NOVARTIS

Patient Safety & Pharmacovigilance

Non-Interventional Study Protocol (PASS) with secondary use of data

REDACTED PROTOCOL

CLNP023C12003

Title	Post-authorization safety study of iptacopan in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) using data from the non-interventional IPIG PNH Registry
Protocol version identifier	v01, Final
Date of last version of protocol	20-Aug-2024
FDA PMR number	4553-1
EU PAS register number	Study not registered
Active substance	Iptacopan
Medicinal product	Fabhalta (iptacopan) capsules for oral use
Product reference	US FDA procedure number: NDA 218276 EU procedure number: EMEA/H/C/5764
Name of Marketing authorization holder(s)	Novartis Pharmaceutical Corporation (US) Novartis Europharm Limited, Ireland (EU)
Joint PASS	No

Research question and objectives	The overall objective of this non-interventional study is to collect data on safety outcomes in paroxysmal nocturnal hemoglobinuria (PNH) patients treated with iptacopan in routine clinical practice. Primary objective: • to describe the risk of infections caused by encapsulated bacteria in patients with PNH treated with iptacopan.
Countries of study	Global study, list of participating countries will change
Author	[redacted] MSc, Epidemiology; MSc ETH, Medicinal and Industrial Pharmaceutical Sciences [redacted] Novartis Pharma AG [redacted] [redacted] 4056 Basel SWITZERLAND

Marketing authorization holder(s)

Marketing authorization holder(s)	**United States (US)** Novartis Pharmaceutical Corporation One Health Plaza East Hanover, NJ 07936 UNITED STATES **European Union (EU)** Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 IRELAND
MAH contact person	[redacted] MSc, Epidemiology; MSc ETH, Medicinal and Industrial Pharmaceutical Sciences [redacted] Novartis Pharma AG [redacted] 4056 Basel SWITZERLAND

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIF	Cumulative incidence function
CRF	Case Report/Record Form
EDC	Electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food & Drug Administration
GPP	Good Pharmacoepidemiology Practices
GRACE	Good Research for Comparative Effectiveness
GVP	Good Pharmacovigilance Practices
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IPIG	International PNH Interest Group
ISPE	International Society for Pharmacoepidemiology
LDH	Lactate dehydrogenase
LMP	Last Menstrual Period
MAH	Marketing Authorization Holder
MAVE	Major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
NIS-SUD	Non-interventional study based on secondary use of data
PASS	Post-Authorization Safety Study
PNH	Paroxysmal nocturnal hemoglobinuria
PT	Preferred Term
REQueST	Registry Evaluation and Quality Standards Tool
RMP	Risk Management Plan
RWD	Real-World Data
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

1 Responsible parties

Table 1-1 Responsible parties

Role	Person
Main protocol author(s)	[redacted] MSc, MSc ETH [redacted] [redacted] Novartis Pharma AG [redacted] [redacted] [redacted] Novartis Pharmaceutical Corporation [redacted] [redacted] [redacted] Novartis Pharma AG [redacted] [redacted] [redacted] Novartis Pharma AG [redacted] [redacted] [redacted] Novartis Pharma AG [redacted] [redacted] [redacted] Novartis Pharma AG [redacted] [redacted] [redacted] Novartis Pharma AG [redacted] [redacted] [redacted] Novartis Pharma AG [redacted] [redacted]

Role	Person
	[redacted] Novartis Pharma AG
Principal investigator (PI)	Not applicable
MAH contact person	[redacted] MSc, MSc ETH [redacted] Novartis Pharma AG [redacted] 4056 Basel SWITZERLAND

2 Abstract

Title

Post-authorization safety study of iptacopan in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) using data from the non-interventional IPIG PNH Registry

Version and date

Version 01, 20-Aug-2024

Name and affiliation of main author

[redacted]

MSc, Epidemiology; MSc ETH, Medicinal and Industrial Pharmaceutical Sciences

[redacted]

Novartis Pharma AG

[redacted]

[redacted]
4056Basel
SWITZERLAND

Rationale and background

Iptacopan (trade name: Fabhalta) is a first-in-class, orally administered factor B inhibitor of the alternative complement pathway developed by Novartis for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). The US Food and Drug Administration (FDA) granted approval for the treatment of adults with PNH on 05-Dec-2023 (NDA 218276) and the submission and review in other health authorities is currently underway.

PNH is a rare, acquired hematological disorder with an estimated prevalence of approximately 10 to 20 cases per million individuals worldwide. Clinically, PNH is characterized by complement mediated hemolysis leading to anemia and severe thrombophilia, and bone marrow failure.

The proposed non-interventional study (NIS) CLNP023C12003 intends to characterize the safety of iptacopan in routine clinical practice and to fulfill the US FDA postmarketing requirement (PMR) 4553-1 “Provide data from a registry that characterizes the long-term safety of Fabhalta in adults with paroxysmal nocturnal hemoglobinuria, with up to 5 years of follow-up”. This study also intends to fulfill the European Medicines Agency (EMA) criteria for a Post-Authorization Safety Study (PASS) and is proposed as an additional pharmacovigilance activity in the iptacopan Risk Management Plan (RMP) for the European Union (EU) submission, with the aim to better characterize the important identified and potential risks and missing information in the iptacopan RMP.

The International PNH Interest Group (IPIG) PNH Registry is a multinational, multi-center, observational registry led by an independent academic group with industry participation. It is designed to collect data on patients with PNH and those receiving treatments for their PNH in routine clinical practice. The IPIG PNH registry began patient enrollment in May 2024 and aims to collect data from 2000+ patients from multiple countries across several continents.

The IPIG PNH Registry will be comprised of the core PNH disease registry (“core PNH registry”), including all patients enrolled in the registry with collection of core variables at enrollment and during follow-up, and several product-specific silo protocols (“silos”) that include patients treated with PNH-specific therapies. The iptacopan-silo will thus include only PNH patients enrolled in the IPIG PNH Registry who are treated with iptacopan and will provide the study database for proposed study CLNP023C12003. This study is thus based on the secondary use of the data collected from the IPIG registry following treatment with iptacopan (“iptacopan silo”).

Research question and objectives

The primary objective of the study CLNP023C12003 is to describe the risk of infections caused by encapsulated bacteria in patients with PNH treated with iptacopan in routine clinical practice.

The following secondary objectives of the study are proposed to further characterize important safety outcomes and effectiveness of additional risk minimization measures in PNH patients treated with iptacopan:

- Describe the risk of serious infections caused by encapsulated bacteria and all serious infections
- Describe the proportion of patients receiving mandatory and recommended vaccinations against encapsulated bacteria
- Describe the risk of hemolysis events (during treatment and following discontinuation of iptacopan)
- Describe the risk of Major adverse vascular events (MAVEs) including thrombotic events
- Describe the risk of malignancies
- Describe the risk of hyperlipidemia
- Describe the risk of thrombocytopenia
- Describe the risk of serious adverse events (SAEs) and all-cause mortality
- Describe the use of iptacopan during pregnancy in PNH patients
- Describe characteristics of pregnancies in patients exposed to iptacopan and frequency of selected pregnancy outcomes.

Study design

This is a multinational non-interventional descriptive single-arm cohort study based on secondary analysis of the data collected within the iptacopan silo (the IPIG PNH Registry data on iptacopan-treated patients made available to Novartis). This study is thus a NIS based on secondary data use, and a "registry-based study". Due to IPIG PNH Registry data access limitations this study has no internal comparator.

Setting and study population

Data collection from the iptacopan-treated patients will begin after iptacopan launch in each country participating in the iptacopan silo. The currently proposed end of data accrual period for this study is Q1 2029, approximately 5 years from the enrollment of the first iptacopan-treated patient.

All patients with PNH confirmed by flow cytometry and who do not currently participate in an interventional PNH clinical trial will be invited to participate in the core PNH registry. Prior to any data collection, patients must sign informed consent or assent form (for minors). For the registry data to be included in the iptacopan silo dataset, the patients must initiate treatment with iptacopan and agree to the transfer of the silo data in the informed consent form.

All adult patients (aged ≥18 years) who meet the criteria for core PNH Registry and iptacopan silo participation will be included in the CLNP023C12003 study analysis. Each eligible patient will contribute data from the initiation of iptacopan treatment. Iptacopan-treated patients will be followed for safety outcomes until either of the following:

- Death
- Consent withdrawal
- Discontinuation of iptacopan or switch to another complement inhibitor (data collected for up to 12 weeks after stop of iptacopan treatment, or until the next documented visit, whichever is longer)
    - this period may be extended if the patient discontinues iptacopan while pregnant
    - for the main study analyses (with the exception of serious hemolysis following discontinuation of iptacopan and pregnancy-related outcomes), only events occurring until discontinuation or switch + 3 days will be considered; a sensitivity analysis for selected events will use all available data

- Discontinuation of data collection to the IPIG PNH registry (e.g., due to participation in an interventional PNH clinical trial, loss to follow-up or the end of IPIG PNH Registry data collection)
- End of the study period, currently expected to be 31-Mar-2029.

Variables

The only exposure of interest is treatment with iptacopan, as recorded by the IPIG PNH Registry investigators. Patients will be considered exposed to iptacopan from the first day of iptacopan treatment initiation until the date of discontinuation. Patients will be considered continuously exposed if the interruptions of iptacopan therapy do not exceed 3 days.

Infections caused by encapsulated bacteria (in particular, *Neisseria meningitidis*, *Streptococcus pneumoniae and Haemophilus influenzae*) in patients with PNH treated with iptacopan are the primary outcome of this study.

The following secondary outcomes are to be assessed among PNH patients treated with iptacopan:

- Serious infections caused by encapsulated bacteria (Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae)
- All serious infections
- Proportion of patients with vaccinations against encapsulated bacteria (*Neisseria meningitidis*, *Streptococcus pneumoniae and Haemophilus influenzae*) at the start of iptacopan treatment and at each subsequent visit)
- Hemolysis events and MAVEs:
- Breakthrough hemolysis
- Serious hemolysis following discontinuation of iptacopan (within 14 days from discontinuation)
- MAVEs including thrombotic events
- Malignancies
    - Solid tumors
    - Hematological malignancies
- Hyperlipidemia
- Thrombocytopenia
- SAEs
- All-cause mortality
- Pregnancy-related outcomes (assessed among patients with PNH exposed to iptacopan during pregnancy) may include the following:
    - Frequency of iptacopan exposure during pregnancy
    - Pregnancy outcomes including miscarriages, abortions, intrauterine death/stillbirths, live births, preterm births, normal newborn, small for gestational age, congenital malformations

Other study variables include demographic information, PNH disease and medical history, anti-complement therapy for PNH and other concomitant treatments.

Data sources

The IPIG PNH Registry is a multinational, multi-center, observational registry designed to collect data on patients with PNH and those receiving treatments for their PNH in a real-world setting. All patients with PNH will be eligible for registry participation, regardless of whether they are receiving PNH-specific therapy and regardless of what type of therapy they are receiving. Prior to any data collection, patients must sign informed consent or assent form. Patients will be followed for at least 5 years after their enrollment in the core PNH registry. Patients' visit schedules will follow standard of care. Patient data are expected to be entered in the electronic data capture system by the clinician and/or qualified designee at the time of registry enrollment and approximately every 6 months thereafter. Historical data from diagnosis prior to entry into the core PNH registry will be collected for individual patients either from sites directly or by transfer of data from previous registries.

In addition to the core PNH registry, several product-specific silo protocols ("silos") will be initiated including patients treated with PNH-specific therapies. Patient data collected within silos will be exclusive to the silo for the most recent 18 months of collected data. Data that are 18 months or older from any silo matching the core registry dataset, will be copied to the core PNH registry and will become available for aggregate analysis within the core PNH registry.

Patient data collected within one silo will be regularly provided to the marketing authorization holder (MAH) supporting the silo, provided the patients have agreed to the transfer of the silo data to the MAHs in the informed consent form. MAHs will not have access to any individual patient data in a silo that they do not support nor to individual patient data for patients only included in the core PNH registry.

Study size

As CLNP023C12003 is a descriptive, non-comparative study without a hypothesis to be tested, the target sample size is assessed in context of the expected precision of the study measures for outcomes related to infections caused by encapsulated bacteria (counts, percentages, and 95% CI).

Assuming that the observed proportion of these events in the iptacopan-treated PNH patient population in the real-world clinical practice is approximately the same as in the clinical trials (4% and 1% for all and serious infections caused by encapsulated bacteria, respectively, with an average treatment duration of approximately 1 year), the expected length of 95%CIs for these proportions would be 1.7% to 7.7% and 0.1% to 3.6%, respectively, in a sample size of 200 patients.

The actual study size achieved will depend on the uptake of Iptacopan in the PNH patient population. The aim is to reach at least 200 iptacopan-treated patients after 5 years of study data collection, to achieve at least a study size comparable to the size of the initial registration clinical trials' PNH safety pool. However, the goal will be to enroll as many iptacopan-treated PNH patients as possible to maximize the study precision.

Data analysis

A statistical analysis plan (SAP) detailing the analysis to be conducted for this study will be developed prior to the first data lock point. Annual interim reports will include the key characteristics of the patient population and the study outcomes based on the cumulative data collected since the beginning of the study. The analyses in the interim reports will include, as the minimum, the analysis of the primary endpoint, a summary of the major safety findings for all patients, and the risk of serious infections with encapsulated bacteria.

Data analyses will be mainly descriptive in nature, with no comparisons planned.

Patient demographics and baseline characteristics, including characteristics of iptacopan use, relevant medical and obstetric history will be summarized descriptively. Distributions of continuous variables will be summarized with means (standard deviations), medians, interquartile range and absolute range. Categorical variables will be summarized with proportions. Missing values will be reported as a separate category.

The analysis in this study will be focused on the while-on-treatment and the hypothetical risk estimands. The treatment policy estimand strategy will not be implemented in this study because subjects discontinuing iptacopan are expected to start another PNH therapy.

The primary study outcomes will be summarized as frequency (counts and percentages), cumulative incidence (event probability as a function of time), incidence rates (number of patients with event per 100 patient-years) and occurrence rates (number of episodes per 100 patient-years) for the primary analysis population. The secondary study outcomes will be summarized as frequency, and, if applicable, cumulative incidence, incidence rates and occurrence rates as well.

Milestones

Planned dates of study milestones:

Start of data collection, i.e. start date of data extraction: 31 March 2025

End of data collection, i.e. date from which the analytical dataset is completely available: 31 July 2029

Interim report 1: 30 September 2025

Interim report 2: 30 September 2026

Interim report 3: 30 September 2027

Interim report 4: 30 September 2028

Registration in the EU PAS register: 01 Mar 2025

Final report of study results: 31 Mar 2030

3 Amendments and updates

Table 3-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
01	20 Aug 2024	2, 6.2, 7.3.2, 7.7.4	Amendment 01 to include new secondary safety outcomes (hyperlipidemia, thrombocytopenia) per FDA request	After review of the study protocol version 00 by the FDA, additional outcomes of hyperlipidemia and thrombocytopenia were added to the study Protocol Amendment 01.
01	20 Aug 2024	2, 4, 7.2, 7.2.2, 7.4.3, 7.5	Update to reflect current status of the registry (incorporated in Amendment 01)	Updated wording throughout to reflect that IPIG PNH Registry initiated patient enrollment since the previous protocol version 00
01	20 Aug 2024	11	Update	Updated the IPIG core registry documents to the versions current as of Amendment 01

4 Milestones

The enrollment of patients in the IPIG PNH Registry (source data for this non-interventional study based on secondary use of data [NIS-SUD]) began in May 2024 in the United States, and the first patient to the iptacopan silo was enrolled in July 2024. Iptacopan patients from other countries are expected to join registry later in 2024, after corresponding Health Authority approvals are granted and the product launches occur. The start of data collection (for NIS-SUD, this is defined as the date from which data extraction starts) is proposed on 31-Mar-2025, after approximately one year has elapsed from the enrollment of the first iptacopan-treated patient in the IPIG PNH Registry.

The currently proposed end of data accrual for NIS CLNP023C12003 is Q1 2029, approximately 5 years from the expected enrollment of the first iptacopan-treated patient in the IPIG PNH Registry. The date from which the final analytical dataset (i.e., the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study, referred to as “End of data collection” as per Good Pharmacovigilance Practices

[GVP] Module VIII) would be completely available is estimated to be 31-Jul-2029, and the final report of the study results is expected to be produced by 31-Mar-2030.

Further planned study milestones are described in the table below.

Table 4-1 Planned dates of study milestones for CLNP023C12003

Milestone	Planned date
Start of data collection (NIS-SUD: start of data extraction)	31 Mar 2025
End of data collection	31 Jul 2029
Final Interim report 1	30 Sep 2025
Final Interim report 2	30 Sep 2026
Final Interim report 3	30 Sep 2027
Final Interim report 4	30 Sep 2028
Registration in the EU PAS register	01 Mar 2025
Final report of study results	31 Mar 2030

5 Rationale and background

Iptacopan (trade name: Fabhalta) is a first-in-class, orally administered factor B inhibitor of the alternative complement pathway developed by Novartis for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). The US Food and Drug Administration (FDA) granted approval for the treatment of adults with PNH on 05-Dec-2023 (NDA 218276) and the submission to other health authorities is currently underway. Iptacopan targets the alternative pathway of the complement cascade proximally and in PNH inhibits both intravascular and C3-mediated extravascular hemolysis. Iptacopan is also being developed for other complement mediated hematologic and renal diseases.

PNH is a rare, acquired hematological disorder with an estimated prevalence of approximately 10 to 20 cases per million individuals worldwide (Cançado et al 2021). PNH can affect any age group but frequently affects young adults. PNH is estimated to affect males and females with slight female preponderance (Hill et al 2017), although in one meta-analysis, the proportion of women with PNH was significantly lower in Asian countries than in western countries (Yu et al 2016). Clinically, PNH is characterized by complement mediated hemolysis leading to anemia and severe thrombophilia, and bone marrow failure (Risitano 2012).

In the Phase III clinical trials (APPLY-PNH [NCT04820530], active-controlled; and APPOINT-PNH [NCT04820530], single arm), 200 mg oral twice-daily iptacopan was highly effective, providing transfusion-free hemoglobin-level increases (relative to baseline) and transfusion independence for the vast majority of the trial participants, with good tolerability and a favorable safety profile (Novartis 2022).

The proposed NIS CLNP023C12003 intends to characterize the safety of iptacopan in routine clinical practice and to fulfill the US FDA postmarketing requirement (PMR) 4553-1 “Provide data from a registry that characterizes the long-term safety of Fabhalta in adults with paroxysmal nocturnal hemoglobinuria, with up to 5 years of follow-up”.

This study also intends to fulfill the European Medicines Agency (EMA) criteria for a Post-Authorization Safety Study (PASS) and is proposed as an additional pharmacovigilance activity

in the iptacopan Risk Management Plan (RMP) for the European Union (EU) submission with the aim to better characterize the important potential risks and missing information in the iptacopan RMP. The study may also potentially be used to generate iptacopan safety data to address questions or requests from other Health Authorities outside of the EU and the US.

The IPIG PNH Registry is a multinational, multi-center, observational registry led by an independent academic group with industry participation. It is designed to collect data on patients with PNH and those receiving treatments for their PNH in routine clinical practice. The IPIG PNH registry began patient enrollment in May 2024 and aims to collect data from 2000+ patients with PNH (any treatment status) from the US, Canada and multiple other countries in Europe, Asia and other continents.

The aim of the IPIG PNH Registry is to develop an international database to collect longitudinal data on patients with PNH covering clinical outcomes, patient reported outcomes, and health-resource utilization on all enrolled patients, as well as long term safety data. This registry is intended to increase knowledge about PNH in the medical community and patient population. All patients (adults and minors) with PNH will be eligible to enroll in the IPIG PNH registry, regardless of whether they are receiving PNH-specific therapy and regardless of what type of therapy they are receiving (IPIG 2024a).

The IPIG PNH Registry will be comprised of the core PNH disease registry ("core PNH registry"), including all patients enrolled in the registry with collection of core variables at enrollment and during follow-up, and several product-specific silo protocols ("silos") that include patients treated with PNH-specific therapies, in order to collect specific data and address specific objectives or requests from regulatory authorities. The iptacopan-silo will thus include only PNH patients enrolled in the IPIG PNH Registry who are treated with iptacopan and will provide the study database for proposed study CLNP023C12003, a NIS based on the secondary use of data.

6 Research question and objectives

The overall objective of this non-interventional study CLNP023C12003 is to collect data on safety outcomes in patients treated with iptacopan for PNH.

6.1 Primary objective

The primary objective of the study is to describe the risk of infections caused by encapsulated bacteria in patients with PNH treated with iptacopan in routine clinical practice. Risk will be evaluated in terms of frequency (counts and percentages), cumulative incidence (event probability as a function of time), incidence rates (number of patients with events per 100 patient-years) and occurrence rates (number of episodes per 100 patient-years). Incidence and occurrence rates will be calculated by year of treatment and for the entire duration of the study.

Table 6-1 Primary objective for CLNP023C12003

Objective:	To describe the risk of infections caused by encapsulated bacteria in patients with PNH treated with iptacopan in routine clinical practice.
Hypothesis:	None

Cohort *(mention key inclusion-exclusion criteria):*	"Iptacopan": PNH patients aged ≥18 years treated with iptacopan and not participating in an interventional clinical trial (see Section 7.2)
Exposure:	Iptacopan
Comparator:	None
Outcome:	Infections caused by encapsulated bacteria (*Neisseria meningitidis*, *Streptococcus pneumoniae, Haemophilus influenzae*)
Time *(when follow up begins and ends):*	Follow up from the initiation of iptacopan until discontinuation or switch to another complement inhibitor, death, consent withdrawal, end of study period, or end of data collection to the registry
Setting:	Outpatient or inpatient care, as recorded by the IPIG PNH Registry investigators
Main measures of effect:	Counts and percentages, cumulative incidence, incidence rate, occurrence rate

6.2 Secondary objectives

The secondary objectives of the study CLNP023C12003 are to further characterize important safety outcomes, including risk of serious infections caused by encapsulated bacteria and all serious infections, serious hemolysis following discontinuation, other clinical events such as breakthrough hemolysis, malignancies, other serious adverse events (SAEs), and pregnancy outcomes. After review of the study protocol version 00 by the FDA, additional secondary outcomes of hyperlipidemia and thrombocytopenia were added in the Protocol Amendment 01. In addition, the study will evaluate effectiveness of additional risk minimization measures related to vaccination requirements in PNH patients treated with iptacopan, as summarized in Table 6-2 below.

Table 6-2 Secondary objectives for CLNP023C12003

Objective	Cohort	Outcomes	Follow-up	Measures of effect
To describe the short- and long-term risk of the following events in patients with PNH treated with iptacopan in routine clinical practice: • Serious infections caused by encapsulated bacteria • All serious infections • Potential breakthrough hemolysis	"Iptacopan": PNH patients aged ≥18 years, treated with iptacopan and not participating in an interventional clinical trial (see Section 7.2)	• Serious infections caused by encapsulated bacteria • All serious infections • Potential breakthrough hemolysis • Solid tumors • Hematological malignancies • MAVEs • Hyperlipidemia • Thrombocytopenia • SAEs • All-cause mortality	From the initiation of iptacopan until discontinuation or switch to another complement inhibitor, death, consent withdrawal, end of study period, or end of data collection to the registry	• Counts and percentages • Cumulative incidence • Incidence rate • Occurrence rate (all outcomes except all-cause mortality) Incidence and occurrence rates calculated by year of treatment and for the entire study period

Objective	Cohort	Outcomes	Follow-up	Measures of effect
• Malignancies (solid tumors, hematological malignancies) • Major adverse vascular events (MAVEs) • Hyperlipidemia • Thrombocytopenia • Serious adverse events (SAEs) • All-cause mortality		Details are provided in Section 7.3.2		
To describe the proportion of patients receiving mandatory and recommended vaccinations against encapsulated bacteria	"Iptacopan": PNH patients aged ≥18 years, treated with iptacopan and not participating in an interventional clinical trial (see Section 7.2)	Recorded vaccinations against each of the following organisms at each study visit: • *Neisseria meningitidis* • *Streptococcus pneumoniae* • *Haemophilus influenzae*	From the initiation of iptacopan until discontinuation or switch to another complement inhibitor, death, consent withdrawal, end of study period, or end of data collection to the registry	• Counts and percentages Vaccination status to be evaluated at the start of iptacopan treatment and at each subsequent visit.
To describe the risk of serious hemolysis following discontinuation of iptacopan in patients with PNH treated with iptacopan in routine clinical practice	"Discontinuation": PNH patients aged ≥18 years who have discontinued previous treatment with iptacopan and not participating in an interventional clinical trial (see Section 7.2)	• Serious hemolysis following discontinuation of iptacopan	From the day of iptacopan discontinuation or switch to another complement inhibitor until 14 days post-discontinuation, death, consent withdrawal, end of study period, or end of data collection to the registry	• Counts and percentages • Incidence rate
To describe the frequency of use of iptacopan during pregnancy in PNH patients, characteristics of pregnancies exposed to iptacopan and frequency of selected pregnancy and birth outcomes	"Pregnancy": PNH patients aged ≥18 years who became pregnant during treatment with iptacopan, not participating in an interventional clinical trial (see Section 7.2)	• Number of patients in this cohort and exposure characteristics (e.g. trimester of exposure) • Pregnancy outcomes; birth outcomes (refer to Section 7.3.2 for detailed description)	From the Last Menstrual Period (LMP) to pregnancy outcome (in case of live birth, up to 12 months post delivery), death, consent withdrawal, end of study period, or end of data collection to the registry	• Counts and percentages

7 Research methods

7.1 Study design

CLNP023C12003 is a multinational non-interventional descriptive single-arm cohort study based on secondary analysis of the data collected within the iptacopan silo (the IPIG PNH Registry data on iptacopan-treated patients made available to Novartis). For the detailed description of the underlying IPIG PNH core registry and the iptacopan silo, please see Section 7.4.

The study CLNP023C12003 is thus a NIS based on secondary data use, and a "registry-based study" according to the definition in the EMA Guideline on registry-based studies (EMA 2021). It has no internal comparator arm due to the data access rules as laid out within the IPIG PNH Registry protocol (IPIG 2024a), where each Marketing Authorization Holder (MAH) may only have access to the data from the PNH patients treated with their own medicinal products.

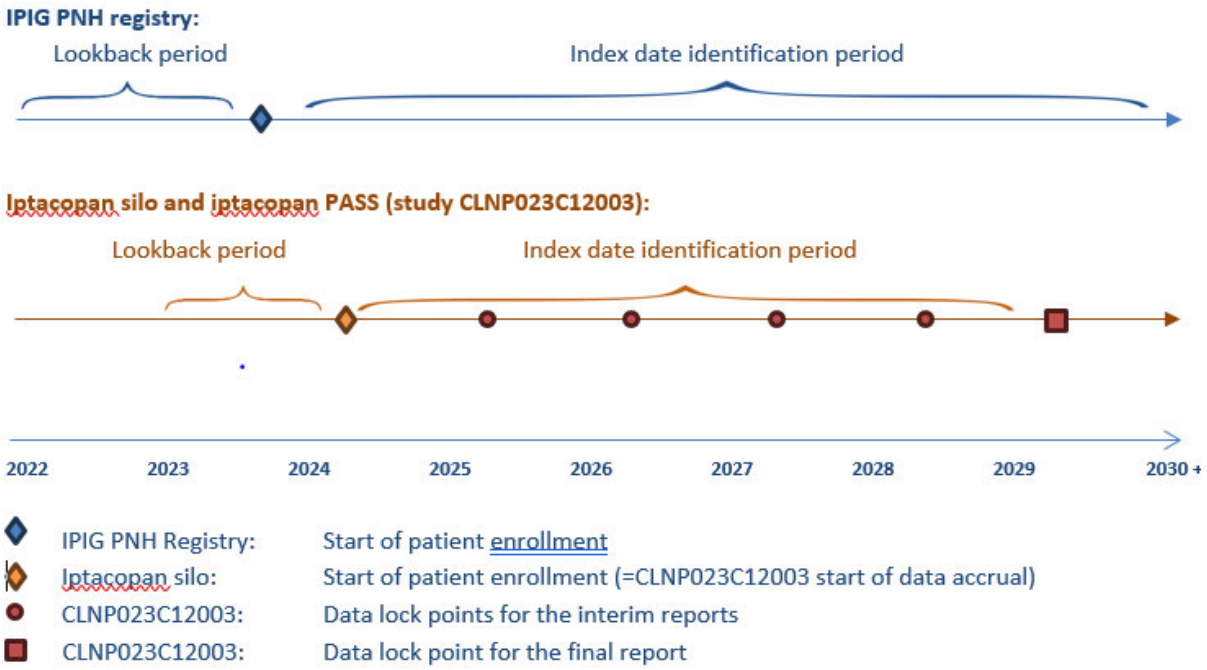
7.2 Setting and study populations

The IPIG PNH Registry is observational and the clinician's drug prescription or therapeutic management of the patient is not influenced by the patients' choice to participate in the registry. No treatment will be provided because of participating in the IPIG PNH registry. The decision to treat patients with a PNH-specific therapy will be independent from the decision to enroll patients in the registry.

Data collection from the iptacopan-treated patients will begin after iptacopan launch in each country participating in the iptacopan silo (number of sites contributing data to iptacopan silo may be less than those participating in the core PNH Registry).

The currently proposed end of data accrual period for this study is Q1 2029, approximately 5 years from the enrollment of the first iptacopan-treated patient; patients in the study will thus be followed for up to 5 years. The major milestones for the IPIG PNH core registry, iptacopan silo and this study CLNP023C12003 (based on secondary data) are further clarified in Figure 7-1 below.

Figure 7-1 Graphical representation of the key milestones in the IPIG PNH core registry, iptacopan silo and study CLNP023C12003



Each eligible patient (see Section 7.2.2) will contribute data from the initiation of iptacopan treatment. Baseline characteristics and patient history will be available for up to twelve months prior to first iptacopan treatment for PNH.

Iptacopan-treated patients will be followed for safety outcomes until either of the following:

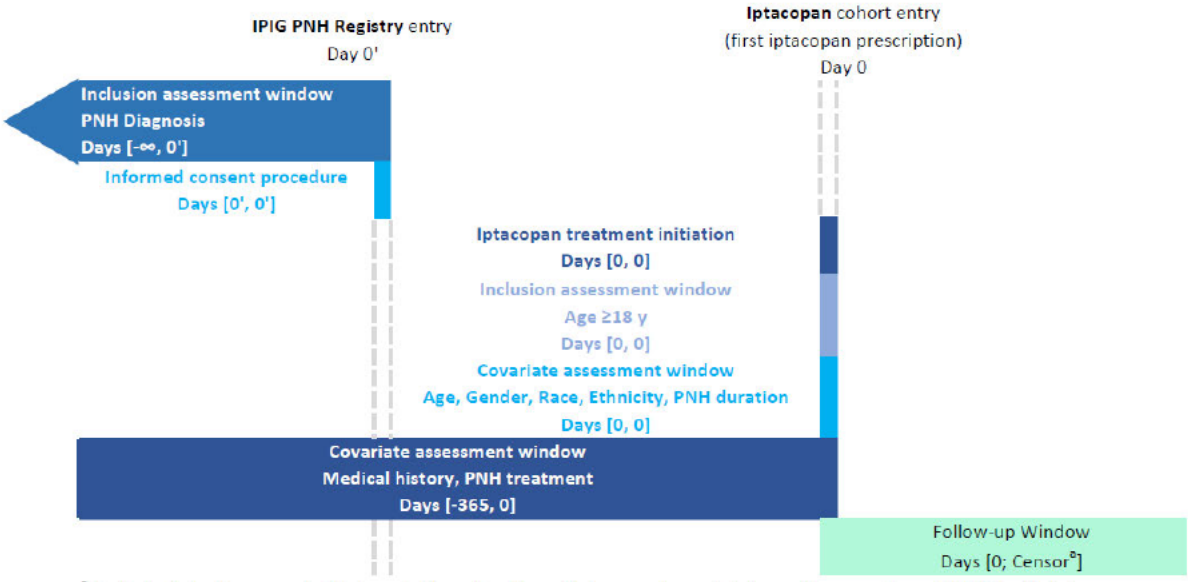
- Death
- Consent withdrawal
- Discontinuation of iptacopan or switch to another complement inhibitor (data collected for up to 12 weeks after stop of iptacopan treatment, or until the next documented visit, whichever is longer)
  - this period may be extended if the patient discontinues iptacopan while pregnant (see Section 7.4.3).
  - for the main study analyses, only events occurring until discontinuation or switch + 3 days will be considered (with the exception of "serious hemolysis following iptacopan discontinuation" and pregnancy outcomes); a sensitivity analysis for selected events will use all available data (see Section 7.7.5)
- Discontinuation of data collection to the IPIG PNH registry (e.g. due to participation in an interventional PNH clinical trial, loss to follow-up or the end of IPIG PNH Registry data collection)
- End of the study period, currently expected to be 31-Mar-2029.

7.2.1 Definition of time 0 (and other primary time anchors) for study cohorts

For the primary study population ("Iptacopan" cohort, patients with PNH exposed to iptacopan), time 0 (index date) will be the day of initiation of iptacopan, as recorded by the IPIG PNH Registry investigators. The primary study population includes only incident patients (i.e. newly

exposed to iptacopan), however patients may contribute patient-time to the analysis cohort from multiple treatment episodes, if patients discontinue iptacopan and then re-start treatment later (applicable for all analyses except the cumulative incidence). The washout period for cohort re-entry is 3 days, i.e. if patients re-initiate iptacopan within this period they are considered continuously exposed. The key study periods for the Iptacopan cohort relative to the IPIG PNH core registry entry are described in the figure below.

Figure 7-2 Graphical representation of the "Iptacopan" study cohort in the study CLNP023C12003



[a] Earliest of: death, consent withdrawal, discontinuation of iptacopan (or switch to another complement inhibitor) + 3 days, discontinuation of data collection to the IPIG PNH Registry, end of the CLNP023C12003 study period

In addition to the primary study population, two additional cohorts are defined for specific secondary outcomes, these together with the Iptacopan cohort are described in the table below.

Table 7-1 Operational definition of time 0 (index date) and other primary time anchors for CLNP023C12003

Study cohort name	Time Anchor Description (e.g. time 0)	Number of entries	Washout window	Type of entry	Incident with respect to…	Measurement characteristics/ validation
Iptacopan *(primary study population)* Patients with PNH exposed to iptacopan	Date of initiation of iptacopan (time 0)	Multiple	[-3 days; 0]	Incident	Previous use of iptacopan	As recorded by IPIG PNH Registry investigators

Discontinuation Patients with PNH after iptacopan discontinuation	Date of iptacopan discontinuation (time 0)	Multiple	None	Other	N/A	Derived from the dates of iptacopan discontinuation or interruption, as recorded by IPIG PNH Registry investigators
Pregnancy Patients with PNH exposed to iptacopan during pregnancy	Last Menstrual Period (LMP) (time 0)	Multiple	None	Other	N/A	Derived from pregnancy due date as recorded by IPIG PNH Registry investigators

7.2.2 Study inclusion criteria

All adult patients (aged ≥18 years) who meet the criteria for core PNH Registry and iptacopan silo participation will be included in the safety evaluation for the duration of the study period of this study CLNP023C12003 (expected as Q2 2024-Q1 2029).

The core PNH Registry and the iptacopan silo dataset do not impose restrictions on the patient age; however, study CLNP023C12003 aims to focus on the patients with PNH who are aged at least 18 years at the iptacopan initiation date per the current approved iptacopan PNH label. If any pediatric patients (aged <18 years at the iptacopan initiation) are enrolled in the core PNH Registry and subsequently the iptacopan silo, they will be noted in the study attrition table.

All patients with PNH confirmed by flow cytometry and who do not currently participate in an interventional PNH clinical trial will be invited by the investigators to participate in the core PNH registry. Prior to any data collection, patients must sign informed consent or assent form [redacted].

For the registry data to be included in the iptacopan silo dataset, the patients must initiate treatment with iptacopan and agree to the transfer of the silo data to the MAHs in the informed consent form. For detailed rules of stopping the data collection to the iptacopan silo, see Section 7.4.3.

The operational definitions of all inclusion criteria that would be applied to the study cohorts are summarized in the Table 7-2 below.

Table 7-2 Operational definitions of inclusion criteria for CLNP023C12003

Criterion	Details	Order of application	Assessment window	Applied to study cohorts	Measurement characteristics/ validation
PNH diagnosis	Confirmed by flow cytometry	Evaluated before joining the IPIG PNH Registry	[-∞, 0']	All	As recorded by IPIG PNH Registry investigators

Criterion	Details	Order of application	Assessment window	Applied to study cohorts	Measurement characteristics/ validation
Informed consent	Patient and/or parent / legally authorized representative provide written informed consent/assent to participate in the IPIG PNH Registry	Evaluated before joining the IPIG PNH Registry	[0', 0']	All	As recorded by IPIG PNH Registry investigators
Iptacopan treatment	Patient initiates treatment with iptacopan as recorded in the registry CRF	Required to contribute data to iptacopan silo	[0, 0]	All	As recorded by IPIG PNH Registry investigators
Age ≥18 yrs	Patient is aged at least 18 years at the iptacopan initiation date	Required for all study cohorts	[0, 0]	All	As recorded by IPIG PNH Registry investigators
Discontinued iptacopan treatment	Discontinuation of treatment with iptacopan as recorded in the registry CRF (if no re-initiation within 3 days)	Required for "Discontinuation" cohort	[0, 0] relative to cohort-specific index date	Discontinuation	Derived from iptacopan discontinuation date as recorded by IPIG PNH Registry investigators if no re-initiation within 3 days
Pregnancy	Patient is pregnant as recorded in the registry CRF and the derived last menstrual period (LMP) falls within the period of iptacopan treatment	Required for "Pregnancy" cohort	[iptacopan initiation, iptacopan discontinuation + 3 days]	Pregnancy	As recorded by IPIG PNH Registry investigators

0': time zero relative to IPIG PNH Registry core data collection
CRF: case report form

7.2.3 Study exclusion criteria

A key exclusion criterion from the core IPIG PNH Registry is participation in an interventional PNH clinical trial. For a patient already included in the registry, who enrolls in an interventional PNH clinical trial, data collection in the registry will be paused during their involvement in the clinical trial/extension study. This data will thus not be available for the planned study analysis. Once the patient stops interventional trial participation, data collection in the registry will resume.

For the study CLNP023C12003, no additional exclusion criteria will be applied.

7.2.4 Follow-up

For most study outcomes, an on-treatment follow-up analysis will be implemented (exception being outcomes after iptacopan discontinuation). Follow-up rules for the three study cohorts are summarized in Table 7-4.

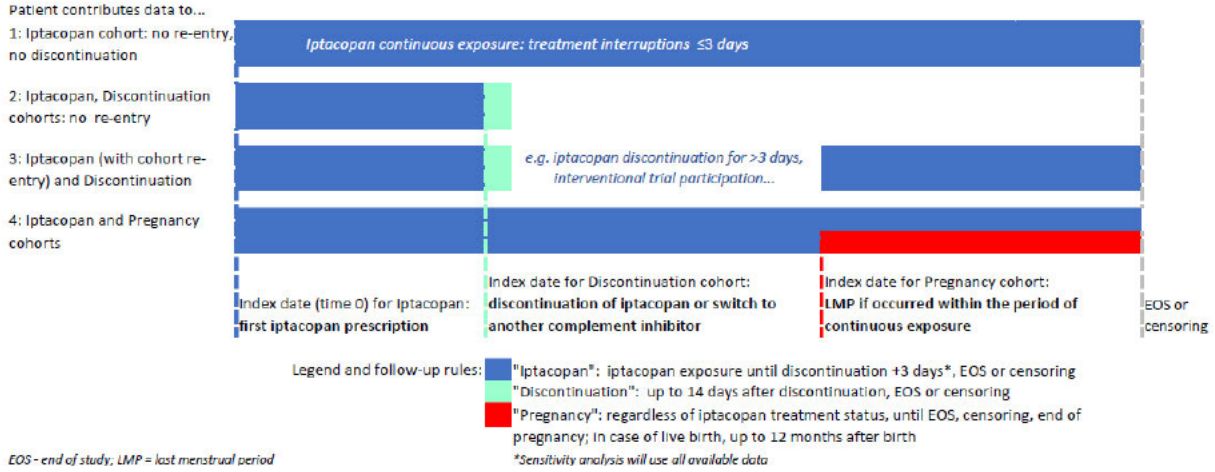
Table 7-3 Operational definitions of follow-up for CLNP023C12003

Cohort	Follow-up start	Follow-up end
Iptacopan	The day of iptacopan initiation	Earliest of discontinuation or switch to another complement inhibitor +3 days, death, consent withdrawal, end of study period, or end of data collection to the registry
Discontinuation	The day of iptacopan discontinuation or switch to another complement inhibitor	Earliest of 14 days post-discontinuation of iptacopan, death, consent withdrawal, end of study period, or end of data collection to the registry
Pregnancy	LMP derived from the data provided by the PNH Registry investigator	Earliest of pregnancy outcome (in case of live birth, up to 12 months post-delivery), death, consent withdrawal, end of study period, or end of data collection to the registry

LMP: last menstrual period

A few possible scenarios that are thus possible for the cohort entry and follow-up (depending on the iptacopan treatment pattern) in the study CLNP023C12003 are illustrated in Figure 7-3.

Figure 7-3 Graphical illustration of a few cohort entry and follow-up scenarios for the study cohorts for CLNP023C12003



7.3 Variables

7.3.1 Exposure of interest

Due to the IPIG PNH Registry data access limitations (see Section 7.4) this study has no internal comparator. The only exposure of interest is treatment with iptacopan (ATC code still pending at the time of protocol finalization) as recorded by the IPIG PNH Registry investigators. Previous/concomitant exposure to other complement therapy (eculizumab, ravulizumab, pegcetacoplan and other if applicable) will be recorded as part of covariates (see Section 7.3.3).

Duration of exposure effect:

Patients will be considered exposed to iptacopan from the first day of iptacopan treatment initiation until the date of discontinuation or treatment switch as recorded in the case report form (CRF) by the IPIG PNH Registry investigators. Patients will be considered continuously exposed if the interruptions of iptacopan therapy (as recorded by the registry investigators) do not exceed 3 days.

7.3.2 Outcomes of interest

Infections caused by encapsulated bacteria (*Neisseria meningitidis*, *Streptococcus pneumoniae and Haemophilus influenzae*) in patients with PNH treated with iptacopan are the primary outcome of the study CLNP023C12003. This outcome was selected as "Infections caused by encapsulated bacteria" was proposed as the important identified risk in the iptacopan EU RMP and is a known class effect for other PNH treatments. The FDA PMR specifically asked for a summary of serious infections caused by encapsulated bacteria; this subset of all infections caused by encapsulated bacteria was also included to the study as one of the secondary outcomes. In addition, after review of the study protocol version 00 by the FDA, additional secondary outcomes of hyperlipidemia and thrombocytopenia were added in the Protocol Amendment 01.

Table 7-4 provides the full list and the proposed operational definitions of primary and secondary study outcomes for CLNP023C12003. The list of the secondary outcomes including any subgroups will be further refined in the study Statistical Analysis Plan (SAP).

Table 7-4 Operational definitions of outcomes for CLNP023C12003

Outcome or outcomes group*	Details	Primary outcome?	Type of outcome	Applied to study cohorts	Measurement characteristics/ validation
Infections caused by encapsulated bacteria	Causative organisms: *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*	Yes	Binary, Categorical	Iptacopan	As recorded by the IPIG PNH Registry investigators
Serious infections caused by encapsulated bacteria	Causative organisms: *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*	No	Binary, Categorical	Iptacopan	"Serious" infections will be defined as those reported as SAEs by the investigators, or resulting in hospitalization or death, as recorded by the IPIG PNH Registry investigators

Outcome or outcomes group*	Details	Primary outcome?	Type of outcome	Applied to study cohorts	Measurement characteristics/ validation
All serious infections	Infection sites in the CRF: • Respiratory • Urine • Gastrointestinal • Nervous system • Skin • Sepsis • Line-related infection • Other (free text)	No	Binary	Iptacopan	"Serious" infections will be defined as those reported as SAEs by the investigators, or resulting in hospitalization or death, as recorded by the IPIG PNH Registry investigators
Vaccinations against encapsulated bacteria	• Neisseria meningitidis (required) • Streptococcus pneumoniae (required) • Haemophilus influenzae (recommended; may not be available in all countries where patient data is collected)	No	Binary, Categorical	Iptacopan	For each vaccine type, information on specific serotypes to be collected if available
Potential breakthrough hemolysis	As recorded on the "Potential Breakthrough Hemolysis" CRF page Sensitivity analysis: see Section 7.7.5	No	Binary	Iptacopan	As recorded by the IPIG PNH Registry investigators
Serious hemolysis following discontinuation of iptacopan	Same definitions as for Potential breakthrough hemolysis Sensitivity analysis: see Section 7.7.5	No	Binary	Discontinuation	"Serious" events will be defined as those reported as SAEs by the investigators, or resulting in hospitalization or death, as recorded by the IPIG PNH Registry investigators
MAVEs including thrombotic events	1: Thrombophlebitis/ Deep Vein Thrombosis 2: Pulmonary Embolus 3: Myocardial Infarction 4: Transient Ischemic Attack 5: Renal Vein Thrombosis 6: Acute Peripheral Vascular Occlusion 7: Mesenteric / visceral Vein Thrombosis 8: Mesenteric / visceral Arterial Thrombosis 9: Dermal Thrombosis 10: Cerebral Arterial Occlusion / CVA 11: Cerebral Venous Occlusion	No	Binary	Iptacopan	As recorded by the IPIG PNH Registry investigators

Outcome or outcomes group*	Details	Primary outcome?	Type of outcome	Applied to study cohorts	Measurement characteristics/ validation
	12: Renal Arterial Thrombosis 13: Hepatic/portal Vein Thrombosis 99: Other Major Adverse Vascular Event				
Hematological malignancies	1: Acute Myelogenous Leukemia 2: Aplastic or Hypoplastic Anemia 3: Myelodysplastic Syndrome 4: Myeloproliferative neoplasm Sensitivity analysis: see Section 7.7.5	No	Binary	Iptacopan	As recorded by the IPIG PNH Registry investigators
Solid tumors	1: Lung 2: Breast 3: Colorectal 4: Prostate 5: Stomach 6: Liver 7: Ovarian 98: Other Sensitivity analysis: see Section 7.7.5	No	Binary	Iptacopan	As recorded by the IPIG PNH Registry investigators
Hyperlipidemia	To be extracted from the AE page using MedDRA preferred terms	No	Binary	Iptacopan	As recorded in the AE page by the IPIG PNH Registry investigators
Thrombocytopenia	To be extracted from the AE page using MedDRA preferred terms	No	Binary	Iptacopan	As recorded in the AE page by the IPIG PNH Registry investigators
SAEs	Grouped by MedDRA preferred terms and system organ class (SOC)	No	Binary, Categorical	Iptacopan	As recorded in the AE page by the IPIG PNH Registry investigators
All-cause mortality	As recorded on the Registry completion / termination form	No	Binary	Iptacopan	As recorded by the IPIG PNH Registry investigators
Pregnancy exposure characteristics	Exposure categories (e.g. by trimester of pregnancy) will be based on the derived LMP, detail to be provided in SAP	No	Categorical	Pregnancy	To be computed based on data recorded by the IPIG PNH Registry investigators
Pregnancy outcomes	• Miscarriage • Ectopic pregnancy • Planned / therapeutic abortion • Intrauterine death / stillbirth • Live birth	No	Binary, Categorical	Pregnancy	As recorded by the IPIG PNH Registry investigators

Outcome or outcomes group*	Details	Primary outcome?	Type of outcome	Applied to study cohorts	Measurement characteristics/ validation
Birth outcomes	• normal newborn • small for gestational age • congenital malformations • Preterm birth (to be calculated from the reported gestational age)	No	Binary, Categorical	Pregnancy (live birth subgroup only)	As recorded by the IPIG PNH Registry investigators

*When groups of outcomes are described (e.g., birth outcomes), details of single variables to be provided in the SAP

CRF: case report form; LMP: last menstrual period; MAVEs: major adverse vascular events; SAP: statistical analysis plan

7.3.3 Covariates (confounding variables and effect modifiers, e.g., risk factors, comorbidities, comedications)

This NIS is not a comparative study so no adjusted analyses are planned. The covariates collected will be used only for tabulating patient characteristics and subgroup analyses. The full list of study covariates and operational definitions will be provided in the study SAP; the key covariates are summarized in Table 7-5.

Table 7-5 Operational definitions of covariates for CLNP023C12003

Variable	Details	Type of variable	Assessment window	Applied to study cohorts	Measurement characteristics/ validation
Age at index date	Derived from the year of birth	Continuous	[0;0]	All	Derived from data recorded by the IPIG PNH Registry investigators
Gender	Based on pre-specified categories in the CRF	Categorical	[0;0]	All	As recorded by the IPIG PNH Registry investigators
Race	Based on pre-specified categories in the CRF	Categorical	[0;0]	All	As recorded by the IPIG PNH Registry investigators
Ethnicity	Based on pre-specified categories in the CRF	Categorical	[0;0]	All	As recorded by the IPIG PNH Registry investigators
PNH disease duration	Derived based on the first diagnosis date	Continuous	[0;0]	All	Derived from data recorded by the IPIG PNH Registry investigators
Medical history	Pre-existing PNH symptoms and clinical events of interest (details to be provided in SAP)	Binary, Categorical	[-365;0]	All	As recorded by the IPIG PNH Registry investigators
PNH anti-complement therapy pre-index	Ravulizumab, pegcetacoplan, eculizumab, other	Binary, Categorical	[-365;0]	All	As recorded by the IPIG PNH Registry investigators

Variable	Details	Type of variable	Assessment window	Applied to study cohorts	Measurement characteristics/ validation
PNH concomitant treatment pre-index	E.g. anticoagulation therapy, antibiotic prophylaxis, immunosuppression, etc. (full list to be defined in SAP)	Binary, Categorical	[-365;0]	All	As recorded by the IPIG PNH Registry investigators
PNH anti-complement therapy, other concomitant treatment post-index	See description for the two variables above	Binary, Categorical	[0; end of follow-up]	All	As recorded by the IPIG PNH Registry investigators
Iptacopan treatment duration	Derived from the dates of iptacopan initiation and discontinuation/switch or end of follow-up	Continuous	[0; end of follow-up]	Iptacopan; Pregnancy	Derived from data recorded by the IPIG PNH Registry investigators
Iptacopan dosing and adherence	Derivation details to be provided in the SAP	Continuous , categorical	[0; end of follow-up]	Iptacopan; Pregnancy	Derived from data recorded by the IPIG PNH Registry investigators
Reason for iptacopan discontinuation	Toxicity, patient decision, physician decision, intolerability, cost/ access, switch to another therapy, lack of efficacy, adverse event, compliance issues, death, other	Categorical	Depending on the study cohort, [0:0] for Discontinuation or at the end of follow-up for the others	Iptacopan; Discontinuation	As recorded by the IPIG PNH Registry investigators
Obstetric history	Number and outcome of previous pregnancies, maternal complications, other variables per CRF (details in SAP)	Binary, Categorical	[-∞;0]	Pregnancy	As recorded by the IPIG PNH Registry investigators
Cohort re-entry	Flag for the patients that re-entered the Iptacopan cohort after discontinuation	Binary	[-∞; end of follow-up]	Iptacopan	Derived from the patient treatment history

CRF: case report form; SAP: statistical analysis plan

7.4 Data sources

7.4.1 Context and rationale for data sources

Context: PNH is an ultra-rare condition, with an estimated prevalence of approximately 10 to 20 cases per million individuals worldwide (Cançado et al 2021). A literature review was previously undertaken by Novartis to identify global real-world data (RWD) sources available for PNH in order to summarize and understand the availability of RWD in this rare disease. Data sources were examined and meta-data for 90 variables was extracted to describe details

around type of data source, study design, population size, epidemiology, clinical, economic and humanistic burden, follow-up duration, data access and linkage (Lavudiya et al 2020a). A total of 45 potential RWD sources were identified, of which ~80% were generic and ~20% disease-specific. Approximately half of the data sources (51%) reported a sample size in the range of 101 to 500; only 5 sources (11%) had sample sizes between 500 and 5000. Further, the identified data sources recorded a maximum of 61% of the 90 assessed variables (Lavudiya et al 2020b). Most commonly cited data sources were the International/Global PNH Registry (owned by Alexion Pharmaceuticals) and the Korean National PNH data registry (established by the Korean Society of Hematology), i.e. data sources that did not grant general access for pharmaceutical industry research. Overall, this review highlighted a gap in existing evidence in this disease area (Lavudiya et al 2020a, Lavudiya et al 2020b).

External academic authors have also highlighted the importance of collaboration to establish a centralized international registry to capture and analyze the data for various new therapies and characterize the clinical challenges related to PNH management (Oliver and Patriquin 2023). IPIG PNH Registry represents such collaborative effort where worldwide data collection on PNH patients is made possible through the contributions of industry stakeholders with the aim to increase knowledge about PNH in the medical community and patient population (IPIG 2024a).

Reason for selection: The IPIG PNH Registry was selected to fulfill the objectives of this study because collection of safety information on PNH treatments is one of the stated objectives of the registry. Consequently, the safety data collection items in the registry core protocol and the CRF are also applicable and relevant for iptacopan safety evaluation. In addition, number of sites and countries participating in the registry potentially allows collecting information on more PNH patients exposed to iptacopan than any data source available from a single country. A structured review of the registry's operational, methodological and scientific aspects has been undertaken using the Registry Evaluation and Quality Standards Tool (REQueST) (EUnetHTA 2019); see Annex 1.

The registry study feasibility evaluation also took into account considerations regarding a registry's fitness-for-use in regulatory decision-making and data quality considerations as described in the US FDA Guidance for industry documents "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products" (US FDA 2023a), "Data Standards for Drug and Biological Product Submissions Containing Real-World Data" (US FDA 2023b), EMA Guideline on registry-based studies (EMA 2021), and EMA Data Quality Framework for EU medicines regulation (EMA 2023). The assessment results are available as a standalone "Registry-based study feasibility assessment report" supporting the study protocol (see Annex 1).

Strengths of data source(s): This data will include longitudinal records from a multinational registry of patients with PNH, and Novartis will gain access to the data from patients treated with iptacopan (iptacopan silo). The planned registry recruitment (at least 2000 PNH patients) would make it one of the largest available data sources on PNH, compared to the existing data sources (Lavudiya et al 2020b) which should enable a meaningful evaluation of the study primary safety objective (see Section 7.5).

The IPIG PNH Registry protocol has been developed with the explicit aims to describe PNH treatment course including clinical outcomes, morbidity, and mortality, and to assess the long-term safety of PNH treatments (IPIG 2024a). The IPIG PNH Registry CRF has thus been developed to contain specific variables relevant to the PNH treatment safety assessment (e.g., infections caused by encapsulated bacteria, potential breakthrough hemolysis), which would not be available from administrative data sources such as claims data.

Limitations of data source(s): A critical limitation identified during the feasibility assessment was that although the IPIG PNH Registry protocol and key study documents (CRF, informed consent forms) were already in place, some documents were not yet finalized at the time of assessment and thus the detailed evaluation of the planned procedures related to data quality and reliability could not be performed. In addition, data samples from the registry were also not yet available for the evaluation of aspects such as data accuracy, completeness, coherence and traceability. To mitigate this risk, a multi-step approach is proposed that includes the evaluation of the registry documentation as it becomes available, and a quantitative evaluation of the actual registry data quality (once available) with standalone Data Quality Assessment Reports. For further information, please refer to the "Registry-based study feasibility assessment report" (Annex 1).

Data source provenance/curation: The detailed documentation about the data sources, data collection and registry enrollment procedures, quality assurance, etc is provided in the IPIG PNH Registry Protocol (IPIG 2024a).

The underlying core PNH registry is described in detail in Section 7.4.2 and the iptacopan silo in Section 7.4.3 below.

7.4.2 IPIG PNH Core Registry

Patients with PNH confirmed by flow cytometry and who do not currently participate in an interventional PNH clinical trial will be invited by the investigators to participate in the core IPIG PNH registry (IPIG 2024a). All patients with PNH will be eligible, regardless of whether they are receiving PNH-specific therapy and regardless of what type of therapy they are receiving. Prior to any data collection, patients must sign informed consent or assent form [redacted]

Patients will be followed for at least 5 years after their enrollment in the core PNH registry. Patients' visit schedules will follow standard of care. Patient data are expected to be entered in the electronic data capture (EDC) system by the clinician and/or qualified designee at the time of registry enrollment and approximately every 6 months thereafter. Historical data from diagnosis prior to entry into the core PNH registry, will be collected for individual patients either from sites directly or by transfer of data from previous registries, as applicable.

Data collection schedule to the IPIG PNH core registry and Iptacopan silo is provided in Table 7-6. Of note, not all variables collected in the IPIG PNH Registry will be used in the planned analyses of this study, CLNP023C12003.

Table 7-6 Data collection schedule – IPIG PNH core registry and iptacopan silo

Data	Core registry Enrollment	Core registry Follow-up	Iptacopan silo

Informed consent/assent	X		
Inclusion/exclusion criteria	X		
Registry completion form	X		
Reason for premature registry discontinuation		X	
Demographic information			
Year of birth	X		
Age	X		
Gender	X		
Site	X		
Body mass index[a]	X		
PNH diagnosis			
Symptomatic PNH	X		
Clinical symptoms			
Symptom	X	X	
Clinical events and outcomes			
Major adverse vascular events, including thrombosis	X	X	
Autoimmune disease	X	X	
Bone marrow pathology or other hematological disorder	X	X	
Bone marrow transplant	X	X	
Infections[b]	X	X	
Impaired renal function	X	X	
Abnormal liver function	X	X	
Pulmonary hypertension	X	X	
High disease activity	X	X	
Malignancies (non-hematological)	X	X	
Potential breakthrough hemolysis		X	
Other medical condition	X	X	
Death		X	
Red blood cell transfusions	X	X	
Proportion of PNH cells			
% PNH cells – granulocytes	X	X	
% PNH cells – monocytes	X	X	
% PNH cells – erythrocytes type II	X	X	
% PNH cells – erythrocytes type III	X	X	
% PNH cells – reticulocytes	X	X	
Laboratory	X	X	
Vaccination	X	X	
Concomitant Medication	X	X	
Pregnancy			
Pregnancy status	X	X	

Pregnancy outcomes	X	X	
Anti-complement therapies for PNH	X		
Pegcetacoplan or eculizumab/ravulizumab	X		
Treatment name		X	
Maintenance dose and frequency/changes		X	
Treatment location		X	
Date of discontinuation		X	
Reason for discontinuation		X	
Iptacopan treatment data			
Start date of iptacopan		X	
Maintenance dose and frequency/changes		X	
Missed or delayed doses			X
Treatment location		X	
Date of discontinuation		X	
Reason for discontinuation		X	
Hospital admissions			
Reason for admission		X	
Other health resources used			
Type of resource		X	
Safety events			
Serious hemolysis following discontinuation of iptacopan			X
Other adverse events and serious adverse events			X
Patient reported outcomes (optional)	X	X	

[a] Derived from height and weight

[b] Including, but not limited to *Neisseria meningitidis*, *Streptococcus*, and *Haemophilus influenzae*

Source: IPIG PNH Registry protocol (IPIG 2024a), iptacopan silo protocol (IPIG 2024b).

7.4.3 Iptacopan silo

As specified in the IPIG PNH Registry protocol (IPIG 2024a), in addition to the core PNH registry, several product-specific silo protocols ("silos") will be initiated including patients treated with PNH-specific therapies, in order to collect specific data and address specific objectives or requests from regulatory authorities. Patient data collected within silos will be exclusive to the silo (i.e., not used for analysis in the core PNH registry) for the most recent 18 months of collected data. Data that are 18 months or older from any silo matching the core registry dataset, will be copied to the core PNH registry and will become available for aggregate analysis within the core PNH registry.

Patient data collected within one silo will be regularly provided to the MAH supporting the silo, provided the patients have agreed to the transfer of the silo data to the MAHs in the informed consent form. MAHs will not have access to any individual patient data in a silo that they do not support nor to individual patient data for patients only included in the core PNH registry.

The iptacopan silo protocol (IPIG 2024b), an appendix to the core IPIG PNH Registry protocol, details the further aspects of silo-specific data collection.

Inclusion of patients in the iptacopan silo began in July 2024 in the United States and will continue in other participating countries shortly after iptacopan becomes available in the clinical practice . The index date for the silo patients will be defined as the iptacopan initiation.

Baseline data (patient characteristics and relevant medical and treatment history) will be provided for the total available time period prior to iptacopan initiation. In case of iptacopan discontinuation, data collection within the silo will continue up to 12 weeks after discontinuation, or to the next documented visit if longer than 12 weeks. An exception is patients who became pregnant while on iptacopan treatment, in which case data regarding the pregnancy and infant outcomes will be provided to the silo until approximately 12 months after birth, even if the patient discontinues iptacopan.

7.5 Study size/power calculation

As this is a descriptive, non-comparative study without a hypothesis to be tested, the target sample size is assessed in context of the expected precision of the study measures for infections-related outcomes (counts, percentages, and 95% CI observed for various study size scenarios).

The primary objective of the study is to estimate the frequency, incidence rate, cumulative incidence and occurrence rate of infections caused by encapsulated bacteria in the PNH patients treated with iptacopan. In the safety pool of iptacopan clinical trials in the PNH indication, at the time of submission for registration there were 7 infections potentially caused by encapsulated bacteria identified among 170 patients exposed to iptacopan, 185.4 patient-years (PY) at risk. The frequency of infections was 4.1% (95% CI 1.7-8.3%) with an average treatment duration of approximately 1 year; occurrence rate (number of episodes per 100 patient-years) was 3.8 (95% CI 1.9-7.6) per 100 PY.

One of the secondary outcomes of the study is serious infections caused by encapsulated bacteria. As described in the RMP at the time of submission for registration, two serious infections potentially caused by encapsulated bacteria were observed in the iptacopan program for the PNH indication, for a frequency of 1.2% (95% CI 0.1-4.2%) over approximately 1 year.

Assuming that the observed proportion of these events in the iptacopan-treated PNH patient population in the real-world clinical practice is approximately the same as in the clinical trials (4% and 1%, respectively), the expected number of events, frequency and corresponding 95% CIs are summarized for different sample size scenarios in Table 7-7.

Table 7-7 Expected number of events and 95% CIs for the observed proportions as a function of sample size for infection-related primary and secondary endpoints for CLNP023C12003

Total number of patients	Primary endpoint: infections caused by encapsulated bacteria			Secondary endpoint: serious infections caused by encapsulated bacteria		
	Expected N	%	95% CI[1]	Expected N	%	95% CI[1]
100	4	4%	1.1-9.9%	1	1%	0.0-5.4%
200	8	4%	1.7-7.7%	2	1%	0.1-3.6%
300	12	4%	2.1-6.9%	3	1%	0.2-2.9%
500	20	4%	2.5-6.1%	5	1%	0.3-2.3%

[1] Exact Clopper-Pearson 95% CI

The actual study size achieved will depend on the uptake of iptacopan in the PNH patient population. The aim is to reach at least 200 iptacopan-treated patients after 5 years of study data collection, to achieve at least a study size comparable to the size of the initial registration clinical trials' safety pool. However, the goal will be to enroll as many iptacopan-treated PNH patients as possible to maximize the study precision.

It is currently expected that the enrollment of iptacopan patients in the IPIG PNH Registry will begin in Q1 2024, after product launch in participating countries. The currently proposed end of data collection period for this study is 31 Mar 2029, approximately 5 years from the enrollment of the first iptacopan-treated patient in the registry. The patient enrollment will be monitored in the interim reports and if at any point it becomes clear that by the end of currently planned data collection period the goal of 200 iptacopan-treated patients is not be likely to be reached, an additional assessment will be performed in consultation with the health authorities, and the study will either be stopped for futility or prolonged to further increase the available study sample.

7.6 Data management

The management of the IPIG PNH Registry data and the generation of aggregate reports for core PNH registry will be performed by IPIG or a designated vendor acting on behalf of IPIG.

For the IPIG PNH Registry, electronic data collection into the EDC system will be done by the site staff, each clinician will be responsible for ensuring that accurate data are entered into the EDC system in a timely manner. Programmed automated checks will be implemented to provide controls for data entry accuracy. Only authorized personnel will have access to the EDC system and an audit trail within the system will track all changes made to the data. Further details regarding the data management for the IPIG PNH Registry are provided in the IPIG PNH Registry protocol (IPIG 2024a).

Medical history and clinical outcomes will be coded by System Organ Class (SOC) and Preferred Term (PT) using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications and vaccinations will be coded with the most recent edition of the World Health Organization (WHO) Drug Dictionary.

Anonymized patient-level data for the iptacopan silo will be transferred by IPIG to Novartis at regular intervals, formatted according to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standards. Transferred SDTM datasets will be managed using Novartis internal resources in accordance with applicable standard operating procedures (SOPs), the Iptacopan silo study protocol (IPIG 2024b) and the SAP for the iptacopan silo (Novartis study number CLNP023N12004R). The database for the study CLNP023N12004R will be stored in a secure GxP-compliant environment and will form the basis for this study. Only a subset of the data required for the purposes of this study (CLNP023C12003) will then be extracted by the dedicated study team into a separate folder specific to CLNP023C12003 and transformed and analyzed according to the specifications in the study SAP, programming plan and the applicable procedures.

7.7 Data analysis

7.7.1 Context and rationale for analysis plan

The analyses for this study will be performed by Novartis using internal resources based on a subset of the iptacopan-silo data (in SDTM format) stored in a secure GxP-compliant environment at Novartis. An SAP detailing the analysis to be conducted for this study will be developed prior to the first data lock point. Annual interim reports will include the key characteristics of the patient population and the study outcomes based on the cumulative data collected since the beginning of the study. The analyses in the final interim reports will include, as the minimum, the analysis of the primary endpoint, a summary of the major safety findings for all patients, and the risk of serious infections with encapsulated bacteria. Further analyses that may be included in the interim reports will depend on the number of accumulated patients or events and will be detailed in the study SAP.

Data analyses will be mainly descriptive in nature, with no comparisons planned.

7.7.2 Patient disposition and baseline characteristics

Patient disposition/ attrition tables will include the total number of patients in the core PNH registry, the number of iptacopan-treated patients meeting the iptacopan silo selection criteria, the number of patients included in the study analyses at each data lock point, and the number of patients forming the analysis sample for each of the study cohorts (refer to Section 7.2):

- Iptacopan
- Discontinuation
- Pregnancy

Patient demographics and baseline characteristics, including characteristics of iptacopan use (dosing, reason for discontinuation if applicable etc.), concomitant medications, relevant medical and obstetric history will be summarized descriptively for each study cohort. Distributions of continuous variables will be summarized with means (standard deviations), medians, interquartile range, and absolute range. Categorical variables will be summarized with proportions. Missing values will be reported as a separate category.

7.7.3 Estimands for the safety outcomes

An estimand is a quantity that is to be estimated in statistical analysis. The term is used to clearly distinguish the target of inference from the method used to obtain an approximation of this target (i.e., the estimator) and the specific value obtained from a given method and dataset (i.e., the estimate). In medical research, a *treatment effect estimand* is a precise description of the treatment effect reflecting the clinical question posed by a given study objective. It summarizes at a population level what the outcomes (e.g., adverse event frequencies) would be in the same patients during the same time under different treatment conditions being compared (e.g., treatment versus control) (FDA 2017, EMA 2017).

Due to absence of a control group, consistent estimation of the treatment effect parameters is not possible in the present study. Nevertheless, because absolute risk places an upper bound on attributable risk, the absolute risk estimates obtained from this study can provide useful information on the safety profile of iptacopan pertaining to rare adverse events.

As a hypothetical example, suppose that in a cohort of 200 patients, the estimated absolute risk of an infection caused by encapsulated bacteria during the first year of treatment with the study drug is 4.0% (95% CI: 1.7%, 7.7%). Based on this estimate, even in the absence of a control arm, any attributable risk >7.7% can be ruled out with at least 95% confidence. In other words, if the drug increases the risk of this adverse event in our study population, the magnitude of this increase is almost certainly well below 10% (i.e., overwhelming majority of patients are not expected to experience this adverse event during the specified treatment period). This upper bound on attributable risk is important because biological plausibility considerations alone (e.g., theoretical risk increase resulting from complement inhibition), do not place any constraints on the magnitude of attributable risk, which can in principle go all the way up to 100%. While an absolute risk estimate is not as useful as an unbiased estimate of attributable risk, such as the risk difference evaluated versus placebo, it can still be useful for the overall benefit-risk assessment, when the placebo arm is not available for ethical or practical reasons, as was the case in the iptacopan clinical development program in PNH.

In the ICH estimands framework (FDA 2017, EMA 2017), an absolute risk parameter can be defined as follows. Let $X(t)$ denote the number of incident events occurring by time t in a cohort of n subject. The absolute risk parameter is the cumulative incidence function (CIF), corresponding to the expectation of $X(t)/n$ in the process generating the study cohort

$$F(t) = E[X(t)/n]$$

Depending on the definition of incident events counted by the variable X in relation to the intercurrent events (i.e., events affecting the existence or the interpretation of the study outcome, such as early study drug discontinuation or death from a competing cause unrelated to the study outcome), at least three different types of the absolute risk parameters can be distinguished.

1. The *treatment policy* estimand counts all incident events occurring by time t, regardless of early discontinuation of the study drug in any given subject or occurrence of any other intercurrent events.

For example, in the analysis of a 1-year risk of infections caused by encapsulated bacteria, all cases of such infections occurring within 1 year of iptacopan initiation would be counted under the "treatment policy" strategy, regardless of the actual duration of exposure to iptacopan in any given subject.

2. The *while-on-treatment* estimand counts only those incident events that occur during exposure to the study drug, up to time t.

For example, in the analysis of a 1-year risk of infections caused by encapsulated bacteria, all cases of such infections occurring during iptacopan exposure, up to 1 year from iptacopan initiation would be counted, while events occurring after discontinuation of iptacopan exposure would not be counted, even if they occurred within the 1-year time frame.

3. The *hypothetical* estimand counts incident events that would be expected to occur in the study cohort under hypothetical elimination of some or all intercurrent events.

For example, the hypothetical estimands framework may help answer the following question: "What would be the 1-year average risk of infections caused by encapsulated bacteria in the iptacopan cohort if treatment discontinuation in the first year did not occur, except possibly due

to the outcome occurrence or death, and the outcome rate (i.e., the cause-specific hazard of infections caused by encapsulated bacteria) was the same as under the actual study conditions?"

Note that unlike the hypothetical estimand, the treatment policy and the while-on-treatment estimands are defined under the actual study conditions, without hypothetical elimination of any intercurrent events.

The analysis in this study will be focused on the while-on-treatment and the hypothetical risk estimands. The treatment policy estimand strategy will not be implemented in this study because subjects discontinuing iptacopan are expected to start another PNH therapy. Thus, with the treatment policy estimand, the upper bound on the risk attributable to iptacopan will be strongly confounded by the effects of subsequent PNH therapies. Furthermore, inference about the treatment policy estimand would not be operationally feasible because events occurring after 12 weeks from the last iptacopan dose are not captured in the iptacopan silo.

In addition to the risk function $F(t)$, *incidence rate* and *occurrence rate* estimands can be defined as follows. Let X denote the number of incident events observed during the at-risk exposure person-time T_X and let Y denote the number of event episodes (including recurring events) observed during the total exposure person-time T_Y. Note that incident events terminate time at-risk in the definition of the incidence rate but not the occurrence rate, and that both T_X and T_Y include time after re-start of iptacopan. The incidence rate and the occurrence rate parameters are defined as expectations of the respective quantities in the process generating the study cohort

$$Incidence\ rate = E(X)/E(T_X), \quad Occurrence\ rate = E(Y)/E(T_Y)$$

If the study outcome is a rare event occurring with constant hazard during the study period, the incidence rate is related to the hypothetical risk function estimand $F_H(t)$ as follows:

$$F_H(t) = 1 - \exp(-t \times Incidence\ rate) \approx t \times Incidence\ rate$$

This relationship allows for estimation of the hypothetical CIF estimand based on all incident events, including those occurring after discontinuation and re-start of iptacopan. However, the relationship only holds under the constant hazard assumption. A more robust estimation of the CIF can be based on the Aalen-Johansen estimator, as explained in the next section.

7.7.4 Primary, secondary, and subgroup analysis specification

The primary study outcomes will be summarized as frequency (counts and percentages), cumulative incidence (event probability as a function of time), incidence rates (number of patients with event per 100 patient-years) and occurrence rates (number of episodes per 100 patient-years) for the primary analysis population (iptacopan cohort).

In the frequency analysis, counts and percentages of adverse events will be calculated based on (i) incident events occurring during continuous iptacopan therapy until the first treatment discontinuation (as defined in Section 7.3.1) + 3 days, and (ii) incident events occurring at any time during iptacopan therapy (up to the last treatment discontinuation + 3 days, including re-start of iptacopan after the first treatment discontinuation). These counts and percentages will be reported along with the mean and median duration of treatment. The 95% confidence intervals (CIs) for the percentages will be constructed based on the exact binomial method (Clopper and Pearson 1934).

The purpose of the cumulative incidence analysis is to estimate the risk of the specified treatment-emergent adverse events as a function of continuous exposure time on iptacopan. The CIF will be estimated using the Aalen-Johansen estimator, treating deaths occurring in patients without the study events as competing risks and coding discontinuation of the iptacopan exposure for any other reason as either (i) additional competing risks (CIF Analysis 1, the while-on-treatment estimand strategy), or (ii) censored observations (CIF Analysis 2, the hypothetical estimand strategy) (FDA 2017, EMA 2017). The CIF Analysis 1 will identify the risk function under the actual study conditions without hypothetical elimination of any intercurrent events. The CIF Analysis 2 will identify the risk function that would be present in the study cohort if the study drug discontinuation did not occur (except possibly due to the study event or death) but all cause-specific hazards were the same as under the actual study conditions. In the CIF Analyses 1 and 2, the risk estimates will be calculated at the following time points after the first iptacopan dose: 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years. The 95% CIs for the CIFs will be constructed based on the Aalen's variance estimator for all endpoints with at least one event (Aalen 1978, Scosyrev 2020). For endpoints with no events, the exact binomial confidence limits will be reported (Clopper and Pearson 1934). Because the purpose of the CIF analysis is to estimate risk as a function of continuous exposure to iptacopan, cohort re-entry after the first treatment discontinuation will not be allowed in the CIF analysis.

Incidence rates will be calculated by dividing the number of patients experiencing AEs by the number of person-years at risk. Occurrence rates will be calculated as the total number of episodes divided by the number of person-years at risk. In the analysis of incidence rates and occurrence rates, event counts and person-time will be calculated based on all available data collected during iptacopan therapy (i.e., cohort re-entry after the first discontinuation of iptacopan is allowed). Incidence and occurrence rates will be calculated with 95% CIs based on the asymptotically robust variance estimator adjusting for over-dispersion (Scosyrev 2016), by year of treatment and for the entire duration of the study.

For the primary outcome, the following subgroup analyses are currently planned (details to be further refined in SAP):

- By age group (≤45, 45< to ≤65, >65 years); further age groups may be defined based on observed age distribution)
- By causative organism (*Neisseria meningitidis*, *Streptococcus pneumoniae, Haemophilus influenzae*; if at least one event is reported in at least two different categories)
- By recorded prophylaxis status (vaccination and/or prophylactic antibiotic use)
- By concomitant use of immunosuppressant therapy (ever recorded from the start of iptacopan therapy)
- By previous history of infections (recorded in the 365 days before starting iptacopan for the first time)
- By use of other complement inhibitors in the 365 days before starting iptacopan

The analyses specification for the secondary safety outcomes is summarized in the following table.

Table 7-8 Secondary analyses specification for CLNP023C12003

Outcome name	Measures	Study cohorts	Missing data methods	Subgroups*
Serious infections caused by encapsulated bacteria	Counts and percentages, incidence rate, cumulative incidence, occurrence rate	Iptacopan	If event not recorded, assume that it did not occur	Causative organism; Age group; antibiotic prophylaxis; concomitant use of immunosuppressants; history of infections pre-iptacopan use
Serious infections	Counts and percentages, incidence rate, cumulative incidence, occurrence rate	Iptacopan	If event not recorded, assume that it did not occur	Infection site (refer to Table 7-3); Age group; prophylaxis; concomitant use of immunosuppressants; history of infections pre-iptacopan use
Vaccinations against encapsulated bacteria	Counts and percentages (overall, at the start of iptacopan treatment and at each subsequent visit)	Iptacopan	Last observation carried forward for vaccination records	Vaccine type: • Neisseria meningitidis • Streptococcus pneumoniae • Haemophilus influenzae + information on specific serotypes if available Age group; Antibiotic prophylaxis
Potential breakthrough hemolysis	Counts and percentages, incidence rate, cumulative incidence, occurrence rate	Iptacopan	If event not recorded, assume that it did not occur	Associated with a complement-amplifying condition? (yes/no/unknown) + condition type Associated with missed or delayed dose of anti-complement therapy? (yes/no/unknown) Age group
Serious hemolysis following discontinuation of iptacopan	Counts and percentages	Discontinuation	If event not recorded, assume that it did not occur	Associated with a complement-amplifying condition? (yes/no/unknown) + condition type Associated with missed or delayed dose of anti-complement therapy? (yes/no/unknown) Age group Reason for iptacopan discontinuation

Outcome name	Measures	Study cohorts	Missing data methods	Subgroups*
MAVEs including thrombotic events	Counts and percentages, incidence rate, cumulative incidence, occurrence rate	Iptacopan	If event not recorded, assume that it did not occur	MAVE subtype, exact groupings to be data-driven (13 subtypes available, refer to Table 7-3); Age group; concomitant use of anticoagulants; history of MAVEs pre-iptacopan use
Hematological malignancies	Counts and percentages, incidence rate, cumulative incidence, occurrence rate	Iptacopan	If event not recorded, assume that it did not occur	Malignancy type (refer to Table 7-3); Age group; concomitant use of immunosuppressants; use of complement inhibitors pre-iptacopan; history of malignancy pre-iptacopan use
Solid tumors	Counts and percentages, incidence rate, cumulative incidence, occurrence rate	Iptacopan	If event not recorded, assume that it did not occur	Malignancy type (refer to Table 7-3); Age group; concomitant use of immunosuppressants; use of complement inhibitors pre-iptacopan; history of malignancy pre-iptacopan use
Hyperlipidemia	Counts and percentages, incidence rate, cumulative incidence, occurrence rate	Iptacopan	If event not recorded, assume that it did not occur	Age group Use of lipid-lowering medications
Thrombocytopenia	Counts and percentages, incidence rate, cumulative incidence, occurrence rate	Iptacopan	If event not recorded, assume that it did not occur	Age group Presence of predisposing condition
SAEs	Counts and percentages, incidence rate, cumulative incidence, occurrence rate	Iptacopan	If event not recorded, assume that it did not occur	Grouped by MedDRA preferred terms and system organ class Age group
All-cause mortality	Counts and percentages, incidence rate, cumulative incidence	Iptacopan	If event not recorded, assume that it did not occur	Age group

Outcome name	Measures	Study cohorts	Missing data methods	Subgroups*
Pregnancy exposure characteristics	Counts and percentages	Pregnancy	LMP to be derived from the available data, details to be provided in SAP	Exposure categories (e.g. by trimester of pregnancy) to be defined in SAP
Pregnancy outcomes: • Miscarriage • Ectopic pregnancy • Planned / therapeutic abortion • Intrauterine death / stillbirth • Live birth	Counts and percentages	Pregnancy	Missing pregnancy outcomes will be reported as a separate category	To be defined in SAP
Birth outcomes: Live birth: • normal newborn • small for gestational age • Congenital malformations • Gestational age categories including preterm birth	Counts and percentages	Pregnancy (live births only)	For binary variables (e.g. congenital malformations), if event not recorded, assume that it did not occur; for categorical outcomes, missing entries reported as separate category	To be defined in SAP

*All subgroup analyses to be performed only if sufficient number of events per subgroup is reached
LMP: last menstrual period; MAVEs: major adverse vascular events; SAP: statistical analysis plan

The following subgroup analyses will be performed for all primary and secondary analyses only if sample size allows: by country (or geographical region, if the number of patients in individual countries is too low).

The details of the planned analysis of the primary and secondary outcomes including any further subgroup analyses will be provided in the study SAP.

7.7.5 Sensitivity analyses

Sensitivity analysis of cohort definition: Selected analyses of the outcomes related to infections, MAVEs, malignancies, SAEs, death and serious hemolysis following iptacopan discontinuation will be repeated using all available follow-up data (up to 12 weeks post-discontinuation or the next visit).

Sensitivity analyses of the outcome definitions:

- "Potential breakthrough hemolysis" and "Serious hemolysis following discontinuation of iptacopan" outcomes: only considering outcomes in presence of laboratory evidence of intravascular hemolysis (Highest level of lactate dehydrogenase [LDH] during breakthrough episode >1.5x upper limit of normal [ULN]).
- "Hematological malignancies" and "Solid tumor" outcomes: extracting outcomes corresponding to the malignant neoplasms from the MedDRA SOC "Neoplasms benign, malignant and unspecified" from the recorded SAEs.

- Sensitivity analyses of the primary outcome definition may be conducted in addition to assess the robustness of the main analyses, to be defined in the SAP.

The details of the planned sensitivity analyses will be provided in the study SAP.

7.8 Quality control

As IPIG is the sponsor of the IPIG PNH Registry, IPIG and any designated third party acting on behalf of IPIG are responsible for the quality and integrity of the data collected as part of the registry operation. Details on the quality and integrity assurance measures, as well as monitoring, site training are available in the IPIG PNH Registry protocol (IPIG 2024a). To aid the registry data quality assessment, a quantitative evaluation of the actual registry data is planned that will be described in the standalone Data Quality Assessment Reports. For further information, please refer to the "Registry-based study feasibility assessment report" (Annex 1).

The analyses for the planned study (CLNP023C12003) will be performed by Novartis using internal resources in a secure GxP-compliant environment according to applicable procedures. To ensure quality control, all analyses will be validated through double programming, which is independent code development by at least two programmers, followed by comparison of analysis outputs, and investigation of all discrepancies.

7.9 Limitations of the research methods

7.9.1 Limitations inherent to the IPIG PNH Registry design

Selection bias is possible, e.g. if the patient population at participating study sites is not representative of the PNH patient population at large, or if certain patient groups do not provide consent for registry data collection. This bias is also possible at the silo level, if certain patient groups refuse to give consent to share the data collected as part of the silo to the respective MAHs, although it is not expected to occur frequently.

The IPIG PNH registry protocol imposes limitations on the maximum follow-up of patients who discontinue iptacopan (IPIG 2024a). The resulting right-censoring of patient data does not allow follow-up of patients for the occurrence of latent outcomes after they have discontinued the treatment (as would be required for the treatment policy estimand strategy). Thus, the evaluation of safety outcomes in this study is limited to on-treatment events or events occurring shortly after discontinuation, with the exception of the pregnancy outcomes. This limitation is expected to most strongly affect the ability to assess the risk of the outcomes with long latency, such as malignancies.

Left-censoring is possible as well in case of patients that may have been previously exposed to iptacopan or other PNH investigational therapies due to participation in interventional clinical trials. As per IPIG PNH Registry exclusion criteria data from the period of interventional trial participation is censored, there may be a possible gap in the patient treatment history that remains unaccounted for in the study analyses. Further, even patients that may have been exposed to iptacopan treatment for a year or longer in the iptacopan trials would still be considered "new iptacopan patients" by the IPIG PNH Registry, potentially impacting the validity of the study results. No linkage of the registry data with the external data sources is currently possible so this limitation is difficult to mitigate.

This non-interventional study does not have an internal comparator arm. An uncontrolled single-arm study design, by necessity, was selected due to the data access terms as specified in the IPIG PNH registry protocol (IPIG 2024a). Accordingly, the study design is characterized by all the limitations inherent to single-arm studies regarding statistical analyses, interpretation, generalizability, and conclusiveness. Most importantly, the risk of adverse events attributable to the study drug cannot be quantified in statistical analysis due to the uncontrolled nature of the study. Nevertheless, because absolute risk represents an upper bound on attributable risk, the absolute risk estimates obtained from this study can provide useful information on the safety profile of iptacopan pertaining to rare adverse events.

In addition, the proposed single-arm study is expected to provide important insights on the safety of iptacopan use in routine clinical practice, especially pertaining to the events (such as infections), the risk of which depends on the patterns of iptacopan use and adherence to risk minimization measures in routine clinical practice.

To mitigate limitations resulting from the uncontrolled nature of the study, a qualitative comparison of the study findings will be performed with the findings from the overall PNH population as reported by the IPIG PNH core registry (first report expected in 2026), or, if made public, findings from the other silo studies conducted by other MAHs. However, direct comparison between the incidence of the outcomes of interest obtained through this study with the other studies using the IPIG PNH registry data is hampered by potential differences in data collection and data analysis methods. Indeed, Novartis cannot ensure that the core PNH registry or other MAH silo studies, in their reports, use comparable definitions of the relevant safety outcomes, or comparable statistical methods to the iptacopan study allowing for a reliable conclusion. Further, a naive side-by-side presentation of unadjusted data may be confounded by disease severity or other disease characteristics (e.g. if patients switch to iptacopan due to poor response to alternative therapies). Therefore, these comparisons should be interpreted with caution.

7.9.2 Risks related to real-world iptacopan use patterns and IPIG PNH Registry operations

The planned study is based on data collected within the IPIG PNH Registry, which due to its non-interventional nature cannot impose on participating patients any requirements regarding treatment choice, treatment duration, visit frequency etc. Thus, neither IPIG nor Novartis can guarantee enrollment of a sufficient number of iptacopan-treated patients to address all study objectives. For example, if the patients do not remain on iptacopan treatment long-term it may not be possible to evaluate long-term safety in a sufficient patient sample.

A specific risk with relation to the secondary outcome evaluating pregnancy safety is the uncertainty regarding the use of iptacopan in PNH patients during pregnancy. The extent of future use of iptacopan in PNH during pregnancy in the real world remains unclear and only a small number of iptacopan-exposed pregnancies is expected to be seen; in addition, patients participating in the IPIH PNH Registry have an option to refuse consent for their pregnancy-related data to be collected in the registry.

The proposed study is not powered to determine a potential increased risk of adverse pregnancy outcomes (e.g., compared to those in PNH patients exposed to other therapies) and likely would

not be able to provide sufficient information to assess the rate of rare pregnancy complications and birth outcomes, such as e.g. malformations, in a statistically robust fashion. Nonetheless, it could address the following important gaps in the evaluation of iptacopan use in pregnant women:

- Assess the actual extent of use of iptacopan during pregnancy
- Aid in safety signal detection for pregnancy and birth outcomes
- Starting from approximately 20 pregnancy cases with known outcome, an evaluation of common pregnancy outcomes may help assess whether the rate in iptacopan-exposed pregnancies differs drastically from that observed in the eculizumab-exposed pregnancies in PNH.

Novartis thus plans a sequential approach for the pregnancy safety evaluation, monitoring the number and the outcomes of iptacopan-exposed pregnancies in the interim reports and using the interim report data to drive decisions about the need for further safety evaluations. If any of the interim or final analyses indicate a potential safety signal in pregnancy or an unexpectedly high number of iptacopan-exposed pregnant patients, an assessment will be performed in consultation with the health authorities on whether to prolong the pregnancy safety assessment, to further increase the available study sample, or to undertake another pregnancy safety evaluation in a different setting.

Further risks related to the registry data quality and completeness, and data continuity as well as the corresponding mitigation measures have been described in the standalone "Registry-based study feasibility assessment report" (Annex 1).

7.10 Other aspects

None

8 Protection of human subjects

Confidentiality of records and the personal data of the subjects remain protected in accordance with applicable law of personal data protection.

Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.

This study follows the 'ENCePP Code of Conduct' (EMA 2016).

Informed consent procedures

This non-interventional study is classified as a PASS with secondary use of data because the study uses already existing data collected in the IPIG PNH registry and the iptacopan silo. No additional informed consent is needed for this study.

The informed consent procedure for the IPIG PNH Registry participation including the submission to ethics committees and other responsible bodies is managed by IPIG.

For participation in the IPIG PNH Registry, each patient (or parent/legally authorized representative) will sign an informed consent form (ICF) indicating their consent to participate in the IPIG PNH registry prior to any registry-related data collection. If applicable, minor patients will be given an assent form and be asked to sign it to confirm their agreement to participate. Minor patients who reach the age of consent during the study period must sign an ICF at their next visit to confirm their consent to continue participation in the registry.

Procedures related to the silo-specific data collection and potential uses of data including reports summarizing the data in the silo databases, analysis of safety and efficacy of specific approved PNH treatment, regulatory and safety reporting related to the PNH treatment, and publication of data in scientific journals and media are also described in the core PNH registry ICF. Data transfer to product-specific silos is also covered by the core ICF, but the individual MAHs must provide silo-specific privacy notices to patients if their data is to be collected in one of the silos.

[redacted]

9 Management and reporting of adverse events/adverse reactions

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, will be provided on an aggregate level only; no reporting on an individual case level to Novartis is required for this NIS.

Reports of adverse events (AEs)/adverse reactions will be summarized in the interim and final study reports, i.e. the overall association between an exposure and an outcome will be presented. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

The safety reporting of the AEs and SAEs occurring in PNH patients enrolled into the IPIG PNH Registry and receiving iptacopan is described in detail in the iptacopan silo appendix to the IPIG PNH Registry protocol (IPIG 2024b).

10 Plans of disseminating and communicating study results

The study protocol and the results will be publicly disclosed according to the applicable regulation and the applicable Novartis SOPs.

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Manuscripts will not be submitted for publication prior to submission of the underlying

reports to the relevant health authorities. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

As this study qualifies as a non-interventional PASS in the EU or mandated by an EU Health Authority outside the EU, the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

11 References

1. Aalen, O (1978). Nonparametric estimation of partial transition probabilities in multiple decrement models. The Annals of Statistics, 6, 534–545.
2. Cançado RD, Araújo ADS, Sandes AF, et al (2021). Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. Hematol Transfus Cell Ther; 43(3): 341-8.
3. Clopper CJ and Pearson ES (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika 26(4), 404-413.
4. EUnetHTA (2019). Vision paper on the sustainable availability of the proposed Registry Evaluation and Quality Standards Tool (REQueST). Available from: https://www.eunethta.eu/wp-content/uploads/2019/10/EUnetHTAJA3_Vision_paper-v.0.44-for-ZIN.pdf
Accessed 11-Apr-2023.
5. European Medicines Agency (2016). The ENCePP Code of Conduct – for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies. Available from: http://www.encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct_Rev3amend.pdf
Accessed 11-August-2023.
6. European Medicines Agency (2017). ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. EMA/CHMP/ICH/436221/2017 Available from https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf
Accessed 10-Sep-2023.
7. European Medicines Agency (2021). Guideline on registry-based studies, EMA/426390/2021. Committee for Human Medicinal Products (CHMP) 22 October 2021. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf
Accessed 09-Jan-2023.
8. European Medicines Agency (2023). Data Quality Framework for EU medicines regulation. Data Analytics and Methods Task Force, 30 October 2023. Available at https://www.ema.europa.eu/documents/regulatory-procedural-guideline/data-quality-framework-eu-medicines-regulation_en.pdf
Accessed 09-Nov-2023.

9. Hill A, Dezern AE, Kinoshita T, et al (2017) Paroxysmal nocturnal haemoglobinuria. Nature reviews. Disease primers; 3: 17028-17028.
10. International PNH Interest Group (2024a). Observational Registry Protocol: The International PNH Interest Group PNH Registry. Version 3.0, 02 April 2024
11. International PNH Interest Group (2024b). Observational Registry Protocol: The International PNH Interest Group PNH Registry. Appendix 3: Iptacopan Silo. Version 3.1, 05 June 2024
12. International Society for Pharmacoepidemiology (2016) Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf; 25:2-10.
13. Lavudiya S, Agrawal R, Rovira G, et al. (2020a) Identification and description of real-world data sources for Paroxysmal Nocturnal Hemoglobinuria (PNH): a review of literature. Value in Health; 23: Supplement 2 S715
14. Lavudiya S, Agrawal R, Rovira G, et al. (2020b) Identification and description of real-world data sources for Paroxysmal Nocturnal Hemoglobinuria (PNH): a review of literature. Poster session presented at the Virtual ISPOR Europe, 16-19 November 2020.
15. Novartis Press Release (2022) Novartis presents pivotal Phase III APPLY-PNH data at ASH demonstrating investigational oral monotherapy iptacopan superiority over anti-C5. Available from: https://www.novartis.com/news/media-releases/novartis-presents-pivotal-phase-iii-apply-pnh-data-ash-demonstrating-investigational-oral-monotherapy-iptacopan-superiority-over-anti-c5
Accessed 6-Sep-2023
16. Oliver M & Patriquin CJ (2023) Paroxysmal Nocturnal Hemoglobinuria: Current Management, Unmet Needs, and Recommendations. J Blood Med; 14: pp.613-628.
17. Risitano AM, et al. (2012) Paroxysmal nocturnal hemoglobinuria and other complement mediated diseases. Immunobiology 217:1080
18. Scosyrev E (2016) Asymptotically robust variance estimation for person-time incidence rates. Biom J 58(3):474-88.
19. Scosyrev E (2020). Improved confidence intervals for a difference of two cause-specific cumulative incidence functions estimated in the presence of competing risks and random censoring. Biom J. 62(6):1394-1407
20. Socie G, Schrezenmeier H, Muus P, et al (2016) Changing prognosis in paroxysmal nocturnal haemoglobinuria disease subcategories: an analysis of the International PNH Registry. Intern Med J; 46: 1044-53.
21. US Food and Drug Administration (2017). CH E9 (R1). Estimands and Sensitivity Analysis in Clinical Trials. Available from https://www.fda.gov/media/108698/download Accessed 09-Sep-2023.
22. US Food and Drug Administration (2023a). Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products: Guidance for Industry. Available from https://www.fda.gov/media/154449/download
Accessed 04-Jan-2024.

23. US Food and Drug Administration (2023b). Data Standards for Drug and Biological Product Submissions Containing Real-World Data: Guidance for Industry. Available from https://www.fda.gov/media/153341/download Accessed 08-Jan-2024.

24. Vandenbroucke JP, von Elm E, Altman DG, et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med; 147(8):W163-94.

25. Yu F, Du Y, Han B (2016) A comparative analysis of clinical characteristics of patients with paroxysmal nocturnal hemoglobinuria between Asia and Europe/America. Int J Hematol; 103: 649-54.

12 Annexes

12.1 Annex 1 – List of stand-alone documents

Table 12-1 List of stand-alone documents

Number	Document reference number	Date	Title
1	0902b6989547195c	10-Sep-2023	CLNP023C12003: Registry Evaluation and Quality Standards Tool (REQueST)
2	0902b698951ff36e	11-Jan-2024	CLNP023C12003: Registry based study feasibility assessment report

12.2 Annex 2 – ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Post-authorization safety study of iptacopan in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) using data from the non-interventional IPIG PNH Registry

EU PAS Register® number: Study not registered **Study reference number (if applicable):** **CLNP023C12003**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	4

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	4
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

1.1.3: No progress reports (separate from interim study reports) are planned

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	5
2.1.2 The objective(s) of the study?	☒	☐	☐	6.1, 6.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	6.1, 6.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	6.1

Comments:

2.1.4: Study has no *a priori* hypothesis

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	5, 7.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	6.1, 6.2, 7.7.4
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9

Comments:

3.4: Measures of association are not applicable as the study has no internal

comparator

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	7.4.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	7.4
4.2.2 Age and sex	☒	☐	☐	7.2.2
4.2.3 Country of origin	☐	☒	☐	
4.2.4 Disease/indication	☒	☐	☐	7.2.2
4.2.5 Duration of follow-up	☒	☐	☐	7.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2

Comments:

4.2.3: The full list of countries participating in the IPIG Registry and the iptacopan silo was not yet final at the time of the initial version of the protocol, will be described in the study reports.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	7.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	7.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	7.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	7.3.1, 7.2.4
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

5.2: Validity of exposure measurement is not addressed as the study is based on an existing registry where exposure will be recorded per CRF by the registry investigators

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	7.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

6.3: Specific validity measures are not defined as the study is based on an existing registry where exposure will be recorded per CRF by the registry investigators

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.9.1
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.9.1

Comments:

7.1: Confounding is not applicable as there are no comparative analyses planned

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	7.3.3, 7.7.4

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	7.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	7.3.1, 7.3.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	7.6
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	7.6
9.3.3 Covariates and other characteristics?	☒	☐	☐	7.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

9.4: No linkage with other data sources is planned

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7.3, 7.7.4
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.5
10.3 Are descriptive analyses included?	☒	☐	☐	7.7.2
10.4 Are stratified analyses included?	☒	☐	☐	7.7.4
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	7.7.5

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	7.7.4
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	7.7.5

Comments:

10.5: Confounding control is not applicable as there are no comparative analyses planned

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	7.6
11.2 Are methods of quality assurance described?	☒	☐	☐	7.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	10

Comments:

11.3: Study results will be submitted to the FDA and EMA, final report of study results to the FDA will be accompanied with the full study dataset

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	7.9.1
12.1.2 Information bias?	☒	☐	☐	7.9.1
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7.4.1, 7.9.2

Comments:

12.2: Study feasibility assessment report is available as a stand-alone document

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	8

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10

Comments:

Name of the main author of the protocol: [redacted]

Date: 11/January/2024

Signature: _____

12.3 Annex 3 – Additional information

Not applicable