (REP; CLNP023C12001B), which will provide access to iptacopan and enable long-term safety monitoring.

For participants not agreeing to continue in the REP after completing Day 168 visit, they may follow the recommended procedures defined in Section 7.1.

4.2 Scientific rationale for study design

CLNP023C12303 is a multicenter, single arm, open-label study designed to evaluate the efficacy and safety of iptacopan at a dose of 200 mg b.i.d. orally in adult PNH patients who have Hb ≥10 g/dL in response to anti-C5 SoC treatment (eculizumab or ravulizumab) switching to iptacopan.

The patient population is chosen for this study for the following reasons:

- The study intends to demonstrate non-inferiority to SoC as well as assessing safety in patients who have already a good/major/complete hematological response to SoC, applying hematologic response categories reported by Risitano et al (2019) by assessing the effect of iptacopan on the change from baseline in Hb levels.
- The data generated will give scientific evidence to switch from the SoC iv infusion to oral iptacopan treatment in adult PNH patients with Hb ≥10 g/dL; according to Debureaux et al 2019, about 60% of the PNH population treated with SoC have Hb >10 g/dl but still suffer from EVH and BTH; according to results from PEGASUS trial, targeting both IVH and EVH may provide an incremental benefit to PNH patients compared to anti-C5 treatment.
- The study will assess frequency of major PNH complications, such as BTH and MAVEs
- The study will also assess PROs, including patient preference on drug administration route, symptoms of fatigue and other specific PNH signs and symptoms.

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

- Primary and majority of secondary, efficacy endpoints are objectively measured via laboratory assessments (i.e. hematological response parameters, Hb, LDH, ARC, transfusion avoidance and BTH).
- Protocol-specific guidelines (see Section 6.8.1) are defined to reduce potential bias due to events (such as transfusions) that may affect the main endpoints.

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

A screening duration of 8 weeks was considered appropriate

- to allow for relevant vaccinations
- to allow for switching from ravulizumab or eculizumab in a safe manner, reducing the risk of BTH, while minimizing potential carry-over effects of prior treatment. The initiation of iptacopan treatment has an overlap of 1 (eculizumab) or 2 (ravulizumab) weeks.

A treatment duration of 24 weeks is considered appropriate to assess the effect of iptacopan on the primary and secondary efficacy endpoints as well as on safety and tolerability. The 24-week treatment duration has been previously used in studies with PNH patients, including the recent Phase 3 studies with eculizumab and ravulizumab (Kulasekararaj et al 2019, Lee et al 2019). Moreover, the treatment duration of 24 weeks is implemented in the iptacopan Phase 3 studies in PNH patients (CLNP023C12301 and CLNP023C12302); thus ensuring alignment within the program.

The primary objective is to assess efficacy of iptacopan after 24 weeks of treatment in PNH patients who have Hb ≥10 g/dL in response to SoC and switch to iptacopan by demonstrating non-inferiority in change from baseline in Hb levels between Day 126 and Day 168. It is proposed to use a non-inferiority margin based on clinical data and experience as well as on precedence with Hb stabilization as endpoint in the Phase 3 PRINCE trial and set it at 1 g/dL of Hb. Assuming that patients have stable Hb at study entry, the mean change from baseline in Hb level between Day 126 and Day 168 is expected to be unchanged should patients continue on anti-C5 treatment. Non-inferiority will be concluded and primary objective will be considered met if the lower bound of the estimated two-sided 95% CI is greater than -1 g/dL.

Secondary objectives include superiority testing over anti-C5 on Hb level, assessment of the proportion of participants achieving sustained Hb levels ≥12 g/dL in the absence of RBC transfusions, BTH rates, MAVEs, changes from baseline in ARC and LDH, transfusion avoidance as well as PRO measure of treatment satisfaction (TSQM) and fatigue (FACIT-fatigue). These endpoints were selected to supplement the primary efficacy endpoint and are clinically meaningful endpoints for PNH.

4.2.1 Participant input into design

Representatives of Aplastic Anemia & MDS Foundation and of Canadian Association of PNH Patients were consulted for the design of the study. The representatives agreed with the proposals in terms of patient population, duration of study, number of visits and types of assessments. Two concerns were raised:

- the compliance to treatment, which as per protocol Section 6.4 will be checked at each visit and that could be supported by an app to remind patients to take iptacopan;
- the efficacy of iptacopan, which was tested in APPLY-PNH and APPOINT-PNH studies supports this claim.

4.3 Justification for dose

A dose of 200 mg iptacopan b.i.d. was chosen based on the available efficacy and safety data from the IA of the two ongoing Phase 2 PNH studies (CLNP023X2201 and CLNP023X2204) and is supported by Pharmacokinetic Pharmacodynamic (PKPD) modeling results. Furthermore, the dose of 200 mg b.i.d. is the dose chosen for the two Phase 3 studies (APPLY-PNH and

APPOINT-PNH) and was expected to provide optimal efficacy required for PNH as monotherapy with an adequate safety profile. In APPLY-PNH study, results of the 24 Week randomized treatment period showed that oral iptacopan 200 mg b.i.d resulted in a significant majority of patients achieving clinically meaningful Hb increases and Hb ≥12 g/dL (Peffault de Latour et al 2022). Results of the 24-week core treatment period of APPOINT-PNH study demonstrated that 200 mg b.i.d. iptacopan monotherapy resulted in a clinically meaningful increase in Hb levels (≥ 2g/dL from baseline), with majority of patients achieving Hb levels of ≥ 12 g/dL, significantly reducing the need for RBC transfusions in nearly all patients (Risitano et al 2023).

Final results from CLNP023X2201 and CLNP023X2204 studies were consistent with IA results and justify a dose of 200 mg iptacopan b.i.d in this study.

In the CLNP023X2201 study, a total of 16 patients with PNH with signs of active hemolysis despite ≥ 3 months of stable treatment with SoC were treated in the study; 10 patients in Cohort 1 (iptacopan 200 mg b.i.d. + anti-C5 therapy for ≥6 months, iptacopan 200 mg b.i.d. monotherapy thereafter) and 6 patients in Cohort 2 (iptacopan 50 or 200 mg b.i.d. + anti-C5 therapy for ≥ 6 months, iptacopan 200 mg b.i.d. monotherapy thereafter). All 16 patients completed the core 13 weeks of study treatment, and 13 patients completed the entire study (up to week 176).

- Study achieved its primary objective. The primary efficacy results showed a clinically meaningful reduction in LDH: at Day 92 (Week 13), iptacopan in addition to SoC treatment resulted in a mean (90% CI) reduction from baseline in LDH of 43.6% (−53.57, −33.58). The reduction in LDH was greater in Cohort 1. A total of 7/15 patients (46.7%) showed complete normalization of LDH levels (< 250 U/L) at 13 weeks.
- Transfusion-free hemoglobin normalization was observed in 9/15 patients (60%), with a rapid increase in mean hemoglobin from baseline (+ 3.20 g/dL from baseline to 12.66 g/dL) at 13 weeks. Nine patients had normal hemoglobin levels at Week 13.
- The majority of patients (14/16; 87.5%) were transfusion free up to Day 92.
- Control of hemolysis was associated further with the reduction of ARC and bilirubin (total and indirect).
- CCI [redacted] on PNH RBCs rapidly decreased, and a CCI [redacted], as a result of hemolysis control.
- A clinically important improvement in fatigue as assessed by FACIT-Fatigue score with increase from 36.3 points at baseline to 44.8 points at Week 13 [mean change (SD) from baseline: 8.14 points (13.114)].
- The effects of iptacopan were durable, such that even after patients discontinued SoC (as allowed per protocol after ≥ 6 months) the treatment benefits, including improvements in LDH, hemoglobin, ARC, FACIT-Fatigue scores, bilirubin, and increase in PNH RBC clone size, as well as the reduction in C3 deposition on RBCs were maintained up to Week 176. Of the 16 patients starting treatment, 12 remained transfusion-free throughout the entire study (3 patients required transfusion in the extension period).

Iptacopan as add-on treatment to anti-C5 therapy inhibited hemolysis (intra- and extravascular) with a rapid onset of effect. As a result, anemia improved in absence of RBC transfusions in the majority of patients, demonstrating clear hematological benefits, as well as symptomatic improvement in patient reported fatigue. Iptacopan at the dose regimen of 200 mg b.i.d. led to a numerically better and more complete inhibition of hemolysis. Following discontinuation of SoC after 6 months and continuation with iptacopan monotherapy, treatment effects were maintained and durable up to 176 weeks.

In the CLNP023X2204 study in PNH patients not treated with eculizumab/complement inhibitors, participants were randomized to iptacopan monotherapy in two sequences with forced titration after 4 weeks from iptacopan 25 mg b.i.d. to 100 mg b.i.d (sequence 1) or iptacopan 50 mg b.i.d. to 200 mg b.i.d. (sequence 2). The study enrolled 13 patients with PNH and active hemolysis: 7 in Cohort 1 (25 mg/100 mg b.i.d. dose) and 6 in Cohort 2 (50 mg/200 mg b.i.d. dose). Twelve patients were assessed for the primary endpoint (1 patient in Cohort 2 discontinued on Study Day 2 due to a non-severe AE of headache). All 12 patients included in the primary endpoint analysis were complement inhibitor treatment naïve.The study achieved its primary objective. Iptacopan monotherapy resulted in rapid and sustained reduction of LDH, and all 12 patients (100%) assessed achieved the primary endpoint (≥ 60% reduction in LDH from baseline or LDH normalization) up to Week 12.

- The inhibition of IVH was reflected by hematological benefits including clinically meaningful increase in total hemoglobin levels observed (mean increases of 2.34 g/dL and 3.71 g/dL at Week 12, in Cohorts 1 and 2 respectively), and improvement of other markers of hemolysis (free hemoglobin, total bilirubin, ARC, erythrocyte count) up to Week 12. Among the 12 patients who completed 12 weeks on study, all except 1 patient remained transfusion-free.
- An early, sustained, and marked increase in PNH RBC (Type II + III) clone size was observed with iptacopan treatment. C3 fragment deposition on PNH RBCs was negligible at baseline and remained so during treatment with iptacopan.
- Symptomatic improvement in fatigue was observed, as assessed by FACIT-Fatigue score, with a clinically important improvement in mean scores from 37.6 and 38.2 points at baseline to 46.8 and 48.6 points at Week 12 in Cohorts 1 and 2, respectively.

The treatment benefits of iptacopan were durable: improvements, including reductions in LDH, bilirubin, ARC, and patient-reported fatigue, and in increases in hemoglobin and PNH clone size were subsequently sustained up to Week 108 of treatment. Among the 11 patients who were followed up until end of study, 10 patients remained transfusion free. Persistence of iptacopan efficacy was also consistently observed up to Week 108 for other efficacy parameters, including improvement in erythrocyte, reduction in bilirubin, increases in PNH RBC clone size and decrease in C3 fragment deposition on PNH RBCs. There were also no thromboembolic events reported in the entire study.

Iptacopan at a dose of 200 mg b.i.d. was safe and well tolerated by participants in both Phase 2 studies, Phase 3 APPLY and APPOINT 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 Phase 3 PNH studies.

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

4.3.1 Rationale for choice of background therapy

Stable background treatment is allowed as per standard of care in PNH. Common treatments, including but not limited to, are folic acid supplementation to increase RBC production; iron supplementation to treat a deficiency caused by chronic hemoglobinuria; anticoagulant prophylaxis to reduce the risk of thrombosis in patients with a substantial proportion of PNH cells, high platelet counts (>100 x10^9/L) and no known hemorrhagic risk. Vaccination against *Neisseria meningitidis* and *S. pneumoniae* infection are required and vaccination against *Haemophilus influenzae* infections is recommended. If participants are not already vaccinated or need a booster vaccine dose, it can be administered as per Section 5.1 and according to local regulations. Antibiotics for prophylaxis are permitted if vaccines are administered in less than 2 weeks of first study treatment dose. Background treatment regimen should be stable prior to starting iptacopan in order to reduce the potential confounding effect on primary and secondary endpoints. Refer to Section 6.8 for the full list of concomitant medication allowed.

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

Not applicable as this is a single arm study.

4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. 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.

4.6 Purpose and timing of interim analyses/design adaptations

If deemed required (e.g., to support regulatory submissions to Health Authorities), interim safety analyses may be produced while the study is still ongoing.

4.7 End of study definition

Study completion is defined as when the last participant finishes their End of Study, Day 168 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.

4.8 Rationale for planned off-site procedures

Off-site procedures are planned in this study to minimize burden on participants and offer them increased flexibility to participate in the study from an off-site location (as describe in Section 3 and defined in Section 8.11). This has the potential to broaden access to clinical trials for both participants and Investigators. The hybrid approach will allow participants to maintain contact with the Investigator, both in person, during clinic visits at site, and through the telemedicine platform during off-site participation.

5 Study population

This study will enroll PNH patients with Hb ≥10 g/dL in response to anti-C5 antibody treatment, on stable regimen (dose and intervals) for at least 6 months and who did not receive any RBC transfusion in the previous 6 months, as well as during screening.

The study targets enrollment of at least 60% of patients with Hb <12 g/dL, therefore the number of patients with mean Hb ≥ 12 g/dL at screening will be restricted to maximum 40%.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Male and female participants ≥ 18 years of age, at the time of ICF signatures and with a diagnosis of PNH confirmed by PNH clone size WBCs ≥ 10% based on historical data performed up to 12 months prior to Screening visit 1.

3a. Stable regimen as per the locally approved label (dose and intervals) of anti-C5 antibody treatment (either eculizumab or ravulizumab) for at least 6 months prior to screening

4. Mean hemoglobin level ≥10 g/dL, documented by the mean of all available Hb assessments (minimum 2 measurements) over a period of 6 months before screening visit, collected at any laboratory. In addition to fulfill the Hb eligibility criterion, participants must have two different samples collected during the screening period and tested by the central laboratory with the mean ≥10 g/dL, prior to starting iptacopan. Note: the study will target enrollment of at least 60% of patients with mean Hb <12 g/dL defined by the central laboratory assessment at screening, therefore the number of patients with mean Hb ≥ 12 g/dL at screening will be restricted to maximum 40%
5. Vaccination against *Neisseria meningitidis* and *S. pneumoniae* infection are required prior to the start of iptacopan treatment. If the patient has not been previously vaccinated, or if a booster is required, vaccines are to be given according to local regulations, at least 2 weeks prior to first dosing. However, administration of these vaccines less than 2 weeks prior to start of iptacopan treatment is at the discretion of the investigator. If iptacopan treatment is started less than 2 weeks post-vaccination, participant must be given prophylactic antibiotic at the start of iptacopan and for at least 2 weeks after vaccination.
6. If not received previously, vaccination against *Haemophilus influenzae* infections is recommended, if available and according to local regulations. The vaccines should be given at least 2 weeks prior to initiation of iptacopan treatment. However, administration of these vaccines less than 2 weeks prior to start of iptacopan treatment, is at the discretion of the

investigator. If iptacopan treatment is started less than 2 weeks post-vaccination, participant must be given prophylactic antibiotic at the start of iptacopan and for at least 2 weeks after vaccination.

7. Able to communicate well with the investigator, to understand and comply with the requirements of the study

5.2 Exclusion criteria

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

1. Participation in any other investigational drug trial or use of other investigational drugs at the time of enrollment, or within 5 elimination half-lives of enrollment, or within 30 days of enrollment whichever is longer; or longer if required by local regulations
2. Patients requiring RBC transfusion in the 6 months prior to screening or during screening
3. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
4. Known or suspected hereditary complement deficiency at screening
5. History of hematopoietic stem cell transplantation or any solid organ transplantation
6. Patients with laboratory evidence of bone marrow failure (reticulocytes $<100x10^9$/L; platelets $<30x10^9$/L; neutrophils $<0.5x10^9$/L). The ARC (only) can be assessed either at local or central laboratory during the Screening period to determine participant's eligibility.
7. Active systemic bacterial, viral (incl. COVID-19) or fungal infection within 14 days prior to study drug administration
8. Presence of fever ≥ 38.0 °C (100.4 °F) within 7 days prior to study drug administration
9. Human immunodeficiency virus (HIV) infection (known history of HIV or test positive for HIV antibody at Screening)
10. A history of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus
11. Major concurrent comorbidities including but not limited to severe kidney disease (e.g., eGFR < 30 mL/min/1.73 m^2, dialysis), advanced cardiac disease (e.g., NYHA class IV), severe pulmonary disease (e.g., severe pulmonary hypertension) (WHO class IV), or hepatic disease (e.g., active hepatitis)
12. Liver disease, such as active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection defined as HBsAg positive or HCV RNA positive, or liver injury indicated by abnormal liver function tests at Screening:
    - Any single parameter of ALT/AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) must not exceed 3 x ULN
13. Unstable medical condition including, but not limited to, myocardial ischemia, active gastrointestinal bleeding, coexisting chronic anemia unrelated to PNH, or unstable thrombotic event not amenable to active treatment as judged by the investigator at Screening.
14. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
15. Ongoing drug or alcohol abuse that could interfere with patient's participation in the trial.

16. Concomitant use of any of the following medications is prohibited if not on a stable regimen for the time period indicated below prior to Screening and those listed in Section 6.8.3:
    - Erythropoiesis-stimulating agents (ESAs) for at least 8 weeks
    - Any immunosuppressants for at least 8 weeks
    - Systemic corticosteroids given for hematological conditions (less than 10 mg or equivalent prednisolone per day) for at least 4 weeks
    - Vitamin K antagonists (e.g. warfarin) with a stable international normalized ratio (INR) for at least 4 weeks
    - Low-molecular-weight heparin, and the direct oral anticoagulants (DOACs) rivaroxaban, apixaban and edoxaban, for at least 4 weeks
    - Iron supplements, vitamin B_{12}, or folic acid for at least 4 weeks
    - Androgens for at least 4 weeks
17. Any medical condition deemed likely to interfere with the patient's participation in the study
18. Female patients who are pregnant or breastfeeding, or intending to conceive during the course of the study
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and for 1 week after stopping iptacopan, 5 months after stopping eculizumab and 8 months after stopping ravulizumab. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For 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 study treatment.

    Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). Women are considered not of child-bearing potential if they are postmenopausal or have had surgical bilateral oophorectomy (with or without

hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to enrollment on the study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

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

5.3 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Participants who sign an ICF and are subsequently found to be ineligible will be considered a screen failure.

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

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

Rescreening participants

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

In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to starting study treatment. If the repeat value remains outside of the specified ranges, the participant is considered to have failed screening.

5.3.1 Replacement policy

Participants will not be replaced in the study.

5.3.2 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is rescreened. The Participant No. consists of the Site

Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the ICF, the participant is assigned to the next sequential Participant No. available.

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

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

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

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

- First iptacopan dose administration for participants on prior eculizumab regimen must occur at Days 7 to 8 after the last infusion
- First iptacopan dose administration for participants on prior ravulizumab iv regimen must occur at Days 41 to 43 after the last infusion

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

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

Table 6-1 Investigational and control drug

Treatment Title	**Iptacopan**
Treatment Description	**Open label, oral capsule 200 mg taken twice a day**
Type	Drug
Dose Formulation	Hard gelatin capsule
Unit Dose Strength(s)	200 mg
Dosage Level(s)	200 mg b.i.d.
Route of Administration	Oral
Use	Experimental
IMP	Yes
Sourcing	Provided centrally by the sponsor.
Packaging and Labeling	Study treatment will be provided in bottles. Each bottle will be labeled as required per country requirement.

6.1.1 Additional study treatments

No other treatment beyond iptacopan (investigational drug) are included in this trial.

6.1.2 Treatment arms/group

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

6.1.3 Treatment duration

The planned treatment duration is 24 weeks. If a participant's study treatment is discontinued for any reason, every effort must be made to continue with the study assessments up to the Day 168 visit.

Refer to Section 7.1 for recommendations for participants who discontinue iptacopan for any reason during the treatment period.

Participants who complete this trial while still receiving iptacopan and continue to derive clinical benefit from the treatment with iptacopan, based on the investigator's evaluation, may join the REP, or other sources of post-trial supply of iptacopan could be considered.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with iptacopan in packaging as described under Table 6-1 Investigational Drug Section.

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

Investigator staff will identify the study medication kits to dispense to the participant by contacting the Interactive Response Technology (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.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of iptacopan directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to continue administration of the study treatment even without performing an on-site visit.

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

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated

site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the IMP bottle label.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization 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 or designated site staff 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 field monitors during site or remote monitoring visits, and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment. For study treatment compliance, refer to Section 6.4.

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.

6.2.2 Handling of other treatment

The administration of RBC transfusion when needed will be monitored continuously during the treatment period as described in Section 6.8.1 .

6.2.3 Instruction for prescribing and taking study treatment

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

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

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

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

During the course of treatment, if vomiting occurs within 4 hours of dosing, the Investigator will instruct the participant to take a dose of iptacopan, if participant does not feel nauseated. Participants should not take the study treatment (iptacopan) again before the next scheduled dose, if vomiting occurs after 4 hours of previous dose.

In case of single missed dose, participants should take the missed dose as soon as possible and then continue with the regular regimen. In case of multiple missed doses, participants should take a dose of iptacopan as soon as possible but not make up for all missed doses, then continue with the regular regimen and contact immediately the Investigator, who should contact the medical monitor for guidance.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

No randomization will be performed in this study.

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

6.3.2 Treatment blinding

Not applicable as this is an open label study.

6.3.3 Emergency breaking of assigned treatment code

Not applicable as this is an open label study.

6.4 Study treatment compliance

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

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

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

6.4.1 Recommended treatment of adverse events

Infections

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

In patients with a suspicion of or confirmed bacterial infection, cultures should be taken and treatment, including appropriate antibiotics, should be considered as per investigator's clinical judgement.

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

Prophylactic antibiotics and early booster vaccinations should be considered in patients with recurrent infections and/or in patients taking concomitant immunosuppressants, as per the investigator's clinical judgement.

If iptacopan treatment is to be permanently discontinued, please refer to Section 7.1 for the appropriate actions.

Medication used to treat AEs must be recorded on the appropriate CRF.

All participants will be provided with a Participant Safety Card. Participants will be instructed to be vigilant for any clinical sign or symptom of infection and to contact the Investigator or local physician immediately.

6.5 Dose modification

Iptacopan will be administered at a dose of 200 mg b.i.d. Dose adjustments are not allowed. Dose interruptions must be justified by clinical judgement and should take into consideration the risk of BTH and other potential AEs.

6.5.1 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.5.2 Follow-up for toxicities

Not applicable

6.6 Continued access to study treatment after the end of the study

6.6.1 Post trial access

After completion of the treatment period, participants who complete this trial while still receiving iptacopan and continue to derive clinical benefit from the treatment based on the Investigator’s evaluation may receive post-trial access by joining the REP, which will provide access to iptacopan and enable long-term safety monitoring, or other sources of post trial supply of iptacopan could be considered.

6.7 Treatment of overdose

The dose of study treatment is 200 mg b.i.d in all participants. If any participant takes more than 200 mg b.i.d of study treatment (except in case of a missed scheduled dose or vomit, please refer to Section 6.2.3), it will be considered as an overdose.

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately
- Document the quantity of the excess dose as well as the duration of the overdose in the appropriate CRF page
- Evaluate the participant to determine, in consultation with the medical monitor, whether study treatment should be interrupted

- Closely monitor the participant for any AE/SAE and laboratory abnormalities for 7 days from the date of the overdose of study treatment Report any AE/SAE as outlined in Section 8.6
- If requested by the medical monitor, obtain a plasma sample for PK analysis within 1 day from the date of the overdose of study treatment determined on a case by case basis.

6.7.1 Reporting of study treatment errors including misuse/abuse

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

Study treatment misuse refers to situations where the study treatment is intentionally and inappropriately used not in accordance with the protocol.

Study treatment abuse corresponds to the persistent or sporadic, intentional excessive use of study treatment, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol, including misuse or abuse, must be reported on the AE (or SAE, if the event meets the definition of an SAE) CRF. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE immediately, without undue delay, under no circumstances later than within 24 hours of Investigator's awareness. (Note: If more stringent, local regulations regarding reporting timelines prevail).

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

Table 6-2 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	Yes	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

6.8 Concomitant and other therapy

6.8.1 RBC transfusions and recommendations for breakthrough hemolysis (BTH)

6.8.1.1 RBC transfusion

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

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

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

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

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

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

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

The Hb 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 Hb assessment by the central laboratory for analysis at the same time as taking a sample for local laboratory analysis.

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

6.8.1.2 Recommendations for BTH

For management of BTH and depending on the severity, the Investigator should consider the following supportive treatments (and record them in the appropriate CRF pages):

- Blood transfusion (packed RBCs), see Section 6.8.1.1
- Anticoagulation as appropriate
- Any other supportive treatment or therapy (incl. hydration) as judged by the Investigator

6.8.2 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 CRFs.

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

6.8.2.1 Permitted concomitant therapy requiring caution and/or action

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

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

Systemic corticosteroids are allowed to be used for hematological conditions if on stable dose (less than 10 mg or equivalent prednisolone per day) at least 4 weeks before Screening. During the study, the dose should not be changed during the treatment period (up to Day 168 Visit)From in vitro data examining potential iptacopan drug interactions, iptacopan was identified as a substrate of drug transporters OATP1B1/1B3 and drug metabolizing enzyme CYP2C8. In addition, iptacopan may impact pharmacokinetics (PK) of P-glycoprotein (P-gp) and OATP substrates. Thus, a DDI study (CLNP023A2104) was conducted where iptacopan was co administered with clopidogrel (CYP2C8 inhibitor), cyclosporin (OATP1B1/1B3 inhibitor) and digoxin (P-gp substrate), rosuvastatin (OATP substrate). The effect of clopidogrel and cyclosporin on iptacopan PK was not considered to be clinically relevant and there was a negligible impact of iptacopan on PK of the P-gp or OATP substrates.

6.8.3 Prohibited medication

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

- Live vaccines are prohibited for the entire study treatment duration.

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

- Combination treatment with other complement inhibitors including anti-C5 antibody treatment is prohibited

6.8.4 Rescue medicine

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 serious BTH (refer to Section 8.6.2 for SAE definition) requiring rescue medication in the opinion of the investigator, rescue medication is allowed and should be managed as per local guidelines and practice.

When rescue medication is administered, Investigator is to contact Novartis medical monitor for guidance on study drug.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

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

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

Study treatment must be discontinued under the following circumstances:

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

If a female becomes pregnant during the study, it is recommended to discontinue treatment with 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 on the appropriate treatment for PNH during pregnancy. The outcome of the discussion with the participant, reflecting benefit-risk considerations, should be documented in the participant's file.

If treatment with iptacopan has to be discontinued it is recommended to promptly re-initiate alternative anti-complement treatment, as judged by the Investigator and discuss with medical monitor for case-by-case guidance.

Close monitoring of participants for signs and symptoms of hemolysis should be performed upon iptacopan discontinuation as defined in the Schedule of Assessments (Table 1-1). It is recommended to monitor at minimum for: increase in LDH, decrease in Hb level, increase in serum creatinine, coagulation/thrombosis markers (PT/INR, aPTT, D-dimer and fibrinogen), dipstick urinalysis, PNH signs and symptoms, all AEs and change in mental status. The described assessments should be performed after 1 week and after 2 weeks from iptacopan discontinuation (Follow-up visit 1 and 2). Samples for central laboratory analysis should also be collected for the same parameters. All data collected should be entered on the appropriate CRF page.

CCI [redacted] are also to be collected at iptacopan discontinuation, but results may not be available immediately and will not drive medical management of the patients.

If serious hemolysis occurs, the Investigator should consider the following supportive treatments (and record them in the appropriate CRF pages):

- Blood transfusion (packed RBCs)
- Anticoagulation
- Any other supportive treatment or therapy (including hydration) as judged by the Investigator

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3).

Permanent treatment discontinuation is defined as discontinuing treatment before the EoS visit (Day 168 visit).

Participants who permanently discontinue study medication during the treatment period, should complete the Early Treatment Discontinuation (ETD) visit as soon as possible after permanent treatment discontinuation, follow-up visit 1 and 2 and visits as scheduled up to Day 168. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

The Investigator must also contact the IRT to register the participant's discontinuation from study treatment.

7.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts the ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

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 their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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 communication or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), 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.

7.5 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 PNH

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

8 Study Assessments and Procedures

The assessment schedule (Table 1-1) 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 on the day of visits.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 1-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. If one visit is delayed, the following visits must keep the original planned dates from Day 1. For the second screening visits and for visits on Day 14/21, Day 28, Day 56, Day 112, Day 126, Day 140 and Day 154, participants that the

investigator identifies as suitable for off site visits may have Off-site Research Nursing available to them (see Section 8.11).

Participants who discontinue iptacopan treatment during the treatment period should continue in the study up to Day 168 visit, completing all scheduled visits assessments. Refer to Section 7.1 for details on the recommended procedures to follow in case of permanent discontinuation.

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

8.1 Screening

Screening activities must be initiated only after the participant has signed the ICF.

8.1.1 Hemoglobin assessments during Screening

When signing the ICF, the participant allows the retrospective review and reporting of Hb values during the last 6 months prior to screening. The mean/average of all Hb assessments collected in those 6 months (minimum of 2 values) must be ≥10 g/dL, without having received any RBC transfusion, to proceed with screening activities.

During the screening period, two Hb measurements will be analyzed by central laboratory; mean Hb must be ≥10 g/dL to be eligible for the study.

8.1.2 Absolute Reticulocytes Count during Screening

The ARC will be measured at Screening to determine eligibility with regards to exclusion criterion # 6. The ARC as assessed by the central or local laboratory during the Screening period (only) can be used to determine participant's eligibility (protocol defined threshold of absolute reticulocytes $<100x10^9$/L). The results of the local laboratory values (including reference ranges) should be included in the eCRF to document eligibility.

8.2 Participant demographics/other baseline characteristics

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

Participants demographic data: full date (only if required and permitted) or year of birth or age, sex, race/predominant ethnicity (if permitted) and baseline characteristic data will be collected on all eligible participants.

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

Relevant medical history/current medical conditions will include: date for diagnosis of PNH (and age or disease duration will be derived up to the date of screening); date and result of PNH WBC clone size in the 12 months prior to Screening; vaccination history; MAVE history (dates and type); the RBC transfusion received in the last 12 months prior to Screening; Hb values in the last 6 months prior to Screening; relevant medical history and current medical conditions till the date of signature of ICF; smoking/vaping and alcohol history will also be collected.

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

Prior anti-C5 antibody treatment regimen for PNH (eculizumab or ravulizumab), which must be stable for the 6 months preceding and during screening (Section 5.1), will be recorded on a dedicated CRF page.

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

8.3 Efficacy assessments

Efficacy/pharmacodynamics assessments are specified below. Planned time points for all efficacy assessments are provided in Section 1.3 Schedule of Activities. Section 3 shows the correlation of the assessments with the objectives.

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

Blood samples for hematology and clinical chemistry will be collected according to Table 1-1 for the treatment period.

The following laboratory parameters are performed to evaluate efficacy at all visits:

- Hb and RBCs
- LDH as a marker of IVH
- Haptoglobin, ARC and bilirubin as markers of EVH
- aPTT, PT, INR, D-dimer and fibrinogen as markers of risk of thrombosis

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

8.3.2 Breakthrough hemolysis

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

The criteria for clinical breakthrough is defined in Table 8-1 below if either one of the two clinical criteria is met, in presence of the laboratory evidence of IVH and should be reported in the 'Breakthrough hemolysis' CRF page in addition to the AE page. The management of clinical BTH is reported in Section 6.8.1.2. In contrast to clinical breakthrough as defined, the isolated laboratory evidence of increased IVH, without meaningful decrease in Hb and without other clinical signs or symptoms of hemolysis (per Table 8-1), is defined as subclinical BTH, and should **not** be reported in the 'Breakthrough hemolysis' CRF page.

In case the event of BTH also qualifies for serious hemolysis the recommended treatment is reported in Section 6.8.4

Table 8-1 Breakthrough definition

	Clinical criteria		Laboratory criteria
	Hemoglobin levels	**Signs or symptoms**	**LDH level**
Clinical breakthrough *	Decrease equal to or more than 2 g/dL (compared to the latest assessment)	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)	No clinical signs or symptoms, except moderate hemoglobinuria	> 1.5-times ULN and increased as compared to the last 2 assessments

LDH: lactate dehydrogenase; ULN: Upper Limit of Normal;
*The breakthrough is defined clinical if either one of the two clinical criteria is demonstrated, in presence of laboratory evidence of IVH (LDH level)

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 Hb, LDH and Bilirubin (total and fractions), whenever possible. A PK sample, a CCI and an additional CCI (defined in Section 8.8) should also be collected in case of clinical BTH; the analysis of these parameters is exploratory in nature and will not drive decision making on BTH treatment.

8.3.3 PNH-related signs and symptoms

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

8.3.4 Major Adverse Vascular Events (MAVEs)

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

- Acute peripheral vascular occlusion
- Amputation (non-traumatic; nondiabetic)
- Cerebral arterial occlusion/cerebrovascular accident
- Cerebral venous occlusion
- Dermal thrombosis

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

8.3.5 Appropriateness of efficacy assessments

The efficacy assessments including laboratory parameters Hb (to determine the degree of anemia), LDH (as marker for IVH), reticulocytes, bilirubin and haptoglobin (as markers for EVH), and the need of RBC transfusions are important parameters for assessing treatment response in PNH. In fact, Hb 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). BTH 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 MAVEs 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.

PROs are also part of the efficacy evaluation of iptacopan treatment and are discussed in Section 8.5.1. The FACIT-Fatigue Scale will measure various aspects of fatigue, one of the most debilitating and commonly reported symptom generally among PNH patients (Hill et al 2007), and among patients currently treated with eculizumab (Socié et al 2019). The use of the FACIT-F in PNH patients has been reported in several publications and is sensitive to changes in disease status, allowing demonstration of statistically significant and clinically meaningful results (Kulasekararaj et al 2019, Ueda et al 2018, Brodsky et al 2008). It has been well validated in general populations (Webster et al 2003; Yellen et al 1997) and content validity has been completed specifically in PNH patients (Weitz et al 2013). From the 302 study (Kulasekararaj et al 2019) with eculizumab/ravulizumab and baseline mean Hb ≥10 g/dL, the percentage of patients presenting with fatigue at baseline was ~30% (rav) and 40% (ecu) and a 3-point improvement in FACIT-Fatigue score, considered clinically meaningful, was observed after 26 weeks of treatment (37.1% (rav) vs 33.7% (ecu)).

Given differences in route of administration, convenience and potential for additional incremental improvement, it will be important to assess areas of satisfaction and preference with the switch study, through use of PRO measures such as TSQM-9.

8.4 Safety assessments

Safety assessments are specified below with Section 1.3 Schedule of Activities detailing when each assessment is to be performed.

A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

For details on AE collection and reporting, refer to AE Section 8.6.

As per Section 4.5, 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, 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 safe for the participant to visit the site again.

8.4.1 Physical examinations

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.

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.

The same route (temporal, tympanic, or axillary) and modality (temporal scanner, tympanic probe, thermometer) for measuring body temperature should be used for ongoing patient observations, as to allow for accurate temperature trend evaluation.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

8.4.2 Vital signs

Vital signs include blood pressure (BP) and pulse measurements. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured with an appropriately sized cuff. If the value reported is out of range, a repeat sitting measurements will be made at 5 - 10 minute later and the second measurement will be used/entered in the CRFs. In specific visits defined in the SoA (Section 1.3) the vital signs may be collected by an Off-site Research Nurse (see Section 8.11)

8.4.3 Electrocardiograms

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position and conducted as a 12-lead recording according to the assessment schedules in Table 1-1. The preferred sequence of cardiovascular data collection during study visits is outlined in Figure 8-1 and includes ECG collection first, followed by vital signs, and blood sampling

(including PK sampling). The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

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

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

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

For any ECGs with participant safety concerns (please refer to Section 10.3.1 for notable abnormalities), two additional ECGs must be performed to confirm the safety finding. If confirmed, a copy of the assessment should be sent to the Novartis global team for expedited review. Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events, as appropriate. Any identifier details must be redacted e.g. participant initials, date of birth.

Figure 8-1 Timing of study procedures

8.4.4 Clinical safety laboratory tests

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

Clinically notable laboratory findings are defined in Section 10.5 and Section 10.6.

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

Table 8-2 Laboratory tests

Test category	Test Name
Hematology - full list	Hematocrit (Ht), Hemoglobin (Hb), Mean corpuscular hemoglobin (MCH), Haptoglobin, Absolute Reticulocytes count (ARC*), Red blood cells (RBC) count, RBC distribution width (RDW), RBC mean corpuscular volume (MCV), white blood cell (WBC) count with differentials (absolute and %) and platelet count
Clinical Chemistry (full)	Albumin, Alkaline phosphatase (ALP), ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, eGFR, hs-C-reactive protein (hsCRP), Serum creatinine, Creatine kinase (CK), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Triglycerides, Blood Urea Nitrogen (BUN) /Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting), Ferritin, Folate, Iron
Clinical Chemistry (abbreviated)	LDH, ALT, AST, ALP, GGT, eGFR, hs-CRP, Serum creatinine, Total Bilirubin and fractions, CK, total cholesterol, LDL, HDL, Triglycerides
Urinalysis/urine dipstick assessments	Dipstick measurements for protein, bilirubin, blood, glucose, ketones, nitrites, pH, specific gravity, urobilinogen, and leukocyte esterase will be performed at the

Test category	Test Name
	site's local laboratory. Results from dipstick measurement will be captured in the eCRF. Microscopy must be assessed locally following an abnormal dipstick test and also be captured in eCRF.
Coagulation/markers of thrombosis	Prothrombin time (PT), INR, activated partial thromboplastin time (aPTT), fibrinogen, D-dimer
Pregnancy test	Serum test at screening / Urine pregnancy test at the end of the trial (source) will be performed at the site's local laboratory
Hepatitis markers	Hepatitis B Virus Surface Antigen, Hepatitis C Virus RNA
HIV	HIV seropositivity testing will be performed as detailed in the Central laboratory manual and in line with local regulatory requirements
CCI	CCI CCI
CCI	CCI

* Refer to exclusion criterion #6: ARC may be performed locally for eligibility, but must be performed centrally in all other visits.

8.4.5 Pregnancy testing

All pre-menopausal women who are not surgically sterile will have pregnancy testing performed according to the Assessment Schedule in Table 1-1. Additional pregnancy testing might be performed if requested by local requirements.

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

The participant should inform the investigator if they believe they might be pregnant. Please refer to Section 7.1 on recommendations for iptacopan therapy in case of a pregnancy.

Assessments of fertility

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

Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

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

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

A woman is considered of childbearing potential from menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.6 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO) and Patient Interview

To further understand the participants' symptoms, functioning, and overall well-being, and their changes during the study, three CCI , in addition to a CCI , will be used in this study:

- FACIT-Fatigue
- TSQM-9
- CCI

The PROs will be completed by participants, on an electronic PRO device (ePRO), before any other procedure or assessment at the screening and assessment visits (see Table 1-1 and Figure 8-1). Detailed instructions describing administrative procedures of the PROs including participant completion via ePRO will be provided to the sites.

As per Section 4.5, 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, COA data may be collected remotely'.

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 to complete a questionnaire(s) is not a protocol deviation. The participant should be made aware that completed measure(s) are not reviewed by the Investigator/ study personnel.

Brief descriptions of each questionnaire are given 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.

TSQM-9

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) is a patient reported outcomes measure that was designed to assess patients' satisfaction with medication across three domains of effectiveness, convenience and global satisfaction. It has been used in many different therapeutic areas with support for its validity and reliability (Bharmal et al 2009). The TSQM-9 contains 3 questions in each domain, that are answered for the past 2 or 3 weeks. Domain scores range from 0 – 100 with higher representing better scores for the domain. It will be used in this study to assess changes in satisfaction after switching therapies, and over the course of the study.

CCI

The CCI with input from patients and clinicians. It CCI This CCI is included in the study to further assess the symptoms, impacts once switching therapies (Niedeggen et al 2019, Groth et al 2017). Due to unavailability of all language translations, only patients who are familiar with the available language will have to complete the questionnaire.

CCI

Participants in the study will have experienced the study medication and may have feedback that has not been asked or elicited through CCI . Qualitative patient feedback on the meaningfulness of changes CCI 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). CCI

CCI by researchers who are trained in CCI techniques to ensure the quality of the interview and data protection. During each interview, interviewers will follow a CCI 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). CCI

CCI [redacted] The interviews will be conducted according to the local regulatory allowance for conduct of these type of interviews.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of AEs and SAEs can be found in Section 8.6.1 and Section 8.6.2 respectively.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, assessing causality and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs or SAEs, considered related to the study treatment or that caused participant to discontinue the study treatment (see Section 7).

For the investigational product and for non-authorized AxMPs (when applicable), information about adverse drug reactions and how to manage them can be found in the Investigator's Brochure (IB) or equivalent documentation. Information about adverse drug reactions can also be found in the product information for marketed products.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

8.6.1 Adverse events

An 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 individual participant and identifying AEs.

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

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. AEs 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.

All cases of clinical BTH must also be reported as AE; MAVEs must always be also reported as AE.

For participants who permanently discontinue iptacopan administration during the course of the study, or do not continue into the REP, AEs will be collected for 7 days after last dose of study drug or until EoS, whichever is longer.

For participants who continue to the REP, AEs will be collected in the database for this study until participant's last study visit (Day 168/EoS).

The investigator will attempt to establish a diagnosis of the event (including lab abnormalities that constitute AEs) based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE.

For each AE, the investigator must assess:

1. The severity grade

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

2. The causality:

The investigator is obliged to assess the relationship between any treatment used in the study (study treatment, AxMP(s)) and each occurrence of AE. The investigator will use clinical judgement to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, should be considered and investigated.

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.

For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

2. The duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
3. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
4. Action taken regarding study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
    - Dose not changed
    - Dose reduced/increased
    - Drug interrupted/withdrawn
6. The outcome

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

Handling of AEs

All adverse events must be treated appropriately. More information about how to manage AEs can be found in the IB. Information about adverse drug reactions can also be found in product information for marketed products.

Once an AE is detected, the Investigator must pro-actively followed up the participant, until resolution of the AE, or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), or until stabilization, or until the participant is lost to follow-up. Any change in severity or suspected relationship to study treatment must be assessed at each visit (or more frequently, if necessary).

Timeframe of recording of AEs

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

Reporting of AEs related to AxMP(s)

All AEs related to any authorized auxiliary medicinal product used in this study must be reported to Novartis.

In assessing causality, the investigators will use the points above.

If a suspicion that medical occurrence could be related to study treatment (and/or interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4

Information about ADRs for the investigational drug can be found in the 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 10.3.

8.6.2 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, fetal death or a congenital abnormality or 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.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than 24

hours of obtaining knowledge of events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the (eSAE with paper back up) Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

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

The investigator must review and provide an assessment of causality for each SAE. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Novartis. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Novartis. The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

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

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

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

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Clinical Trial Regulation 536/2014 or as per national regulatory requirements in participating countries.

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

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law) (In patients with transaminases above the ULN at baseline, the Hy's Law criteria may be changed to increases 2-fold above baseline values). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of

liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Reporting of SAEs related to AxMP(s)

All SAEs related to any auxiliary medicinal product (whether authorized or not) used in this study must be reported to Novartis within 24 hours of the site becoming aware of it. In assessing causality, the investigators will use the points above. If a suspicion that the medical occurrence could be related to study treatment (or and interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

8.6.4 Pregnancy

If a female trial participant becomes pregnant, the stopping of investigational drug should be considered as described in Section 7.1, and the trial participant must be asked to read and sign the pregnancy consent form to allow the Study Doctor to ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the study informed consent must be reported to Novartis within 24 hours of learning of its occurrence. Details of all pregnancies in female participants will be collected after the start of study treatment and until 12 months after the birth.

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. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis as described in Section 8.6.3. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Pregnancy should be recorded and reported by the Investigator to Novartis. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must also be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.6.6 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.

8.7 CCI

CCI in all participants at the visits defined in the assessment schedule (Table 1-1) to determine CCI . Additional CCI will also be collected in case of CCI (see Section 8.3.2) and CCI (see Section 7.1).

CCI collected at CCI are intended to CCI

CCI is limited to CCI to limit the burden on patients that are otherwise stable and are already asked to come to the clinic more often than their regular care would require.

The CCI must be collected CCI administration to measure the CCI The Investigator or representative should remind the participant prior to the visit that during that CCI

The Investigator or representative should remind participants to CCI and to report if the CCI on the day prior to the visit was missed, as these events need to be captured in the dedicated eCRF page.

Iptacopan will be determined in CCI .

CCI to be determined and reported CCI

CCI will reported as CCI and missing data will be labeled as such in the Bioanalytical Data Report.

8.8 CCI

CCI will be analyzed to investigate the effect of iptacopan in CCI The CCI .

CCI

CCI
CCI
CCI
defined in Table 1-1; they will also be collected in case of CCI (see Section 8.3.2) and CCI (see Section 7.1).

The list of CCI may change during the course of the study due to CCI ay also be analyzed retrospectively after closeout of the trial with decisions dependent on study outcome or new information on iptacopan's mechanism of action.

While the goal of the CCI , there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g. CCI Therefore, depending on the results obtained during the study, CCI may be omitted at the discretion of Novartis.

CCI

The study includes an CCI which requires a CCI . As permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the Investigator present these options to the participant. Sample will be collected, on CCI as indicated in Table 1-1. If CCI , it can be taken at any visit thereafter. The purpose CCI may be toCCI CCI The goal is to CCI , or to learn more about CCI . As technology changes over time, the most appropriate technology will be used at the time the CCI . CCI he use of CCI is exploratory. Any results from this CCI To maximize confidentiality, CCI . This CCI As an additional confidentiality measure, CCI

8.9 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10 Medical resource utilization and health economics

CCI [redacted].

8.11 Off-site Procedures

At the Investigator's discretion and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option of Off-site Healthcare professional (OHP) procedures at an off-site location.

Procedures for off-site visits utilizing OHPs are further detailed in separate manual (s) provided to the site's participations in the off-site visits.

The off-site procedures will be utilized in certain countries and sites and as determined by the protocol needs., if Sponsor allows, and based on national and local/site regulations.

Participants, that the Investigator identifies as suitable for off-site visits, must provide informed consent (i.e., signature on the optional consent. The following conditions must be met for off-site visits to occur:

- Off-site visits may occur during the study for the following visits: second screening visit, Day 14/21, Day 28, Day 56, Day 112, Day 126, Day 140 and Day 154 or under exceptional circumstances (in the case of BTH where the patient cannot travel to the site) and if agreed between Investigator and Sponsor.
- The participant must have completed at least Screening visit 1 (i.e., confirmed eligibility based on Screening visit 1).
- If a participant has begun off-site visits and s/he suffers from either (1) a severe AE or an SAE (possibly related to study medication), and/or (2) any concurrent medical conditions which, in the opinion of the Investigator, could cause unacceptable safety risks, then the participant must resume the on-site visits. The participant may resume the off-site visits when, based on the Investigator's judgment, there are no further safety risks for the participant.

8.11.1 Responsibility of investigator oversight of off-site activities

Procedures that are performed off-site remain under the oversight of the Investigator, who retains accountability for the conduct of all safety and efficacy assessments delegated to an OHP, and will ensure the rights, safety, and wellbeing of participants. This includes the following (including, but not limited to):

- the identification, management and reporting of AEs and SAEs are performed in accordance with the protocol and applicable regulations
- verification that OHPs have appropriate qualifications, training, and experience to successfully conduct off-site procedures
- source data collected off-site are reviewed and evaluated in a timely manner
- the Investigator or delegate is available to be contacted by the OHP if any issues or concerns are noted during an off-site visit

- where relevant, the Investigator or delegate will be present via telemedicine for a portion of the off-site visit to support the physical examination.

8.11.2 Responsibility of OHPs

OHPs must have the required qualifications, training, and experience to conduct off-site assessments. OHPs are responsible to conduct delegated assessments and collect relevant data at off-site visits in accordance with the clinical trial protocol, International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and national and local regulations and guidelines.

Any issues or safety concerns identified by the OHP will be promptly communicated to the Investigator or delegate according to a pre-defined communication plan.

The ORN may collect vital signs, collect and process laboratory samples according to Table 8-2, which will then be shipped to the Central Laboratory. Assessment will be performed following the timing indicated in the Schedule of Assessments.

The OHPs will be provided by a third-party vendor sourced by Novartis/Sponsor. Where a site wishes to use off-site healthcare professionals that are not provided by Novartis this must be agreed with Novartis/Sponsor before use.

9 Statistical considerations

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

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

9.1 Analysis sets

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

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

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

9.2 Statistical analyses

9.2.1 General considerations

Baseline for primary and key secondary objectives is defined as the mean of three Hb assessments conducted at central laboratory: two during screening and the third on Day1 before starting treatment.

Baseline for FACIT-F is defined as the mean of scores obtained pre-treatment (Screening visit) and Day 1. Baseline for all other objectives is defined as the Day 1 assessment or, in case of missing data on Day 1, any previous assessment done during Screening.

9.2.2 Participant demographics and other baseline characteristics

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

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

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

9.2.3 Treatments

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

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

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

9.3 Primary endpoint(s)/estimand(s) analysis

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.

9.3.1 Definition of primary endpoint(s)

The primary endpoint is defined as: Change from baseline in Hb levels as mean of visits between Day 126 and Day 168.

9.3.2 Statistical model, hypothesis, and method of analysis

The primary objective is to assess the efficacy of iptacopan after 24 weeks of treatment in PNH patients who have Hb ≥10 g/dL in response to prior SoC treatment with eculizumab or ravulizumab and switch to iptacopan by demonstrating non-inferiority to -1 g/dL in change from baseline in Hb levels between Day 126 and Day 168.

It is proposed to use a NI margin based on clinical data and experience as well as on precedence with Hb stabilization as endpoints. In the 301 study (Lee et al 2019) and 302 study (Kulasekararaj et al 2019) with ravulizumab, Hb stabilization is defined as the avoidance of a ≥2 g/dL decrease in Hb level from baseline in the absence of transfusion, while in the Phase 3 PRINCE study with pegcetacoplan, a more conservative cutoff value of -1 g/dL was used (Wong et al 2021). Hence a decrease of less than 1 g/dL in Hb level from baseline at Day 168 does not indicate a decline in hematological response. Moreover, data from the ongoing study CLNP023C12301 indicates that the SD (inter-subject variability) of change from baseline in Hb levels between Day 126 and Day 168 is around 1.5 g/dL. This indicates that the NI margin

of -1 g/dL is within natural variability and is sufficient to demonstrate non-inferiority in Hb levels after treatment switch to iptacopan vs baseline (anti-C5).

Assuming that patients have stable Hb at study entry, the mean change from baseline in Hb level between Day 126 and Day 168 is expected to be unchanged should patients have continued on anti-C5 treatment. Non-inferiority of iptacopan will therefore be tested by the null hypothesis (H0) against the alternate hypothesis (H1) comparing the mean change from baseline in Hb level in iptacopan between Day 126 and Day 168 (μ) to -1 g/dL:

$H0: \mu <= -1$

$H1: \mu > -1$

Hypothesis testing for the primary objective is a 1-sided test with nominal significance level 0.025. Non-inferiority will be concluded, and primary objective will be considered met if the lower bound of the estimated two-sided 95% CI is greater than -1 g/dL.

The primary analysis of the primary endpoint will be a mixed model for repeated measures (MMRM) considering an unstructured covariance structure. The model will include age, sex, visit, baseline hemoglobin and the interaction between visits and baseline Hb levels. The treatment estimates will be computed as the mean changes from baseline corresponding to the average of Hb levels measured between Day 126 and Day 168.

Estimation of change from baseline in Hb levels is under the hypothetical situation in which participants would not have received transfusions on iptacopan treatment.

9.3.3 Handling of intercurrent events of primary estimand (if applicable)

Intercurrent events stemming from discontinuations of study medication for any reason, BTH events, and MAVEs will be handled with a treatment policy. RBC transfusions will be handled using an hypothetical strategy. Hb data 30 days after RBC transfusion will be excluded and imputed as if patient would not have received transfusions on iptacopan treatment.

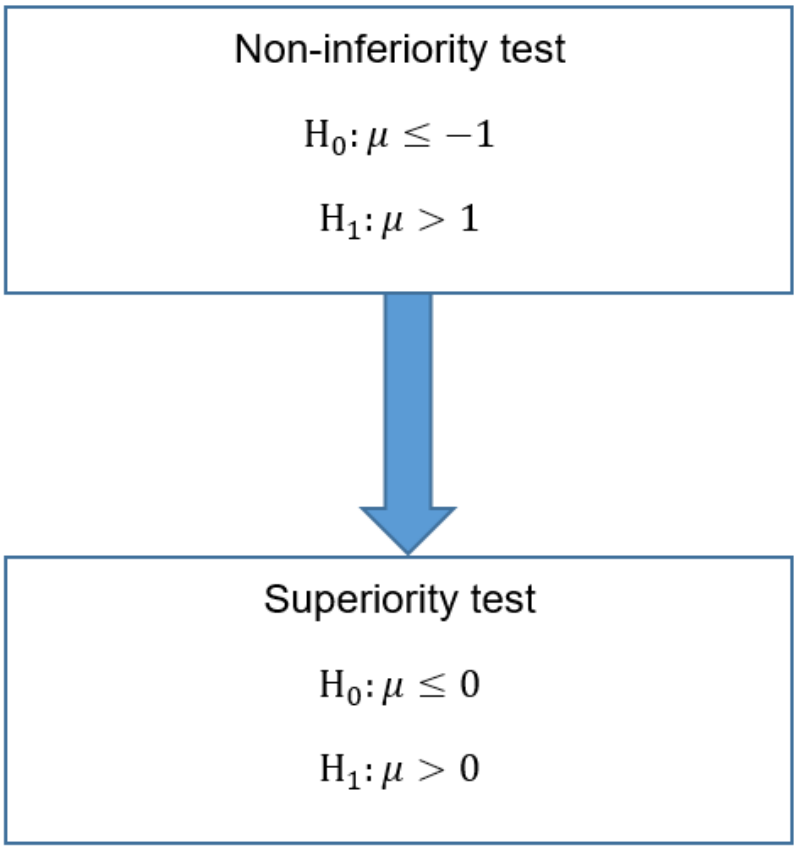
9.3.4 Handling of missing values not related to intercurrent event

Missing Hb data due to withdrawal from study or after treatment discontinuation will be imputed based on a “back to pre-treatment level” approach to be consistent with the inclusion of Hb data under the treatment policy strategy following all other intercurrent events. For participants with intermittent missing data during study follow up where reasons for missingness are assumed to be unrelated to response or compliance status, their missing data will be handled under the missing at random assumption. The full specification will be provided in the SAP.

9.3.5 Multiplicity adjustment (if applicable)

The non-inferiority test of iptacopan on primary endpoint and superiority test of iptacopan will be tested hierarchically. Multiplicity adjustment is not needed.

Figure 9-1 Hierarchy of testing non-inferiority and superiority of iptacopan



9.3.6 Sensitivity analyses

The sensitivity analyses on the primary endpoint and key secondary endpoint will be performed where missing central laboratory Hb data will be replaced by available local laboratory data collected at the same visit. The MMRM which is used for primary analysis and key secondary analysis will be performed for these sensitivity analyses.

9.3.7 Supplementary analysis

Not applicable.

9.4 Secondary endpoint(s)/estimand(s) analysis

9.4.1 Efficacy and/or pharmacodynamic endpoint(s)

The key secondary objective is to assess efficacy of iptacopan after 24 weeks of treatment in PNH patients who have Hb ≥10 g/dL in response to SoC and switch to iptacopan by demonstrating superiority in change from baseline in Hb levels between Day 126 and Day 168.

Ultomiris CHMP Assessment Report (EMA 2019) indicate that change from baseline in Hb levels at Day 168 is close to zero for PNH patients who received anti-C5 treatment. Suppose

PNH patients continue anti-C5 treatment without switch to iptacopan, the mean Hb levels at Day 168 should be close to mean Hb levels at baseline. Data from the PEGASUS study (Hillmen et al 2021) show that the least-square mean change from baseline in Hb was 2.37 g/dL with pegcetacoplan and -1.47 g/dL with eculizumab, indicating that patients of treatment with eculizumab may also worsen after 4 months of treatment. The results of a supportive analysis of the primary end point that included all available data (not censored for transfusions) showed that the adjusted mean change from baseline to Week 16 was 2.66 g /dL with pegcetacoplan and −0.03 g /dL with eculizumab indicating that the population of patients treated with eculizumab remained stable with the support of RBC transfusion. In the eculizumab group, patients with fewer than 4 transfusions in the 12 months before screening had a decrease in Hb of 0.01 g/dL**.** This indicated that the margin of 0 g/dL is an acceptable one to declare superiority of iptacopan over eculizumab/ravulizumab treatment. Based on the justification, superiority will be tested by the null hypothesis (H0) against alternative hypothesis (H1) comparing the mean change from baseline in Hb level in iptacopan between Day 126 and Day 168 (μ) to 0:

$$H0: \mu \leq 0$$

$$H1: \mu > 0$$

Hypothesis testing for the key secondary objective is a 1-sided test with nominal significance level 0.025. Superiority will be concluded and the key secondary objective will be considered met if the lower bound of the estimated two-sided 95% CI is greater than 0 g/dL. The statistical model for the key secondary endpoint is the same as for the primary analysis. The overall study Type I error is one-sided 0.025. The non-inferiority test of iptacopan on primary endpoint and superiority test of iptacopan will be tested hierarchically. Multiplicity adjustment is not needed.

The proportion of participants achieving sustained Hb levels ≥12 g/dL on three out of four measurements assessed between Day 126 and Day 168 in the absence of RBC transfusions will be evaluated by means of logistic regression with baseline Hb as a covariate, if feasible. In case of non-convergence, crude proportions will be reported. The analysis will be described in detail in the SAP.

Transfusion avoidance will be evaluated as the proportion of participants not requiring any RBC transfusion between Day 1 and Day 168, i.e., not received and not met the criteria for administration as per Section 6.8.1.1 The estimation will be evaluated as the estimand described above (logistic regression or crude proportions).

The estimation of the change from baseline in ARC will be derived from an MMRM. The model will include age, sex, visit, baseline ARC and the interaction between visits and baseline ARC. The treatment estimates will be computed as the mean changes from baseline corresponding to the average of ARC measured between Day 126 and Day 168.

The treatment effect on percent change from baseline in LDH will be assessed using an MMRM of log-transformed ratio to baseline based on all observations collected during follow-up. The model will include age, sex, visit, log-transformed baseline LDH and the interaction between visits and log-transformed baseline LDH. The estimation will be derived based on the average of the log-transformed ratio estimated between Day 126 and Day 168.

The difference in scores of treatment satisfaction using TSQM-9 and changes from baseline in scores of fatigue using the FACIT-F questionnaire will be derived from separate models for

repeated measures including test scores collected at all visits. For FACIT-F, the baseline is defined as the mean of scores obtained pre-treatment (Screening visit) and Day 1. The model will include age, sex, and visit. For Facit-F the model will also include the baseline score and the interaction between visits and baseline score.

The estimation of rates of BTH will be carried out using a negative binomial model. No covariates are planned to be included.

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

If the negative binomial model fails to converge or to give valid estimates, the Wilson method will be applied (Miettinen, Nurminen 1985).

9.4.2 Safety endpoints

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

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

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

Adverse events

All information obtained on AEs will be displayed by participant.

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

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

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant AEs leading to discontinuation, and AEs leading to discontinuation of study medication.

The number (and proportion) of participants with AESI / AEs related to identified and potential risks will be summarized.

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

Vital signs

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

12-lead ECG

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

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

Summary statistics will be provided by visit/time.

Clinical laboratory evaluations

Laboratory data for participants with relevant abnormalities will be listed by participant and visit/time relative to the start of study medication. Summary statistics and descriptive summaries will be provided by visit/time.

9.4.3 Patient reported outcomes

In this study, the question addressed by the analysis of PRO measurements is whether treatment with iptacopan improves patient-reported fatigue symptoms as measured by the FACIT-Fatigue, and satisfaction as measured by the TSQM-9, and these analyses are secondary endpoints described with the secondary endpoints/estimands.

9.5 Exploratory endpoint(s)/estimand(s) analysis

Detailed information on the analysis of the exploratory endpoints is provided in the SAP. The following endpoints have been identified as exploratory endpoints, between Day 1 and Day 168:

- Response defined as Hb ≥12 g/dL assessed between visits Day 126 and Day 168 on three out of four measurements taken at the visits occurring in last six weeks in the absence of CCI
- CCI
- CCI between Day 1 and Day 168
- CCI between Day 1 and Day 168
- CCI at Day 168
- Participant responses to a CCI . These results may be reported separately.
- CCI
- Occurrence of CCI between Day 1 and Day 168

The CCI [redacted] are described in subsequent sections.

The exploratory CCI [redacted] will be summarized descriptively.

The proportion of patients with CCI [redacted] will be summarized descriptively.

The CCI [redacted] will be summarized descriptively.

The details of each analysis will be provided in SAP.

9.5.1 Pharmacokinetics

All iptacopan plasma concentration data collected will be summarized by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ. Concentrations below the LLOQ will be reported as zero. Summary statistics will be presented as mean (arithmetic and geometric), SD, coefficient of variation (CV) (arithmetic and geometric), median, minimum, and maximum. Box plots by visit/sampling time may be provided as summaries if appropriate. If a data set contains concentrations below the LLOQ a geometric mean and the corresponding geometric mean CV% will not be reported.

Due to the sparse nature of the CCI [redacted], conventional noncompartmental CCI [redacted] will not be calculated. CCI [redacted] values will be reported.

Any model-based analyses using the PK and PD data collected in this study will be separately documented and not included in the CSR.

9.5.2 Biomarkers

Biomarker data constitute exploratory objectives and therefore are not described in term of estimands. Biomarkers assessment is mostly about mechanistic effect of the drug and therefore in this context summaries based on entirety of the data are appropriate.

Assessing the effect of iptacopan on CCI [redacted] and CCI [redacted] is an exploratory objective of the study. Hence the following endpoints on CCI [redacted] are exploratory:

- Percentage of CCI [redacted] Day 1 and Day 168
- CCI [redacted] collected between Day 1 and Day 168

The biomarkers will be summarized using descriptive statistics. Graphical depictions of percentage of CCI [redacted] over time will be provided. There will be separate summaries presented on on-treatment biomarker data and all available (including data after patients have

discontinued treatment) biomarker data. On-treatment biomarker data refers to data on biomarkers collected between first day of administration and last day of administration + 1 day.

Additional biomarkers, including but not limited to CCI may also be analysed to better characterize the CCI .

9.5.3 CCI

CCI studies are designed to investigate the association CCI which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with CCI . A range of statistical tests are used for the analyses. Additional data, from other clinical trials, are often needed to confirm associations. Alternatively, if the number of participants enrolled in the study is CCI .

Data generated on hypothesis-free platforms will be reported separately (e.g. CSR addendum).

9.5.4 CCI

As CCI

9.6 (Other) Safety analyses

Not applicable

9.7 Other analyses

Not applicable.

9.8 Interim analysis

If deemed required (e.g., to support regulatory submissions to Health Authorities), interim safety analyses may be produced while the study is still ongoing.

9.9 Sample size determination

Sample size is calculated based on the assumption that the true average change from baseline in Hb levels as mean of visits between Day 126 and Day 168 is 1.0 g/dL with SD 2.0 g/dL.

9.9.1 Primary endpoint(s)

For a sample size of 50 participants, the power for testing against a NI margin of -1 g/dL would be more than 94% based on the assumption that the true mean change from baseline in Hb levels as mean of visits between Day 126 and Day 168 is more than 0 g/dL with SD of 2.0 g/dL.

Table 9-1 Power for non-inferiority test based on different assumptions

True mean change from baseline in Hb (g/dL)	Standard deviation (g/dL)	Power
0.8	2.0	>99%
0.8	1.5	>99%
0.2	2.0	99%
0.2	1.5	>99%
0.0	2.0	94%
0.0	1.5	>99%
-0.2	2.0	81%
-0.2	1.5	96%
-0.6	2.0	29%
-0.6	1.5	47%

9.9.2 Secondary endpoint(s)

For a sample size of 50 participants, the power for testing against superiority would be 94% based on the same assumption the true mean change from baseline in Hb levels as mean of visits between Day 126 and Day 168 is 1.0 g/dL with SD of 2.0 g/dL.

Table 9-2 Power for superiority test based on different assumptions

True mean change from baseline in Hb levels (g/dL)	Standard deviation (g/dL)	Power
1.5	2.0	>99%
1.5	1.5	>99%
1.2	2.0	99%
1.2	1.5	>99%
1.0	2.0	94%
1.0	1.5	>99%
0.8	2.0	81%
0.8	1.5	96%
0.6	2.0	56%
0.6	1.5	81%

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, [IDFU], and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Signing 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
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), European In Vitro Diagnostic Regulation (IVDR) (EU) 2017/746 and all other applicable local regulations
- Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

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 Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

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

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

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

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

Information about common side effects already known about the investigational treatment can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also 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.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- Pregnancy Outcomes Reporting Consent for female participants
- Optional Genetics Consent to provide a sample for CCI studies
- Optional consent for patient experience interview

The study includes an optional CCI component which requires a separate signature if the participant agrees to participate. It is required as part of this protocol that the Investigator

presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

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

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

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

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

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

10.1.4.1 Data Monitoring Committee

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

10.1.4.2 Steering Committee

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

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

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan, contracts.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

Data not requiring a separate written record will be defined in the protocol and Section 1.3 Schedule of Activities 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

Designated Investigator staff will enter the data required by the protocol into the 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.

10.1.5.2 Database management and quality control

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

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

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in, e.g. source data acknowledgment or monitoring guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by Novartis. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in CTIS public website. In addition, after study completion (defined as last participant 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, CTIS public website etc.).

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

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

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

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.

10.1.8.1 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.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Alternative Pathway
aPTT	Activated partial thromboplastin time
ARC	Absolute Reticulocyte Count
AST	Aspartate Aminotransferase
AUC	Area under the curve
AxMP	Auxiliary Medicinal Product
b.i.d.	bis in die/twice a day
BMF	Bone Marrow Failure
BP	Blood Pressure
BTH	Breakthrough hemolysis
BTH	Break through hemolysis
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
Covid-19	Coronavirus Disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CV	coefficient of variation
DDI	Drug Drug Interaction
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EBMT	European Group for Bone Marrow Transplantation
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EoS	End of Study
ePRO	Electronic Patient Reported Outcome
ESA	Erythropoiesis-stimulating agents
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
ETD	Early Treatment Discontinuation
EVH	Extravascular Hemolysis
FACIT-F	Functional Assessment of Chronic Illness Therapy- Fatigue

FAS	Full Analysis Set
FB	Factor B
FDA	Food and Drug Administration
FIH	First in human
FSH	Follicle Stimulating Hormone
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	Hour
Hb	Hemoglobin
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High density lipoprotein
HIF-PHIs	Hypoxia Inducible Factors Prolyl Hydroxylase Inhibitors
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
i.v.	intravenous
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
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVDR	In Vitro Diagnostic Device Regulation
IVH	Intravascular Hemolysis
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
LOAEL	lowest dose where effect was seen
MAVE	Major Adverse Vascular Event
MCH	Mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed Model for Repeated Measures
NI	Non-inferiority
NO	Nitric Oxide
NTI	Narrow Therapeutic Index
OATP1B1	Organic Anion-transporting Polypeptide 1B1
OHP	Off-site Healthcare Professional

PD	Pharmacodynamic(s)
PIGA	phosphatidylinositol N acetylglucosaminyltransferase subunit A
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
PPD	Premature Participant Discontinuation
PRO	Patient Reported Outcomes
PT	prothrombin time
CCI	[redacted]
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
RBC	Red Blood Cell
RDW	Red blood cell distribution width
REP	Roll-over Extension Program
RU	Resource Utilization
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SCR	Screening set
SD	standard deviation
SoA	Schedule of Activities
SoC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
WBC	White Blood Cell
WHO	World Health Organization

10.2.2 Definitions

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
Auxiliary Medicinal Product (AxMP)	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess endpoints in the clinical trial). Concomitant therapy is not considered as AxMP.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.

Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents 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.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the ICH E9(R1) addendum, estimand is 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 participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
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.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else
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
Remote	Describes any trial activities performed at a location that is not the investigative site.
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 device	Study device is a medical device (marketed or investigational) that is used in a circumstance that makes it part of the investigation.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

ECG alert values

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

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

10.4 Appendix 4: Participant Engagement

Not applicable

10.5 Appendix 5: 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 10-1 in Section 10.5.1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 10-1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 10-1. Repeat liver chemistry tests (i.e. ALT, AST, etc.) to confirm elevation.

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

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), exposure to environmental chemical agents, alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease

These investigations can include based on Investigator's discretion:

- Imaging such as abdominal US, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), as appropriate
- Considering gastroenterology or hepatology consultations.

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

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-1 Definitions of Triggers, Actions and Follow-up requirements for liver events

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case (Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN – or 3 x ULN in the presence of bone pathology) (In patients with transaminases above the ULN at baseline, the Hy's Law criteria may be changed to increases 2-	● Discontinue the study treatment immediately (if possibly related to study treatment) ● Hospitalize, if clinically appropriate ● Report as SAE (even before all other possible causes of liver injury have been excluded) ● Establish causality (investigate alternative etiologies)[a] ● Record 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]

Criteria	Actions required	Follow-up monitoring
fold above baseline values)		
ALT		
> 8 × ULN	● Interrupt the study treatment (if possibly related to study treatment) ● Hospitalize if clinically appropriate ● Establish causality (investigate alternative etiologies)[a] ● Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	● ALT, AST, TBL, Alb, PT/INR, ALP and GGT (frequency at Investigator discretion) ● Monitor for symptoms[b] ● Report outcome[c]
> 3 × ULN and INR > 1.5 (in the absence of anticoagulation) If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	● Interrupt the study treatment (if possibly related to study treatment) ● Hospitalize if clinically appropriate ● Establish causality (investigate alternative etiologies)[a] ● Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline ● Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	● ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
> 5 to ≤ 8 × ULN If elevated at baseline: > 3 x baseline or > 300 U/L (whichever occurs first)	● Repeat LFT within 48 hours ● If elevation persists, continue follow-up monitoring ● If elevation persists for more than 2 weeks, discontinue the study drug ● Establish causality (investigate alternative etiologies)[a] ● Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	● ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
> 3 × ULN to ≤ 5 × ULN (accompanied by symptoms)[b] If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	● Interrupt the study treatment (if possibly related to study treatment) ● Hospitalize if clinically appropriate ● Establish causality (investigate alternative etiologies)[a] ● Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline ● Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	● ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion) ● Monitor for symptoms[b] ● Report outcome[c]
> 3 to ≤ 5 × ULN (patient is asymptomatic)[b] If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	● Repeat LFT within the next week ● If elevation is confirmed, initiate close observation of the participant	● Investigator discretion ● Monitor LFT within 1 to 4 weeks
ALP (isolated		
> 2 × ULN (in the absence of known bone pathology) >3 x ULN in the presence of if bone pathology	● Repeat LFT within 48 hours ● If elevation persists, establish causality (investigate alternative etiologies)[a] ● Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	● Investigator discretion ● Monitor LFT within 1 to 4 weeks or at next visit
Liver events		
Jaundice	● Interrupt the study treatment (if possibly related to study treatment) ● Hospitalize the participant ● Establish causality (investigate alternative	● ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)

Criteria	Actions required	Follow-up monitoring
	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	● 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.

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

10.6 Appendix 6: Renal safety monitoring

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.

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