NOVARTIS

Patient Safety & Pharmacovigilance

Registry-based study feasibility assessment report: IPIG PNH Registry

CLNP023C12003

Document authors [redacted]

Document type: Report

Document status: Final

Release date: 11-Jan-2024

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List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CIF	Cumulative incidence function
CRF	Case Report Form
CRO	Contract Research Organization
DAPI	Dynamic Assessment of Pregnancies and Infants
EC	Ethic Committee
EMA	European Medicines Agency
EMR	Electronic Medical Records
EU	European Union
FDA	Food & Drug Administration
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HA	Health Authority
HCP	Health Care Provider
ICD-10	International Classification of Diseases, 10th Revision
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IPIG	International PNH Interest Group
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LMP	Last Menstrual Period
MAH	Marketing Authorization Holder
MAVE	Major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
NI	Non-Interventional
NIS	Non-Interventional Study
NVS	Novartis
PASS	Post-Authorization Safety Study
PNH	Paroxysmal nocturnal hemoglobinuria
RMP	Risk Management Plan
RWD	Real-World Data
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
US	United States
WHO	World Health Organisation

1 Background

1.1 Product and indication

Iptacopan 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). Iptacopan targets the alternative pathway of the complement cascade proximally and in PNH inhibits both intravascular and C3-mediated extravascular hemolysis.

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 underway.

Paroxysmal nocturnal hemoglobinuria is a rare hematological disorder with an estimated prevalence of approximately 10 to 20 cases per million individuals worldwide (Cançado et al 2021). This acquired disease can affect any age group but frequently affects young adults. Itis estimated that PNH affects 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 (BMF) (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).

1.2 Non-interventional post-authorization safety study (PASS) CLNP023C12003

A non-interventional study (NIS) CLNP023C12003 titled “Post-authorization safety study (PASS) of iptacopan in adult patients with paroxysmal nocturnal hemoglobinuria using data from the non-interventional IPIG PNH Registry” is planned by Novartis with an intent to characterize the safety of iptacopan in routine clinical practice and to fulfill the US FDA postmarketing requirement (PMR) 4553-1, specifically to provide data from a registry that characterizes the long-term safety of Fabhalta in adults with PNH, with up to 5 years of follow-up. This study is also proposed as an additional pharmacovigilance activity in the iptacopan Risk Management Plan (RMP) for the European Union (EU) submission. The study may also potentially be used to generate iptacopan safety data to address questions or requests from other Health Authorities outside the EU.

It is expected that the data collection for the study CLNP023C12003 will begin in Q1 2025, with interim reports of the study to be submitted to the respective health authorities yearly starting in 2025, and the final report to be prepared in Q1 2030. At the time of writing this feasibility assessment report, the study protocol was under preparation, with the aim to submit to the health authorities in early 2024 and finalize no later than 31-Dec-2024.

The main 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. The secondary objectives of the study are to further characterize important safety outcomes (including risk of serious infections, serious hemolysis following discontinuation, other clinical events such as breakthrough hemolysis, malignancies and other serious adverse events (SAEs), and pregnancy outcomes). In addition, the study will evaluate effectiveness of additional risk minimization measures related to vaccination requirements in PNH patients treated with iptacopan. The study protocol is under development and will be submitted to the respective Health Authorities before finalization.

The study CLNP023C12003, a NIS with secondary use of data (NIS-SUD) will be based on the data collected from the International PNH Interest Group (IPIG) registry. 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 intends to begin patient enrollment in Q1 2024 and aims to collect clinical and safety data from 2000+ PNH patients from the United States, Canada and other countries in Europe, Asia and other regions.

The aim of the IPIG PNH Registry is to develop an international database collecting 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. All patients 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 2023a).

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" (IPIG 2023b) 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.

1.3 Rationale for the initial data source selection

A "data sweep" exercise was undertaken by Novartis in 2019 to identify global real-world data (RWD) sources available for PNH to summarize and understand the availability of RWD in this rare disease. A targeted literature review was performed on 17-Jun-2019 in Embase and Medline; the search terms included keywords and medical subject headings (MeSH terms) focused on disease, and study design. Studies extracted that were eligible for review according to the following inclusion criteria:

- Population: adult patients with PNH
- Intervention: any
- Comparator: any
- Outcome: a variety of observational study designs focusing on PNH epidemiology or patient characteristics, clinical burden, treatment and outcomes; with a sample size of at least 30 patients

- Publication type: a variety of types reflecting longitudinal and cross-sectional observational study designs
- Other: English language

Data sources fitting the inclusion criteria 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. The methods and the results have been partially published (Lavudiya et al 2020a, Lavudiya et al 2020b).

A total of 45 potential RWD sources were identified, of which ~80% were generic and ~20% disease-specific. The only identified multi-regional data sources included the International/Global PNH registry, the International bone marrow transplant registry and Aplastic anemia-myelodysplastic syndrome International foundation (Lavudiya et al 2020b).

Most commonly cited data sources as well as the only two sources that contained over 50% of the pre-specified 90 variables were the International/Global PNH Registry owned by Alexion Pharmaceuticals (Alexion 2019) and the Korean National PNH data registry (established by the Korean Society of Hematology), i.e., data sources that do not grant general access for pharmaceutical industry research. PNH diagnosis, age, sex, PNH clone size, thrombotic events and all-cause mortality were among the most frequent variables appearing in 55% to 93% of the evaluated data sources. Variables related to treatment, hospitalizations, adherence, quality of life and PNH symptoms were the least commonly recorded. 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 2023a). It is important to note that the IPIG PNH Registry data collection scheme approximates that of the International/Global PNH Registry owned by Alexion that was identified by the data sweep as the data source with the largest proportion of the relevant PNH variables. However, this registry did not make its data available for industry research and was scheduled to complete in 2025 (Alexion 2019).

To evaluate the study feasibility and the fitness for purpose of the selected data source, a structured evaluation of the IPIG PNH Registry governance, data collection procedures, quality assurance and other aspects was undertaken prior to the full study protocol development. In the evaluation, several approaches were used: as primary guidelines, we have referred to the 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), EMA Data Quality Framework for EU medicines regulation (EMA 2023) and the Novartis internal procedures for registry suitability assessment. For the regulatory guidance documents finalized in October-December 2023, draft versions were used to guide the initial steps of the feasibility assessment.

The methods, findings and the proposed strategies to mitigate the identified risks are described in this report.

2 Objectives

The overall objective of this assessment was to evaluate in a structured manner the feasibility of using IPIG PNH Registry data for the planned study CLNP023C12003 and, to the extent possible, the fitness for purpose of the registry data. The sections below list the key aspects of the planned study that were used to guide the feasibility and fitness for purpose assessment.

2.1 Scientific objectives of the planned registry-based study

The overall objective of the NIS CLNP023C12003 is to collect data on safety outcomes in patients treated with iptacopan for PNH in routine clinical care.

According to the study protocol (under development), the study primary objective is to describe the risk of infections caused by encapsulated bacteria in PNH patients treated with iptacopan in routine clinical practice.

The secondary objectives of the study were 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 SAEs and all-cause mortality
- Describe the use of iptacopan during pregnancy in PNH patients
- Describe characteristics of pregnancies in PNH patients exposed to iptacopan and frequency of selected pregnancy outcomes.

2.2 Key data elements

Based on the variables listed in the protocol of the study CLNP023C12003, the following variables were defined as the most important required for the planned study analyses.

Table 2-1 Key variables for the planned study CLNP023C12003

Variable or group of variables	What?	Comments / minimum requirements
Use of iptacopan	Exposure	Dosing, start and end of treatment (exact dates)
Infections caused by encapsulated bacteria	Primary outcome	Event date, causative organism, infection site

Variable or group of variables	What?	Comments / minimum requirements
Serious infections caused by encapsulated bacteria	Secondary outcome	Date, causative organism, infection site, seriousness criteria
All serious infections	Secondary outcome	Date; infection site, seriousness criteria
Vaccinations against encapsulated bacteria	Secondary outcome	Exact date; organisms in scope: • Neisseria meningitidis • Streptococcus pneumoniae • Hemophilus influenzae
Breakthrough hemolysis	Secondary outcome	Date; criteria that could be used for validation or sensitivity analyses
Serious hemolysis following discontinuation of iptacopan	Secondary outcome	Iptacopan discontinuation (exact date); date of event, seriousness criteria
MAVEs including thrombotic events	Secondary outcome	Date, site of the thrombotic event
Malignancies	Secondary outcome	Date, site of the malignancy
SAEs	Secondary outcome	Date, seriousness criteria
All-cause mortality	Secondary outcome	Date
Pregnancy exposure characteristics	Secondary outcome	Last menstrual period; or estimated delivery date; or trimester of exposure
Pregnancy and birth outcomes	Secondary outcome	Miscarriage, Intrauterine death / stillbirth, live birth, gestational age or birthweight, congenital malformations
Demographic characteristics	Important covariates	Age; sex/gender; desired: race/ethnicity
PNH history and treatment	Important covariates	Date of the first diagnosis, previous treatment with anti-complement therapy and other treatment (prior to iptacopan initiation)
Medical history	Important covariates	History of all outcomes of interest;
Concomitant treatment	Important covariates	Anti-complement therapy, anticoagulation therapy, antibiotic prophylaxis, immunosuppression
Obstetric history	Important covariates	Number and outcome of previous pregnancies

The list above is not exhaustive of all the variables planned to be collected in the study CLNP023C12003 but was used as a starting point for the evaluation of the data relevance and suitability, as described below.

3 Methods

3.1 Data relevance evaluation of the IPIG PNH Registry compared to alternative data sources

The evaluation of the relevance of the IPIG PNH Registry for the planned safety study was guided by considerations regarding a registry's fitness-for-use in regulatory decision-making as described in the FDA Draft guidance for industry "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (US FDA 2023a). Specifically, the structured evaluation form for the data relevance aspect was developed according to the recommendations and structure presented in the FDA Draft Guidance.

The evaluation also incorporated elements of "data timeliness" and "data coverage" evaluation from the EMA Guideline on registry-based studies (EMA 2021), and EMA Data Quality Framework for EU medicines regulation (EMA 2023). The selection of specific variables of interest (see Section 2.2) was based on the study CLNP023C12003 objectives (Section 2.1) and the variables listed in the draft study protocol.

The information regarding the data sources and the variables collected in the IPIG PNH Registry was extracted from the IPIG PNH Registry Protocol (latest version available at the time of assessment: v.2.0 dated 02-Oct-2023) that was used as the main source for this assessment (IPIG 2023a), as well as the IPIG PNH Registry case report form (CRF) v2.0 dated 21-Aug-2023 and the iptacopan silo Appendix to the IPIG PNH Registry Protocol v.00 dated 16-Oct-2023 (IPIG 2023b).

Aside from the IPIG PNH Registry, the assessment considered potential alternative secondary sources of data, such as electronic medical records (EMRs) and insurance claims databases. Recently completed and published real-world evidence (RWE) research at Novartis was used as a starting point for the data relevance assessment: publications by (Tantravahi et al 2023) for IQVIA PharMetrics® Plus database, and (Shammo et al 2023a, Shammo et al 2023b) for TriNetX as an example of a large EMR database in the United States. Internally available data sources descriptions, data dictionaries and other data literacy documents were used as supporting tools for the assessment of TriNetX, IQVIA Pharmetrics® Plus and Optum Clinformatics Data Mart (CDM) databases. In addition, for the TriNetX database, the data completeness was assessed using data from an internal feasibility assessment performed in April 2022.

3.2 Suitability evaluation of the IPIG PNH Registry

For structured evaluation of data reliability and other key aspects of the registry design we have used the questionnaire "Evaluation of the registry suitability" developed by Novartis based on the available guidance from health authorities on the registry-based studies. Same as for the data relevance evaluation, the key information about the data collection and registry enrollment procedures, data elements and the quality assurance was extracted from the IPIG PNH Registry Protocol v2.0 and CRF v2.0. In addition, the assessment had used information from the IPIG PNH Registry Participation Agreement with Novartis and personal communication with the registry personnel where appropriate.

In addition to the Novartis internal questionnaire, a structured review of the registry operational, methodological and scientific aspects has been undertaken in September 2023 using the Registry Evaluation and Quality Standards Tool (REQueST) (Allen et al 2022, EUnetHTA 2019) (using IPIG PNH Registry Protocol version 1.0 available at the time). The form completion was also guided by the instructions provided in the EMA Guideline on registry-based studies (EMA 2021) and the items specified in the "Checklist for evaluating the suitability of registries for registry-based studies" in the Appendix 1 of this Guideline.

The items collected in the REQueST form partially overlapped with the items collected in the Novartis questionnaire so the results from the two assessments were evaluated simultaneously. Not all aspects of the questionnaires could be assessed in full as the IPIG PNH Registry, at the

time of assessment, did not yet begin patient recruitment and so a sample of the registry data was not yet available for evaluation.

4 Results

In the following section, the results of each evaluation described above are provided in detail.

4.1 Data relevance evaluation

The IPIG PNH Registry was initially selected to fulfill the objectives of this NIS because collection of safety information on PNH treatments is one of the stated objectives of the registry. Consequently, the variables in the registry core protocol and the CRF that relate to safety data collection are also applicable and relevant for iptacopan safety evaluation. The structured assessment of the data relevance has confirmed that, in terms of PNH-specific variables, the IPIG PNH Registry data is indeed expected to be characterized with better breadth and depth, compared to the alternative data sources (EMRs and insurance claims databases). According to the assessment, only IPIG PNH Registry is expected to satisfactorily address the requirements for the key variables as defined in Section 2.2.

Details of the evaluation are presented in Table 7-1 in Annex.

To summarize main concerns that arose while evaluating the data relevance as available from the IPIG PNH Registry and alternative sources of data, the evaluation of the IPIG PNH Registry identified the following concerns:

1. According to the IPIG PNH Registry protocol, Novartis can only access individual patient level data from PNH patients treated with iptacopan. Thus, any study based on the IPIG PNH Registry data may not have an internal comparator and could only evaluate rates of the events of interest as they occur in the iptacopan-treated PNH patients.
2. The IPIG PNH registry protocol imposes limitations on the maximum follow-up of patients who discontinue iptacopan. 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 (“intent to treat”-like approach). Thus, the evaluation of safety outcomes in the study CLNP023C12003 is limited to on-treatment events or events occurring shortly after discontinuation (with the exception of the pregnancy outcomes).
3. Left-censoring is possible as well and may result in falsely assigning patients previously exposed to iptacopan as treatment-naïve patients.

For further discussion of these design limitations and the proposed mitigation measures, please refer to Section 5.1.2.

Major concerns that were inherent to both claims and EMR data could be summarized as follows:

1. Evaluation of the primary outcome “Infections due to encapsulated bacteria” and secondary outcome “serious infections due to encapsulated bacteria” appeared to be possible in principle based on the ICD-10 codes for the specific infections; however, no validated algorithms for the identification of infections due to encapsulated bacteria that could be used were identified in the literature.

- A paper using the FDA's Sentinel Distributed Database confirmed that ICD-10 diagnoses could be used to identify hospitalizations for serious infections among patients treated with biologic therapies. Although positive predictive value [PPV] for pneumonia was 83.3% (95% CI 70.7 to 92.1%), for acute meningitis it was relatively low: PPV=69.2% (95%CI 48.2 to 85.7%) (Lo Re et al 2021). This study did not evaluate PPVs for specific etiologies.
- Another study assessed the accuracy of ICD-9 coding for pneumonia cases among hospitalized patients in the US and found that although the specificity for the ICD-9 codes for pneumonia cases caused by encapsulated bacteria was high (99.2% for *Streptococcus pneumoniae* and 99.9% for *Haemophilus influenzae*), the sensitivity was low (60.1% and 42.8%, respectively) (Higgins et al 2020).

2. Evaluation of the safety outcomes "breakthrough hemolysis" and "serious hemolysis following iptacopan discontinuation" did not appear to be possible based on the following aspects:
   - No validated algorithm for the identification of the event via the ICD-10 coding systems
   - Absence or limited availability of laboratory data that could be used to validate the event of breakthrough hemolysis
   - For the event "serious hemolysis following iptacopan discontinuation", no information on the timing of iptacopan discontinuation
3. Evaluation of pregnancy safety especially with regards to fetal outcomes is either not possible in an open EMR setting (TriNetX) or only possible for a small subset of cases for whom mother-to-child linkage is possible (e.g. Optum DAPI as example of such database).

Taken together, the concerns identified during the evaluation of the alternative data sources precluded them from being used for the purposes of the planned safety study. The concerns related to the IPIG PNH Registry study design and data access rules require mitigation and are described further in the Discussion (Section 5).

4.2 Registry suitability evaluation

4.2.1 Evaluation of registry suitability according to the Novartis process

A standard questionnaire "Evaluation of the registry suitability" developed by Novartis was completed for the IPIG PNH Registry and is available as Table 7-2 in Annex. A summary of the major findings is provided below.

The questionnaire focuses on the following dimensions:

- **Admin and organization**: no outstanding issues were identified. The registry covers multiple countries in several continents and intends to begin enrollment in 2024; informed consent procedures were assessed as appropriate; data sharing agreements and schedule have been finalized by the time of assessment and are appropriate for the purposes of the planned study.
- **Data quality and indicators**: several outstanding issues identified, most of them related to the fact that the registry at the time of assessment was still in the start-up

phase and not all key documents were available. To provide further insight into the issue, this section is copied below as a standalone table (Table 3-1).

- **Data adequacy**: all items are marked as satisfactory / not requiring further follow-up except a question on the core/optional data elements, as to confirm this Annotated CRF or the Data Management Plan would be required, which was not available at the time of assessment. The definitions for the clinical events according to the CRF were satisfactory; Medical history and clinical outcomes will be coded 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. The anonymized dataset transferred to Novartis will be formatted according to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standards.
- **Population**: The aim of the IPIG PNH core registry is to enroll at least 2000 PNH patients regardless of treatment; patients that give consent will also be transferred from the International PNH Registry (currently owned by Alexion, to be discontinued by 2025). Most items in this section were satisfactory, although a potential risk was identified related to the fact that the registry enrollment did not start at the time of assessment, and thus the actual sample size for the planned study (iptacopan-treated PNH patients) as well as the actual duration of iptacopan treatment was unknown. This risk is further described in Section 5.4.2.
- **Variable groups of interest**: marked as satisfactory based on the assessment in Section 4.1.

Table 3-1 The "data quality and indicators" section of the registry suitability assessment – IPIG PNH Registry

	Identified through desk research? (Y/N)	To be followed-up / confirmed with the registry? (Y/N)	Additional notes
Data quality (and indicators)			
Are there any dedicated resources for the data collection, monitoring and review?	Y	Y	[redacted] will dedicate staff, however monitoring and data review processes are still not clear, to be followed up with IPIG/[redacted]
Is a data dictionary available?	N	Y	Data dictionary not available at the time of review, requested from [redacted]
Are the data collected consistently (e.g. eCRF)?	Y	Y	Core CRF v2.0 available at the time of review; iptacopan-specific CRF pages and annotated CRF still pending.
Who collects or enters the data? Are there consistency checks in place?	Y	Y	HCPs at the sites will enter the data; CRF consistency checks were promised by [redacted] but annotated CRF still not provided
Are the data accurate (i.e. are existing auditing mechanisms in place [e.g. 10% of data reassessed, IT-implemented fallback mechanisms])?	N	Y	Data management plan, annotated CRF and SAP not provided by [redacted] at the time of assessment, requires follow-up

	Identified through desk research? (Y/N)	To be followed-up / confirmed with the registry? (Y/N)	Additional notes
Are the data representative of the population of interest (are the registry data comparable to the overall population)?	Y	Y	The registry inclusion criteria are maximally broad to include all PNH patients consecutively regardless of disease stage/type and treatment status. The actual patient population is not available at the time of the review as the registry is still in the start-up phase
Are the data complete? If not what is the proportion of missing data? Is there any particular data frequently missing (e.g lab results)?	N	Y	This information could not be assessed as at the time of review the registry was still in the start-up phase
Are the data reported with adequate detail with which to conduct the research study?	Y	Y	According to the CRF, the data granularity and the variables collected are sufficient to conduct a research study with safety objectives; however, data accuracy and completeness indicators were not available at the time of review

CRF – case report form; HCP – healthcare professional

A summary of the comprehensive data quality evaluation based on the above table and the other assessments is provided in Section 5.3, and the proposed mitigation of the resulting risks is described in Section 5.4.3.

4.2.2 Registry Evaluation and Quality Standards Tool (REQueST)

The completed REQueST form is available as a standalone document (available upon request). The summary output automatically generated by the tool is presented in the figure below.

Registry name: IPIG PNH Registry
Date of assessment: 10-Sep-23

Satisfactory
Needs development / clarification
Not suitable

Area	Item	Colour rating
Methodological Information	1. Type of registry	
	2. Use for registry-based studies and previous publications	
	3. Geographical and organisational setting	
	4. Duration	
	5. Size	
	6. Inclusion and exclusion criteria	
	7. Follow-up	
	8. Confounders	
Essential Standards	9. Registry aims and methodology	
	10. Governance	
	11. Informed consent	
	12. Data dictionary	
	13. Minimum data set	
	14. Standard definitions, terminology and specifications	
	15. Data collection	
	16. Quality assurance	
	17. Data cleaning	
	18. Missing data	
	19. Financing	
	20. Protection, security and safeguards	
Additional Requirements	21. Interoperability and readiness for data linkage	
	22. Data sources	
	23. Ethics	

Figure 3-1 Summary output from the REQueST Tool – IPIG PNH Registry, assessed on 10-Sep-2023

The assessment was performed using the registry protocol v1.0 before the updated registry protocol (v2.0) became available; however, there were no major changes in the updated protocol that would require an update of the initial assessment.

The seven aspects that were flagged by the tool as those requiring further development or clarification were as follows:

- Size: planned size of the registry is at least 2000 patients, however, at the time of completion the registry did not yet begin enrollment so this aspect must remain closely monitored.
- Governance: some discrepancies were identified in the descriptions of the IPIG PNH Registry Committee, and the Stakeholder Committee provided in the IPIG PNH Registry Participation Agreement and IPIG PNH Registry protocol.
- Data dictionary: not available at the time of assessment, was expected to become available by early 2024.
- Quality assurance: open questions remain regarding the consistency checks implementation, whether Novartis would be able to raise queries, and regarding the quality of the adverse event (AE) reporting.

- Data cleaning: Process has not been clearly described to date, needs further clarification.
- Financing: Identified as potential risk: if one or several industry Stakeholders discontinue registry participation, cost for remaining stakeholders may inflate such that continued participation may become infeasible.
- Interoperability and readiness for data linkage: according to the information available at the time of assessment, there would be no possibility for data linkage with external data sources. This was however considered acceptable for the purposes of the planned study.

One additional aspect in the REQueST tool not covered by the other questionnaires was "Ethics". According to the IPIG PNH Registry protocol, the registry shall be conducted in compliance with International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practice (GPP) guidelines (ISPE 2016), the ethical principles arising from the Declaration of Helsinki, the EU Guideline on Good Pharmacovigilance Practices (GVP), European and National laws in terms of data protection and all current local regulations. This aspect therefore was assessed as satisfactory.

5 Discussion

5.1 Rationale for the data source selection

Initially the IPIG PNH Registry was selected as a potential data source for the safety study CLNP023C12003 based on the results of the internal "data sweep" exercise that concluded that at the time of the analysis there was only a limited collection of RWD sources available, and none of the sources available at the time were suitable for the purposes of a non-interventional study addressing aspects of iptacopan real-world safety (see Section 1.3).

IPIG PNH Registry was considered appropriate to fulfill the objectives of the study CLNP023C12003 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.

5.1.1 Strengths of the selected data source

The IPIG PNH Registry data will include longitudinal records from a multinational registry of patients with PNH, and Novartis will gain access to the subset of 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.

The study 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 2023a). 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. The structured assessment of the data relevance has confirmed that the IPIG PNH Registry data is expected to be characterized with better breadth and depth (in terms of PNH-specific variables) than the alternative data sources, and thus to better address the requirements for the key variables as defined in Section 2.2.

As the clinical sites invited to participate in the IPIG PNH Registry overlap with those contributing to the Alexion-owned International PNH Registry (Alexion 2019), the IPIG PNH Registry protocol states that "Data from the Alexion PNH registry, which has been running since 2004, may be transferred to the IPIG PNH registry following patient consent" (IPIG 2023a). This is expected to further enrich the data collected in the IPIG PNH Registry by providing more detailed clinical history of those patients that were transferred from the Alexion registry. The fact that the sites that previously participated in the Alexion-owned registry are already well familiar with the registry data entry procedures is also encouraging.

5.1.2 Limitations of the selected data source

Limitations related to the registry start-up status

A critical limitation identified during the assessment was that although the 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. These included, first of all, the statistical analysis plan (SAP), data dictionary or annotated CRF, Data Management Plan or similar document, and the Monitoring Plan. Similarly, as the patient enrollment into the registry did not begin at the time of assessment, the assumptions regarding the enrollment, duration of follow-up, data completeness etc. could not be verified. For further information, please see Section 5.3 "Data quality evaluation" and Section 5.4 "Summary of the identified risks and mitigation plans" below.

Lack of internal comparator

According to the IPIG PNH Registry protocol, Novartis will only have access to the data from PNH patients treated with iptacopan. The planned study will thus only analyze data from adult PNH patients treated with iptacopan that are enrolled in the IPIG PNH Registry, with no internal comparator. To mitigate limitations resulting from the lack of internal comparator in the study CLNP023C12003, 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.

Right censoring

The IPIG PNH registry protocol imposes limitations on the maximum follow-up of patients who discontinue iptacopan (IPIG 2023a). 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 ("intent to treat"-like approach). Thus, the evaluation of safety outcomes in the planned safety study is limited to on-treatment events or events occurring shortly after discontinuation, with the exception of the pregnancy outcomes. This limitation is not expected to have an effect on the study planned primary outcome (infections caused by encapsulated bacteria), but may be of relevance to the outcomes with long latency such as e.g. malignancies. Duration of follow-up will be monitored in the study interim reports and if the average follow-up time is very short, a modification of the study design may be undertaken, in consultation with the health authorities.

Left censoring

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. At the same time, this limitation is also inherent to alternative data sources such as claims data, so potential misclassification of some prevalent patients as new users was considered acceptable for the planned study and will be reflected in the "Bias" section of the study protocol.

5.2 Data relevance evaluation

Data **relevance** is broadly defined by the FDA as the assessment on whether the data captured in the registry is adequate for evaluating the study's scientific objectives (US FDA 2023a). The corresponding concepts from the EMA guidelines are "data relevance", "data timeliness" and "data coverage" (EMA 2023).

As described in Section 4.1, the structured data relevance evaluation against the planned study objectives and key data elements has confirmed that the IPIG PNH Registry is most suitable for conducting a study to evaluate PNH safety outcomes when compared to alternative data sources. In particular, the IPIG PNH Registry appears to be better suited (compared to EMR or claims data) for the evaluation of the the primary outcome "Infections due to encapsulated bacteria" and secondary outcomes related to hemolysis events, as there are no validated algorithms for the identification of these events via the ICD-10 coding systems. In the IPIG PNH Registry, these outcomes were pre-specified in the registry protocol and included in the CRFs. Further, as these represent common safety concerns in the PNH treatment setting, one may expect that the HCPs entering data are alerted to the possibility of these events, reducing probability of under-reporting.

In the IPIG PNH Registry setting, the timeliness of the data entry is inherently compromised by the 6-monthly visit schedule. However, the visit frequency is an important trade-off to reduce reporter fatigue and potentially improve compliance and loss to follow-up. Thus, the data timeliness was considered acceptable.

Coverage, as defined by EMA, measures the amount of information available with respect to what exists in the real world, whether it is inside the capture process and data format or not. An example of a coverage issue is whether a set of individuals present in a dataset is representative of a population under study (EMA 2023). This dimension cannot be easily measured; however, it is important to note that in the extremely rare disease setting, such as PNH, a standard notion of representative population sampling does not apply or may not be achievable. In the IPIG PNH Registry, participating HCPs are selected among the PNH experts worldwide that are already treating at least one PNH patient in their practice. In the view of the extreme rarity of this condition this is considered to be an acceptable approach for the purposes of the planned study.

In terms of the inclusion and inclusion criteria, the IPIG PNH Registry has very broad inclusion criteria that allows recruitment of all PNH patients that do not currently participate in an interventional PNH trial and have signed an informed consent. From this perspective, the registry is expected to have good coverage of the PNH patient population as long as there are no selective consent withdrawals.

5.3 Data quality evaluation

As the guiding documents from the EMA and the FDA focus on different (although partially overlapping) data quality and suitability aspects, a summary of the evaluation results is provided below separately for each guidance, according to their definitions.

Data **reliability** as defined by the US FDA draft Guidance (US FDA 2023a) contains four dimensions:

- **Accuracy**: although some assurance has been received that there will be data quality and consistency checks on the CRF level as well as the data management level, key documents such as the Data Management Plan and the actual subset of registry data for analysis were not available at the time of assessment, so this was identified as a potential risk.
- **Completeness**: could not be assessed due to the registry start-up status so it remains a risk.
- **Traceability**: key documents such as the Data Management Plan, the Monitoring Plan and the evidence of the maintenance of audit trails were not yet made available at the time of review so this remains a risk

The anonymized dataset transferred to Novartis will be formatted according to the CDISC SDTM standards and thus comply with the requirements of the US FDA Guidance “Data Standards for Drug and Biological Product Submissions Containing Real-World Data” (US FDA 2023b). However, as highlighted in the Guidance, potential challenges in mapping the CRF entries to the SDTM standards may remain. As the Data Management Plan was not available for review at the time of assessment, this was also flagged as potential risk. For a

summary of the identified risks related to the data quality and the proposed mitigation plans, see Section 5.4.3.

In addition to "data relevance" and "data timeliness" (covered in Section 5.3) the Data Quality Framework for EU medicines regulation (EMA 2023) defines the following data quality dimensions:

- **Reliability**, covering the sub-dimensions of precision, accuracy and plausibility. This dimension appears to broadly correlate to the "Accuracy" dimension defined to the FDA and has been identified as a potential risk (for details, see the corresponding item above).
- **Extensiveness**, covering the sub-dimensions of completeness and coverage. The "coverage" dimension is discussed in Section 5.3; completeness could not be assessed due to the registry start-up status and thus remains a risk (see Section 5.4.3).
- **Coherence**, defined as the dimension that expresses how different parts of an overall datasets are consistent in their representation and meaning and covering sub-dimensions of format coherence, structural coherence and semantic coherence. In the setting of the IPIG PNH Registry with structured data entry via standard CRFs that specify entry options, units and applicable coding systems, there should not be major coherence issues. Nonetheless, some free-text entries as well as clinical events may lend themselves to potentially discrepant definitions, so coherence remains a dimension to be evaluated in the Data Quality Assessment report as described in Section 5.4.3 below.

Taken together, based on the results of the comprehensive assessment, the data accuracy, completeness, coherence and traceability-related aspects were identified as the greatest potential risk for the IPIG PNH Registry. The proposed steps to mitigate this risk are described in Section 5.4.3.

5.4 Summary of the identified risks and mitigation plans

5.4.1 Financial / continuity risk

A continuity risk has been identified based on the registry financing scheme (see Section 4.2.2). The current registry budget and the individual stakeholder contributions were established under the assumption that 6 industry stakeholders participate in the registry. If one or several industry stakeholders discontinue their participation, cost for remaining stakeholders may inflate such that continued participation may become infeasible.

Mitigation: an internal feasibility assessment is ongoing to establish whether alternative sources of data collection would be more feasible or cost-effective in case of the registry budget inflation.

5.4.2 Patient enrollment and follow-up

The data collected within the IPIG PNH Registry due to its non-interventional nature cannot impose on participating patients any requirements regarding treatment choice, treatment duration, visit frequency etc. Thus, even if the registry enrollment is according to the target, there may be still not enough iptacopan-treated patients for meaningful analyses of the safety study.

Same consideration applies to the patient follow-up: even if the loss to follow-up within the registry is low and most patients are followed up to 5 years as planned, the actual follow-up of iptacopan-treated patients will depend on the duration of iptacopan use. In the scenario where patients only take iptacopan for relatively short time and switch to other PNH treatments, the average follow-up of iptacopan patients available for analysis will be low.

Mitigation: Patient enrollment and follow-up duration will be monitored in the study interim reports, and if the number of iptacopan-treated patients is clearly below the expected enrollment (expected approximately 200 patients by the end of the study) and/or if the patient average follow-up time is very short, a modification of the study design may be undertaken, in consultation with the health authorities.

5.4.3 Data quality aspects

Although the IPIG PHN Registry protocol and the Registry Participation Agreement addresses a number of data quality-related aspects, a thorough evaluation of the registry data quality was not possible, because a few key documents including Data Management Plan, Statistical Analysis Plan etc. were still under development at the time of assessment. Accordingly, data samples from the registry were also not yet available for the evaluation of aspects such as data completeness and so on.

As described in Section 5.3, data accuracy, completeness, coherence and traceability-related aspects were flagged as the greatest potential risks in the IPIG PNH Registry that could not be evaluated because of missing documentation.

Mitigation: a multi-step approach is proposed to address this major risk. First, the missing documentation must be collected from the IPIG PNH Registry once available and reviewed, in particular:

- Data management plan or similar documentation
- Data dictionary or annotated CRF (as applicable)
- Statistical analysis plan
- Monitoring plan, if applicable

Thorough review of these documents once available will allow further evaluation of the potentially problematic aspects of the data collection and data quality assurance procedures and to further refine the data quality evaluation, which will be performed subsequently.

As a second step, the actual subset of the registry data, once made available to Novartis, will be analyzed to generate a standalone Data Quality Assessment Report. The exact methodology will be defined based on the potential data issues identified in Step 1, but will follow the general framework outlined by (Schmidt et al 2021) that focuses on four following key data quality indicators:

- integrity (compliance with pre-specified structural and technical requirements);
- completeness (presence of expected data values);
- consistency (no inadmissible or uncertain data values and contradictions);
- accuracy (evaluated via unexpected distributions and associations).

The process will be iterative, repeating the Data Quality Assessment at regular intervals (e.g., corresponding to the annual interim study reports) and addressing identified data quality issues according to the problems identified. E.g., if presence of inadmissible values is detected, the study SAP could be amended to ensure these are censored from the analyses; other identified issues may need to be reported back to the IPIG PNH Registry with the request to implement procedures to improve data quality and completeness.

6 Conclusions

A comprehensive assessment of the feasibility and fitness for purpose of the IPIG PNH Registry data for use in the planned study CLNP023C12003 was performed, using a variety of structured assessments. Although the conclusion was that the IPIG PNH Registry is the best suitable to address the objectives of the planned study CLNP023C12003, compared to alternative available data sources, several design-related and operational limitations and risks were identified. Proposed mitigation measures are described in the report for the key risks, including financial/continuity risk, patient enrollment and follow-up and data quality issues.

In particular, the data quality aspect was flagged as a major risk because the comprehensive data quality evaluation could not be performed at the time of the initial assessment. A two-step mitigation approach including both qualitative and quantitative data quality evaluation is proposed and will be implemented during the study conduct.

7 References

1. Alexion Pharmaceuticals, Inc. (2019) Protocol Number: M07-001 Paroxysmal Nocturnal Hemoglobinuria (PNH) Registry. Amendment 7, 18. Jan 2019. Available from: https://www.encepp.eu/encepp/openAttachment/fullProtocolLatest/47881 Accessed 10-Apr-2023.
2. Allen A, Patrick H, Ruof J et al (2022) Development and Pilot Test of the Registry Evaluation and Quality Standards Tool: An Information Technology–Based Tool to Support and Review Registries. Value Health; 25(8):1390–1398
3. 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.
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 (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.

6. 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.
7. Higgins TL, Deshpande A, Zilberberg MD, et al (2020). Assessment of ICD-9 Diagnosis Codes to Identify Pneumonia Etiology in Hospitalized Patients. JAMA Network Open; 3(7): e207750.
8. Hill A, Dezern AE, Kinoshita T, et al (2017) Paroxysmal nocturnal haemoglobinuria. Nature reviews. Disease primers; 3: 17028-17028.
9. International PNH Interest Group (2023a). Observational Registry Protocol: The International PNH Interest Group PNH Registry. Version 2.0, 02 October 2023
10. International PNH Interest Group (2023b). Observational Registry Protocol: The International PNH Interest Group PNH Registry. Appendix 3: Iptacopan Silo. Version 00, 16 October 2023
11. International Society for Pharmacoepidemiology (2016) Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf; 25: pp.2-10.
12. 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
13. 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.
14. Lo Re III V, Carbonari D, Jacob J, et al (2021) Validity of ICD-10-CM diagnoses to identify hospitalizations for serious infections among patients treated with biologic therapies. Pharmacoepidemiol Drug Saf; 30: pp.899–909
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. Schmidt CO, Struckmann S, Enzenbach C, et al (2021) Facilitating harmonized data quality assessments. A data quality framework for observational health research data collections with software implementations in R. BMC Med Res Methodol 21(1):63.
19. Shammo JM, Kim J, Georget M, et al (2023a) P796 Hospitalization in patients with paroxysmal nocturnal hemoglobinuria: a retrospective analysis of observational study data

from the United States. Poster presented at EHA 2023 hybrid congress, held virtually and in person in Frankfurt, Germany on 8–11 June 2023

20. Shammo JM, Vijapur SM, Snellman J, et al (2023b) Disease Management and Outcomes in Patients with Paroxysmal Nocturnal Hemoglobinuria: A Retrospective Analysis of Observational Data from the United States. Blood 142; pp. 5639–5640Tantravahi S, Latremouille-Viau D, Desai R et al (2023). IR043 Dosing Patterns of Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Treated with Complement Inhibitors: A Retrospective Claims Data Analysis. Poster presented at the 2023 NORD Rare Diseases and Orphan Products Breakthrough Summit, Washington, DC, 16-17 October, 2023
21. US Food and Drug Administration (FDA) (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.
22. 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.

8 Annex

8.1 Data relevance evaluation

Structured data relevance evaluation following the scheme as suggested the FDA Draft guidance for industry "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (US FDA 2023a) and incorporating elements of "data timeliness" and "data coverage" evaluation from the EMA Guideline on registry-based studies (EMA 2021), and EMA Data Quality Framework for EU medicines regulation (EMA 2023) is presented in Table 7-1.

To improve readability, color coding has been used to highlight potentially problematic aspects:

- **Mustard**: potentially concerning aspect, may limit the data availability and/or validity, or limit the ability to collect information on some potential confounders.
- **Red**: flagged as a problem aspect, will limit ability to evaluate specific safety outcomes, perform planned subgroup analyses or implement other study design aspects.

Table 7-1 Data relevance evaluation – IPIG PNH Registry, EMR data (TriNetX used as example), insurance claims data (Optum CDM, IQVIA PharMetrics Plus used as examples)

Aspect of interest	IPIG PNH Registry	EMR database (TriNetX)	Claims database (Optum, PharMetrics)
Geographical coverage	~ca 20 countries worldwide	United States (Midwest/Atlantic over-represented)	United States
Time period coverage	to begin enrollment Q4 2023, however will use available historical data from EMR	From Oct 2015 - open-ended	From Oct 2015 - open-ended
Timeliness	Data available at pre-defined time points per contract and on-demand. Data download will reflect all data collected in the EDC to date, however patient visit frequency is expected about once every 6 months	Data available on-demand with ~1 month time lag (less for some contributing centers)	Data available on-demand with ~6 month time lag
Sample size (all PNH patients)	2000 planned to be enrolled; % treated with complement inhibitors to depend on the real-world clinical practice Patients currently enrolled in the Alexion International PNH Registry will transfer data to the IPIG Registry if they give consent to do so	Between 01-Jan-2007 and 06-May-2023 (Shammo et al 2023b): • 1227 adults with ≥1 PNH code (D59.5) and at least 6 months follow-up • Of them, 127 treated with C5 inhibitors (eculizumab or ravulizumab)	Optum: 750 adults with PNH as of June 2021 (internal feasibility assessment); PharMetrics. as of Sep 2022 (Tantravahi et al 2023): • 2,241 adults with ≥1 PNH code (D59.5) • Of them, 788 treated with eculizumab or ravulizumab

Aspect of interest	IPIG PNH Registry	EMR database (TriNetX)	Claims database (Optum, PharMetrics)
Demographic data			
Age	yes	yes	yes
Sex/gender	Gender per CRF (6 answer options)	Sex	Sex
Race/ethnicity	both race and ethnicity collected per CRF	15% unknown	Unreliable (large % missing)
Height/weight	collected per CRF	BMI available for 64% PNH patients	no
PNH diagnosis			
PNH diagnosis	Confirmed by flow cytometry	ICD-10 code D59.5	ICD-10 code D59.5
First diagnosis date	yes	yes	yes
Clone size	yes, in different cell types	no	no
Laboratory data	yes related to PNH	limited (e.g. hemoglobin available for only 20% PNH patients)	no
PNH therapy			
Anti-complement therapy	only if concomitant / prior same aspects as for iptacopan (below)	yes, same aspects as for iptacopan (below)	yes, same aspects as for iptacopan (below)
Iptacopan: starting date	yes, however previous use may not be reflected if iptacopan was taken as part of investigational trial	yes, however previous use may not be reflected if iptacopan was taken as part of investigational trial or in a different care setting	yes, however previous use may not be reflected if iptacopan was taken as part of investigational trial or under a different insurance plan
Iptacopan: stopping date	yes	may be imputed	may be imputed
Iptacopan: dose, route, frequency	yes	no	no
Iptacopan: reason for discontinuation	yes	no	no
Comorbidities / medical history			
Thrombosis/MAVEs	yes (CRF)	May be extracted from ICD-10, procedure codes	May be extracted from ICD-10, procedure codes
Malignancies	yes (CRF)		
Infections	yes (CRF)		
Vaccinations against encapsulated bacteria	yes (CRF)	only if performed within the same practice (open database)	yes, via procedure codes
Breakthrough hemolysis	yes (CRF)	no	no
Blood transfusions, bone marrow transplants	yes (CRF)	yes (procedure code)	yes (procedure code)
Cardiovascular risk factors	Diabetes, hypertension, ischemic heart disease	ICD-10, procedure codes	ICD-10, procedure codes
Other	Impaired renal function, impaired liver function, autoimmune disease, asthma,	ICD-10, procedure codes	ICD-10, procedure codes

Aspect of interest	IPIG PNH Registry	EMR database (TriNetX)	Claims database (Optum, PharMetrics)
	bronchitis/COPD, high PNH disease activity		
Comedications	Anticoagulation therapy; Antibiotic prophylaxis; Growth factors; Immunosuppression; Thrombopoietin receptor agonists; Iron chelation therapy	ATC, procedure codes – only if treatment is administered or prescribed within the same practice (open database)	ATC, procedure codes
Safety outcomes of interest			
Infections due to encapsulated bacteria (**primary outcome**)	N. meningitidis, Streptococcus spp., H. influenzae infections specified in the CRF	ICD-10 codes A39*, A40.3, J15.3, B95.3, B96.3 etc. may be used but not validated, low sensitivity expected	ICD-10 codes A39*, A40.3, J15.3, B95.3, B96.3 etc. may be used but not validated, low sensitivity expected
Serious infections due to encapsulated bacteria	N. meningitidis, Streptococcus spp., H. influenzae infections specified in the CRF Seriousness criteria: to be defined analytically based on the event details in the CRF or extracted from the corresponding SAE	ICD-10 codes A39*, A40.3, J15.3, B95.3, B96.3 etc. may be used but not validated, low sensitivity expected Seriousness criteria: to be defined analytically based on the presence of hospitalization codes, death etc.	ICD-10 codes A39*, A40.3, J15.3, B95.3, B96.3 etc. may be used but not validated, low sensitivity expected Seriousness criteria: to be defined analytically based on the presence of hospitalization codes, death etc.
Serious infections	yes (CRF) Seriousness criteria: to be defined analytically based on the event details in the CRF or extracted from the corresponding SAE	ICD-10, procedure codes Seriousness criteria: to be defined analytically based on the presence of hospitalization codes, death etc.	ICD-10, procedure codes Seriousness criteria: to be defined analytically based on the presence of hospitalization codes, death etc.
Vaccinations against encapsulated bacteria and prophylactic antibiotic use	yes (CRF)	yes (procedure codes, medication codes)	yes (procedure codes, medication codes)
Thrombosis/MAVEs	yes (CRF) – prespecified events of interest in the PNH treatment setting	ICD-10, procedure codes	ICD-10, procedure codes
Malignancies	Selected solid tumors, hematological tumors per CRF Also could be extracted from the corresponding SAE	ICD-10, procedure codes	ICD-10, procedure codes
Breakthrough hemolysis	yes (CRF)	no	No
Serious hemolysis following iptacopan discontinuation	May be defined analytically based on the details of the potential breakthrough hemolysis event in the CRF	no	No
Death	yes (CRF), including information on the cause of death and exact date	limited	limited (cause, exact date may not be available)
Other adverse events, including Serious Adverse Events (SAEs)	adverse events, including SAEs, will be collected systematically per CRF	May be extracted from ICD-10, procedure codes	May be extracted from ICD-10, procedure codes

Aspect of interest	IPIG PNH Registry	EMR database (TriNetX)	Claims database (Optum, PharMetrics)
		Seriousness criteria: to be defined analytically based on the presence of hospitalization codes, death etc.	Seriousness criteria: to be defined analytically based on the presence of hospitalization codes, death etc.
Long-term safety, other aspects	patients to be followed for up to 5 years but only for 12 weeks post-iptacopan discontinuation	Concerns related to open database nature (events happening outside of hematology practice may not be reflected) - applies to all safety events above	Long-term safety evaluation possible as long as patients do not switch insurance
Pregnancy-related variables			
Prior obstetric history	Recorded per CRF	May be incomplete (see below)	Available for the duration of insurance enrollment
Date of last menstrual period	Will need to be imputed from the estimated delivery date	Will need to be imputed	Will need to be imputed
Gestational timing of drug exposure	Will need to be imputed from the estimated delivery date	Will need to be imputed	Will need to be imputed
Maternal outcomes (thrombosis, death etc.)	Recorded per CRF	May be extracted from ICD-10, procedure codes	May be extracted from ICD-10, procedure codes
Pregnancy outcomes (minimum: live birth, stillbirth, miscarriage)	Recorded per CRF	May be extracted from ICD-10, procedure codes	May be extracted from ICD-10, procedure codes
Fetal outcomes (as a minimum, gestational age or birthweight; presence of congenital anomalies)	Recorded per CRF: major congenital malformations, small-for-gestational age, preterm birth, low birth weight	Not available	available for a subset that may be linkable via mother-child linkage (e.g. ~20% of data for Optum DAPI) – sample size concerns
Other aspects	Although a dedicated pregnancy characteristics and outcomes CRF page exists, the information collected is limited and does not meet the requirements for a proper pregnancy safety registry	Pregnancy information in TriNetX EMR is expected to be incomplete, as events are expected to be followed outside of treating practice (usually hematologist)	Validated algorithms are available, however, proper evaluation of pregnancy safety only possible in a linked mother-child subset of data (e.g. Optum DAPI)

ATC – anatomic therapeutic classification; CRF – case report form; DAPI – dynamic assessment of pregnancies and infants; EMR – electronic medical records; ICD-10 – International Classification of Diseases, 10th Revision

8.2 Registry suitability and data reliability

A questionnaire "Evaluation of the registry suitability" developed by Novartis was completed for the IPIG PNH Registry and is available as Table 7-2 below. The aspects that were identified as requiring further attention or follow-up were highlighted in yellow.

Table 7-2 Evaluation of the registry suitability – IPIG PNH Registry

Registry information	Notes
Registry name	IPIG PNH Registry
Country(ies)	list continuously updated. As of 30.09.2023: Canada, China, France, Germany, Italy, Japan, South Korea, Spain, Switzerland, United Kingdom, United States
Inclusion/exclusion criteria	Patients with PNH confirmed by flow cytometry and who do not currently participate in an interventional PNH clinical trial
Main contact person	[redacted]
Main contact details (email and phone)	[redacted]

	Identified through desk research? (Y/N)	To be followed-up / confirmed with the registry? (Y/N)	Additional notes
Admin and organization			
Who is the primary point of contact (e.g. coordinating site, name of registry coordinator, website)?	Y		Primary point of contact for Novartis queries is [redacted] (above) who serves as liaison with [redacted] representatives
What is the scale of the data coverage (e.g. site, national, regional)?	Y		Worldwide coverage, see country list above. Between 1 and 9 sites planned in each country
How many years' worth of data are covered in registry?	Y		Enrollment to begin in 2024 and open-ended; each patient to be followed for at least 5 years (if not lost to follow-up)
What language are the data entered and stored in?	Y		English
Has informed consent been obtained and has liaison with the data privacy office occurred?	Y		ICF forms were reviewed by Novartis and submitted to ethics committees / IRBs as appropriate by IPIG . ICF includes an explicit question on whether patient consents to have their data shared with the Marketing Authorization holders of the respective silos for further analysis and research
Have data sharing agreements and restrictions (willingness to collaborate) been obtained?	Y		Specified in the IPIG-Novartis Research Collaboration Agreement
What is the data upload process and schedule?	Y		[redacted] to transfer data yearly + 2 times a year ad-hoc

	Identified through desk research? (Y/N)	To be followed-up / confirmed with the registry? (Y/N)	Additional notes
What are the timelines for the data requests?	Y		Specified in the IPIG-Novartis Silo Agreement and was agreed taking into account the needs of the study CLNP023C12003
What are the affiliations associated with the data and are there any existing data sharing agreements (e.g. academia)?	Y		Specified in the IPIG-Novartis Silo Agreement
Are there any existing linkages to other data sources?	Y		No linkages currently planned or available
Are there any previous publications in which the data have been used?	Y		No publications yet, registry only starting operations in 2023
Data quality (and indicators)			
Are there any dedicated resources for the data collection, monitoring and review?	Y	Y	[redacted] will dedicate staff, however monitoring and data review processes are still not clear, to be followed up with IPIG/[redacted]
Is a data dictionary available?	N	Y	Data dictionary not available at the time of review, requested from [redacted]
Are the data collected consistently (e.g. eCRF)?	Y	Y	Core CRF v2.0 available at the time of review; iptacopan-specific CRF pages and annotated CRF still pending.
Who collects or enters the data? Are there consistency checks in place?	Y	Y	HCPs at the sites will enter the data; CRF consistency checks were promised by [redacted] but annotated CRF still not provided
Are the data accurate (i.e. are existing auditing mechanisms in place [e.g. 10% of data reassessed, IT-implemented fallback mechanisms])?	N	Y	Data management plan, annotated CRF and SAP not provided by [redacted] at the time of assessment, requires follow-up
Are the data representative of the population of interest (are the registry data comparable to the overall population)?	Y	Y	The registry inclusion criteria are maximally broad to include all PNH patients consecutively regardless of disease stage/type and treatment status. The actual patient population is not available at the time of the review as the registry is still in the start-up phase
Are the data complete? If not what is the proportion of missing data? Is there any particular data frequently missing (e.g lab results)?	N	Y	This information could not be assessed as at the time of review the registry was still in the start-up phase
Are the data reported with adequate detail with which to conduct the research study?	Y	Y	According to the CRF, the data granularity and the variables collected are sufficient to conduct a research study with safety objectives; however, data accuracy and completeness indicators were not available at the time of review

Data adequacy			

	Identified through desk research? (Y/N)	To be followed-up / confirmed with the registry? (Y/N)	Additional notes
Are core data elements defined and have they been marked as crucial/optional as appropriate? (e.g. demographics, care setting, safety and tolerability, outcomes, treatment sequencing, treatment start and stop, reasons for discontinuation, dosage, laboratory results, death, cost)	Y	Y	The CRF contains all the key elements required for a research study conduct and contains appropriate cross-checks and reminders for key variables. Annotated CRF would be required to perform the complete assessment
Are definitions, terminology and coding of data present (e.g. International Classification of Diseases [ICD]-10/ ICD-11, Medical Dictionary for Regulatory Activities [MedDRA])?	Y		The definitions for the clinical events according to the CRF were satisfactory. 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. The anonymized dataset transferred to Novartis will be formatted according to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standards.
Have linkages with other data sources (e.g. prescription registries) and the possibility to introduce linkages post-hoc been described?	Y		No linkages are planned or possible at present. This is considered acceptable for the purposes of the planned study.
Are there opportunities for additional data collection?	Y		Limited collection of additional data was possible via silo as part of research collaboration (per silo Agreement). No additional data can be collected as part of the safety study as it is a secondary use of data study and will use the registry database as-is
Have non-interventional studies using primary data collection been done using the registry before? If so, can those patients be identified and what was collected?	Y		IPIG plans to begin registry enrollment in early 2024, however patients that give consent will also be transferred from the International PNH Registry (owned by Alexion), a previously well-characterized PNH population

Population			
What is the total number of patients in the registry? Is the sample size sufficient for the purpose of the study?	Y	Y	At least 2000 patients planned to be enrolled in the core registry; patients that give consent will also be transferred from the International PNH Registry (owned by Alexion, to be discontinued by 2025) Potential risk: as the enrollment did not yet start, the total enrollment as well as the % of patients on iptacopan and the iptacopan treatment duration is not yet known.
What is the population of interest in registry (e.g. on drug, pregnancy, pediatrics)?	Y		Disease registry aiming to enroll all PNH patients regardless of treatment

	Identified through desk research? (Y/N)	To be followed-up / confirmed with the registry? (Y/N)	Additional notes
If the scope of the registry is regional, is the standard of care and overall survival comparable between countries?	Y		The registry coverage is worldwide and the standards of care and survival are expected to be different. This will be addressed in the study SAP

Variable groups of interest			
Are variables present that are of interest (e.g. genomics, pregnancy, disease progression tests)?	Y		According to the CRF, the variables collected are adequate for the safety study conduct

CRF – case report form; HCP – healthcare professional; SAP – statistical analysis plan