NI PASS PROTOCOL (SECONDARY DATA USE)

TITLE:	**A POST-AUTHORIZATION SAFETY STUDY (PASS) TO CHARACTERIZE SAFETY EVENTS AND SPECIAL CONDITIONS, SUCH AS PREGNANCY AND INFANT OUTCOMES, IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) PATIENTS TREATED WITH CROVALIMAB WITHIN THE IPIG REGISTRY**
PROTOCOL VERSION IDENTIFIER:	3.0
DATE OF LAST VERSION OF PROTOCOL	19-Jun-2025
EU PAS REGISTER NUMBER:	To be registered
ACTIVE SUBSTANCE:	L04AJ07: Crovalimab
MEDICINAL PRODUCT:	Crovalimab
PRODUCT REFERENCE:	RO7112689
PROCEDURE NUMBER{S}:	EMEA/H/C/006061
MARKETING AUTHORIZATION HOLDER(S):	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The aim of this study is to characterize the safety profile of crovalimab in participants with paroxysmal nocturnal hemoglobinuria (PNH), with a specific focus on adverse events of special interest (AESIs).

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
19-Jun-2025 16:33:31	Company Signatory	[redacted]
20-Jun-2025 06:52:28	Deputy EU QPPV	[redacted]

	This study also aims to assess serious adverse events (SAEs), pregnancy, and infant outcomes in female participants with PNH exposed to crovalimab during pregnancy and through breastfeeding. The primary objectives for this study are as follows: • To characterize and estimate the frequency of adverse events of special interest among participants with PNH exposed to crovalimab. AESIs are as follows: ○ Serious infections ○ Meningococcal infection and other infections with encapsulated bacteria ○ Development or worsening of any neurological condition (e.g., axonal neuropathy, multifocal mononeuropathy) ○ Malignancies and hematologic abnormalities ○ Serious hemolysis ○ Transient immune complex reactions ○ Infusion and injection-related reactions • To characterize and estimate the frequency of adverse events (AEs), SAEs, pregnancy outcomes, and infant outcomes in participants with PNH exposed to crovalimab during pregnancy and through breastfeeding. Specifically: ○ To estimate the frequency and further characterize all AEs, adverse pregnancy outcomes, and birth outcomes (during pregnancy and until date of delivery), in pregnant female participants with PNH. ○ To estimate the frequency and further characterize adverse fetal/neonatal/infant outcomes (e.g., major, and minor congenital malformations, gestational age, postnatal growth and development) and all AEs at birth, and through at least the first year of life of infants of mothers exposed to crovalimab during pregnancy. ○ To estimate the frequency and further characterize all AEs for lactating females and

	infants exposed to crovalimab through breastfeeding. The secondary objectives for this study are as follows: • To estimate the frequency and further characterize AEs and SAEs (not included as adverse events of special interest) in all participants with PNH exposed to crovalimab. • To characterize clinical outcomes and laboratory test results relevant to PNH among participants with PNH who experienced an AESI. • To characterize patient-reported outcomes among participants with PNH who experienced an AESI via a patient-reported fatigue assessment using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire.
COUNTRY(IES) OF STUDY:	Belgium, Canada, France, Germany, Italy, Netherlands, South Korea, Spain, United Kingdom, and United States and (China under feasibility).
AUTHOR:	[redacted] R. Hoffmann-La Roche AG
MARKETING AUTHORIZATION HOLDER(S):	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany
MAH CONTACT PERSON:	Ms. [redacted] c/o Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany

1. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACOG	American College of Obstetricians and Gynecologists
AE	adverse event
AESI	adverse event of special interest
BTH	breakthrough hemolysis
CDC	Centers for Disease Control and Prevention
CSR	Clinical Study Report
DTDC	drug-target drug complexes
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
DOC	Date of conception
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	[U.S.] Food and Drug Administration
FTT	failure to thrive
GPP	Guidelines for Good Pharmacoepidemiological Practice
HDA	high disease activity
HSCT	hematopoietic stem cell transplantation
IEC	Independent Ethics Committee
IPIG	International PNH Interest Group
IR	incidence rate
IRB	Institutional Review Board
IRR	Infusion and injection related reaction
ISPE	International Society of Pharmacoepidemiology
IV	intravenous
LDH	lactate dehydrogenase
LLT	lowest level term
mAb	monoclonal antibody
MAH	Marketing Authorization Holder
MAVE	major adverse vascular event
MedDRA®	Medical Dictionary for Regulatory Activities
NIS	non-interventional study

PASS	post-authorization safety study
PIGA	phosphatidylinositol glycan class A
PNH	paroxysmal nocturnal hemoglobinuria
PPROM	preterm prelabor rupture of membrane
PRO	patient-reported outcome
QoL	quality of life
SAE	serious adverse event
SAP	Statistical analysis plan
SC	subcutaneous
SDU	secondary data use
SOC	standard of care
TICR	transient immune complex reaction
ULN	upper limit of normal
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Protocol Development Responsible

[redacted], [redacted]
F. Hoffman-La Roche AG, 4070 Basel, Switzerland
[redacted]

Scientific Responsible

[redacted], [redacted],
F. Hoffman-La Roche AG, 4070 Basel, Switzerland
[redacted]

Safety Responsible

[redacted]
Roche Products Limited
Welwyn, UK
[redacted]

NIS Data Science Responsible

[redacted], [redacted]
F. Hoffman-La Roche AG, 4070 Basel, Switzerland
[redacted]

Complementary information is given in Annexe 1.

4. ABSTRACT/SYNOPSIS

TITLE:	**A POST-AUTHORIZATION SAFETY STUDY (PASS) TO CHARACTERIZE SAFETY EVENTS AND SPECIAL CONDITIONS, SUCH AS PREGNANCY AND INFANT OUTCOMES, IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) PATIENTS TREATED WITH CROVALIMAB WITHIN THE IPIG REGISTRY**
PROTOCOL NUMBER:	MO45473
VERSION NUMBER:	3.0
DATE OF SYNOPSIS:	19 June 2025
EU PAS REGISTER NUMBER:	To be registered
STUDIED MEDICINAL PRODUCT:	Crovalimab
SCIENTIFIC RESPONSIBLE	[redacted] F. Hoffman-La Roche AG
MAIN AUTHOR	[redacted] R. Hoffmann-La Roche AG
PHASE:	IV, non-interventional study
INDICATION:	Paroxysmal nocturnal hemoglobinuria
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany

RATIONALE AND BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, chronic, life-threatening blood disorder associated with anemia due to hemolysis. Although there have been reports of spontaneous remission, the course of the disease is generally chronically progressive. The goal of PNH therapy is to control complement-mediated hemolysis and thus counteracting anemia. The disorder requires life-long treatment.

PNH appears to equally affect males and females, although there may be a slight female preponderance (NORD 2024). Although patients can develop PNH at any age, the typical age of presentation is between 30 and 40 years. Children can be diagnosed with PNH, though PNH diagnosis predominantly occurs during adolescence (Curran et al. 2012; Shah and Bhatt 2023). Pregnancy-related complications are also apparent in PNH, including worsening cytopenia,

thrombosis, infections, bleeding, miscarriages, and increased maternal mortality; as well as adverse fetal outcomes of fetal death and premature delivery (Alashkar et al. 2020).

The current standard of care (SOC) for PNH involves complement inhibition, which has significantly improved patient outcomes. In countries where complement inhibitors are not currently available, management of patients is mainly through supportive care (Cançado et al. 2021).

Crovalimab, a novel, long-acting monoclonal antibody (mAb) targeting C5, has demonstrated efficacy in reducing hemolysis, improving quality of life (QoL), and potentially offers a more convenient dosing schedule compared to existing therapies. However, as crovalimab is a new treatment, comprehensive post-marketing surveillance is essential to fully understand its long-term safety profile and potential risks.

The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have requested additional data on specific crovalimab safety concerns, including:

- Serious infections
- Meningococcal infections
- Hemolysis after discontinuation
- Malignancies and hematologic abnormalities
- Transient immune complex reactions (TICRs)
- Infusion and injection-related reactions (IRRs)
- Pregnancy and infant outcomes
- Use in pregnancy and/or breastfeeding

To gather more information on the safety profile of crovalimab in a real-world setting, Roche has entered a partnership with the International PNH Interest Group (IPIG), to participate in the existing registry (further referred to as the “Core Registry”, ClinicalTrials.gov ID NCT06524726). A crovalimab sub-registry (further referred to as the “Crovalimab Silo” or Study MO44987) will be established, to enable additional safety data collection in participants with PNH treated with crovalimab. The study described herein (MO45473) is a secondary data use (SDU) study which aims to analyze data from the participants enrolled in the Crovalimab Silo.

RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to characterize the safety profile of crovalimab in participants with PNH, with a specific focus on adverse events of special interest (AESIs). This study also aims to assess adverse events (AEs), serious adverse events (SAEs), pregnancy, and infant outcomes in female participants with PNH exposed to crovalimab during pregnancy and through breastfeeding.

The primary objectives for this study are as follows:

- To characterize and estimate the frequency of AESIs among participants with PNH exposed to crovalimab. Adverse events of special interest are as follows:
  - Serious infections
  - Meningococcal infection and other infections with encapsulated bacteria
  - Development or worsening of any neurological condition (e.g., axonal neuropathy, multifocal mononeuropathy)
  - Malignancies and hematologic abnormalities
  - Serious hemolysis
  - TICRs
  - Infusion and injection-related reactions
- To characterize and estimate the frequency of AEs, SAEs, pregnancy outcomes, and infant outcomes in participants with PNH exposed to crovalimab during pregnancy and through breastfeeding. Specifically:
  - To estimate the frequency and further characterize all AEs, adverse pregnancy outcomes, and birth outcomes (during pregnancy and until date of delivery), in pregnant female participants with PNH.
  - To estimate the frequency and further characterize adverse fetal/neonatal/infant outcomes (e.g., major and minor congenital malformations, gestational age, postnatal growth and development) and SAEs at birth and through at least the first year of life of infants of mothers exposed to crovalimab during pregnancy.
  - To estimate the frequency and further characterize all AEs for lactating females and infants exposed to crovalimab through breastfeeding.

The secondary objectives for this study are as follows:

- To estimate the frequency and further characterize AEs and SAEs (not included as AESIs) in all participants with PNH exposed to crovalimab.
- To characterize clinical outcomes and laboratory test results relevant to PNH disease among participants with PNH who experienced an AESI.
- To characterize patient-reported outcomes (PROs) among participants with PNH who experienced an AESI via a patient-reported fatigue assessment using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire.

STUDY DESIGN

This study is a multi-center, multi-country, non-interventional, registry-based post-authorization safety study (PASS) using secondary data collected as part of the Crovalimab Silo registry (Study MO44987) of participants with PNH exposed to crovalimab, including pregnant women and their infants.

Product-specific silos initiated by the IPIG can be created on request by the respective Marketing Authorization Holders (MAHs) and will include participants treated with PNH-specific therapy from a single MAH. These silos will be established to collect specific data on treated participants with PNH and address research objectives, which are treatment-related, and/or requests from regulatory authorities. The Crovalimab Silo is a product-specific registry enrolling participants with PNH treated with crovalimab.

Participants enrolled in the Core Registry are expected to sign an Informed Consent Form for the purposes of that study. Following crovalimab treatment initiation, a separate privacy notice will be provided to the study participants, which will explain in more detail how their data will be used, the specific data processing purposes, as well as the applicable legal bases for processing the data. Participants should acknowledge and receive the privacy notice to be part of the Crovalimab Silo.

The Crovalimab Silo will encompass retrospective and prospective data from all enrolled participants with PNH treated with crovalimab, including data from female pregnant participants with PNH and their infants. Participant demographics and medical history data will be collected at enrollment. Both prospective and retrospective data will cover participants' characteristics and clinical outcomes (including safety data, pregnancy, infant outcomes, and breastfeeding), and crovalimab exposure.

Prospective data collection will commence at the initiation of treatment for participants with PNH who began therapy with crovalimab on or after the start of the Crovalimab Silo registry. For participants with PNH who began treatment with crovalimab before the Crovalimab Silo was established, retrospective data will be collected from the Core Registry into the silo, if available, while prospective data collection will begin from the time of silo enrollment.

Participants' visit schedules will follow standard of care. Participants' data are expected to be entered in the electronic data capture (EDC) system by the clinicians and/or their qualified designee at the time of registry enrollment and approximately every 6 months thereafter. In addition, participants with PNH and/or their parents/legally authorized representatives have the option to complete electronic patient-reported outcome (ePRO) questionnaires (i.e., the FACIT-Fatigue questionnaire) at registry enrollment, and every 6 months thereafter.

POPULATION

This study will include all participants with PNH who are treated with crovalimab and have available data from the Crovalimab Silo, including participants with PNH who are pregnant and information from their infants.

VARIABLES

VARIABLES FOR ALL PARTICIPANTS WITH PNH

The primary variables for all participants with PNH enrolled in this study are as follows (described as adverse events of special interest [AESIs]):

- Serious infections

- Meningococcal infections and other infections with encapsulated bacteria
- Development or worsening of any neurological condition
- Malignancies and hematologic abnormalities
- Serious hemolysis
- Transient immune complex reaction
- Infusion- and injection-related reactions

The secondary variables for all participants with PNH this study are as follows:

- All other adverse events and SAEs (not including an AESI)
- Clinical outcomes and laboratory test results relevant to PNH among participants with PNH who experienced an AESI

One PRO instrument (the FACIT-Fatigue questionnaire) will also be used during this study.

VARIABLES FOR PARTICIPANTS WITH PNH WHO ARE PREGNANT OR BREASTFEEDING AND THEIR INFANTS

The primary variables for participants with PNH who are pregnant and their infants in this study are as follows:

- Ectopic pregnancy
- Spontaneous abortion
- Pregnancy terminations (with or without presence of fetal defects)
- Fetal death or stillbirth (with or without fetal defects)
- Live birth (with or without congenital anomaly)
- Preterm birth
- Size for gestational age
- Low birth weight
- Postnatal growth deficiency or failure to thrive (FTT)
- Infant developmental deficiency
- Congenital malformations
- Serious and severe infections and hospitalization of infants
- Neonatal death
- Perinatal death
- Infant death
- Preeclampsia
- Eclampsia
- Preterm Prelabor Rupture of Membrane (PPROM)

- Maternal death
- Any adverse events during pregnancy
- Any adverse events for lactating females and infants through breastfeeding
- Any adverse event experienced by the infant

BASELINE AND FOLLOW-UP VARIABLES

The following baseline and follow-up variables will be collected at enrollment for all participants with PNH, during pregnancy and infant birth:

- Patient characteristics and demographics
- Clinical history relevant to PNH, including previous PNH treatment, and date of last administration
- Any concomitant medication
- Vaccination
- Breastfeeding status
- Potential confounding factors affecting safety, pregnancy, and infant outcomes

DATA SOURCES

This study will analyze data collected from the Crovalimab Silo registry.

STUDY SIZE

Enrollment depends on the approval timelines, uptake, and treatment course in each country where the sites are open, as well as the total number of evaluable participants with PNH for AESIs. However, based on patient projections in selected countries, the MAH expects 300 participants with PNH to be enrolled with up to 7 years of follow-up during the duration of the Crovalimab Silo registry (7 years).

The IPIG aims to enroll approximately 25 participants with PNH who are pregnant in the Crovalimab Silo registry. Nevertheless, since the management of PNH during pregnancy has been challenging and pregnancy has been discouraged in participants with PNH, there are very few reported cases of pregnant participants with PNH treated with C5 inhibitors. For example, in a similar registry there were only 94 pregnancies in fewer than 1,086 females treated with eculizumab from June 2006 to November 2014 (Kelly et al. 2015; Höchsmann et al. 2022).

DATA ANALYSIS

No formal statistical testing will be performed. Descriptive statistics will be reported using summary tables and figures (where appropriate). Continuous variables will be summarized using mean, standard deviation, median, range (min–max) and interquartile range. Categorical variables will be summarized using counts and proportions (%).

Additionally, incidence and incidence rate (IRs; in person-years) and their 95% CIs of AESIs, SAEs and AEs will be calculated. The exact 95% CIs will be computed using the

Clopper-Pearson method (Clopper and Pearson 1934). For the calculation of IRs, the denominator will be the pooled person-time of all the participants within the cohort. The patient time-at-risk will be calculated from index date until the date of an incident event or censoring, whichever occurs first. All first events occurring during follow-up period will be counted in the total number of events (thus, for each participant, only the first event will be counted) and divided by the total patient-years at risk. In addition to IRs, incidence proportions will be calculated as proportion of participants afflicted with each of the AESIs, SAEs, and AEs up to the data extraction date.

Subgroup and sensitivity analyses will be implemented when sample size allows.

Analyses will be presented separately for the entire PNH participant cohort, pregnant female participants with PNH, all infants, and infants categorized by breastfeeding status (yes/no). When feasible, these analyses will be further detailed according to each trimester of pregnancy and each quarter within the infant's first year of development. Additionally, where data allows, outcomes will be analyzed based on prior PNH treatment and using the classifications of naïve new users and prevalent new users.

Potential confounding factors influencing safety and pregnancy outcomes, such as demographic information (e.g., age, race/ethnicity), clinical characteristics, maternal medical history, obstetrical history, comorbidities, and concomitant medications will be used in subgroup analyses among participants with PNH who experience an AESI, as well as for pregnancy or infant outcomes. Adverse events of special interest proportions and incidence rates will be compared between subgroups. Similarly, subgroup analysis by clinical and laboratory test outcomes for PNH will be performed when feasible. Safety events will be also described by causality.

Sensitivity analysis will be performed restricting the data to safety events and crovalimab exposure that was collected prospectively only. The effects of the timing of crovalimab exposure before and during pregnancy and cumulative exposure periods on each outcome will be also evaluated as sensitivity analysis. Sensitivity analysis may also include timing variations of failure to thrive (FTT) and development deficiency outcomes, when available.

Full details on all statistical analyses, including other subgroup and sensitivity analyses, will be described in the Statistical Analysis Plan (SAP).

MILESTONES

FIRST DATA EXTRACTION:

The date of first data extraction is the date when the variables used for the data analysis as per protocol are extracted for the first time. The planned first data extraction is after 6 months of Crovalimab Silo inception. The planned first data extraction is in Q1 2026.

LAST DATA EXTRACTION:

The last data extraction is the date of the end of the Crovalimab Silo registry, plus an additional 6 months to account for final data transfer. The planned last data extraction is in Q2 2032.

5. AMENDMENTS AND UPDATES

Substantial protocol amendments/updates so far: None

6. MILESTONES

Milestone [a]	Planned Date
Registration of protocol in the E.U. PAS register	Q3 2025
First data extraction	Q1 2026
Annual interim report #1	Q4 2026
Annual interim report #2[b]	Q4 2027
Annual interim report #3	Q4 2028
Annual interim report #4 [b]	Q4 2029
Annual interim report #5	Q4 2030
Annual interim report #6 [b]	Q4 2031
Last data extraction	Q2 2032
Final report of study results (CSR)	Q4 2032
Registration of the results in the E.U. PAS register	To be determined

CSR = Clinical Study Report; FDA = Food and Drug Administration; PAS = post-authorization study; PSUR = Periodic Safety Update Report; Q = quarter.

[a] Study progress will be provided in every PSUR.

[b] Additional interim report for U.S. FDA submission only.

7. RATIONALE AND BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, chronic, life-threatening blood disorder associated with anemia due to hemolysis. It is most frequently caused by a somatic mutation in the phosphatidylinositol glycan class A (PIGA) gene of hematopoietic stem cells. The onset of PNH is often insidious. Although there have been reports of spontaneous remission, the course of the disease is generally chronically progressive.

The goal of PNH therapy is to control complement-mediated hemolysis and thus counteracting anemia. Hemolysis can result in a range of debilitating consequences, such as severe fatigue, chest pain, and transfusion dependence, all of which contribute to a reduced quality of life (QoL). If left untreated, PNH can cause severe and potentially fatal complications for patients. Thrombotic events are the main cause of severe complications and death in PNH. The disorder requires life-long treatment.

PNH appears to equally affect males and females, although there may be a slight female preponderance (NORD 2024). The disorder has no clear tendency toward a specific

race or ethnicity (Shah and Bhatt 2023). PNH has an annual incidence as high as 0.6 per 100,000 persons (Farooq 2020) and its prevalence is estimated to be 1–2 per 100,000 persons in the general population (Cançado et al. 2021). In the U.S., Europe, and Japan, the overall estimated number of patients with PNH is about 10,000 (Mandala et al. 2013; Ninomiya and Okura 2022). Although patients can develop PNH at any age, the typical age of presentation is between 30 and 40 years. Children can be diagnosed with PNH, though PNH diagnosis predominantly occurs during adolescence (Curran et al. 2012; Shah and Bhatt 2023). Pregnancy-related complications are also apparent in PNH, including worsening cytopenia, thrombosis, infections, bleeding, miscarriages, and increased maternal mortality; as well as adverse fetal outcomes of fetal death and premature delivery (Alashkar et al. 2020).

The treatment options available to patients with PNH differ significantly by country and geographical region. The current standard of care (SOC) for PNH involves complement inhibition, which has significantly improved patient outcomes. Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative option that is available in certain countries but presents significant risks. In countries where complement inhibitors are not currently available, management of patients is mainly through supportive care (Cançado et al. 2021).

Crovalimab, a novel, long-acting monoclonal antibody (mAb) targeting C5, has demonstrated efficacy in reducing hemolysis, improving QoL, and potentially offers a more convenient dosing schedule compared to existing therapies (eculizumab and ravulizumab). Overall, crovalimab has shown a well-tolerated safety profile, similar to that of eculizumab in patients with PNH, both in treatment naïve patients and in patients already on treatment with eculizumab or ravulizumab (Roth et al. 2025; Roth et al. 2024).

However, as crovalimab is a new treatment, comprehensive post-marketing surveillance is essential to fully understand its long-term safety profile and potential risks. This is particularly important given the chronic nature of PNH and the need for long-term treatment.

The most commonly reported adverse events (AEs) with crovalimab treatment are pyrexia, headache, infections, infusion and injection-related reactions (IRRs), injection-related reactions (only affecting crovalimab SC administration) and transient immune complex reaction (TICR), also known as Type III hypersensitivity reaction (affecting only patients switching treatments). Meningococcal infection is an important AE of crovalimab treatment, related to its mode of action.

The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have requested additional data on specific safety concerns, including:

- Serious infections: Complement inhibition can increase the risk of infections.

- Meningococcal infections: Infections caused by encapsulated bacteria are of special interest, as patients treated with the current SOC have very high-risk to encapsulate infections.
- Hemolysis after discontinuation: The potential for rebound hemolysis upon treatment cessation is high. Nevertheless, the likelihood that a patient with PNH will discontinue treatment with a complement inhibitor without switching to another similar treatment is low.
- Malignancies and hematologic abnormalities: Long-term immunosuppression may be associated with an increased risk of malignancy, including hematologic and non-hematologic malignancies.
- TICRs: Such immune reactions could occur when patients are switching from eculizumab or ravulizumab to crovalimab (and vice versa), as crovalimab and other C5 inhibitors bind to different epitopes of C5 and can form large drug-target-drug complexes (DTDCs).
- Infusion and injection-related reactions (IRRs): IRRs are considered a risk for all biologic medications, including mAbs, that are administered by intravenous (IV) and/or subcutaneous (SC) routes.
- Use in pregnancy and/or breastfeeding. The safety of crovalimab during pregnancy and breastfeeding is unknown.

To gather more information on the safety profile of crovalimab in a real-world setting, Roche has entered a partnership with the International PNH Interest Group (IPIG), to participate in the existing registry (further referred to as the "Core Registry", ClinicalTrials.gov ID NCT06524726). A crovalimab sub-registry (further referred to as the "Crovalimab Silo" or Study MO44987) will be established, to enable additional safety data collection in patients with PNH treated with crovalimab. The study described herein (MO45473) is a secondary data use (SDU) study which aims to analyze data from the participants enrolled in the Crovalimab Silo.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RESEARCH QUESTION

The aim of this study is to characterize the safety profile of crovalimab in participants with PNH, with a specific focus on adverse events of special interest (AESIs). This study also aims to assess AEs, serious adverse events (SAEs), pregnancy, and infant outcomes in female participants with PNH exposed to crovalimab during pregnancy and through breastfeeding.

8.2 OBJECTIVES

The primary objectives for this study are as follows:

- To characterize and estimate the frequency of AESIs among participants with PNH exposed to crovalimab. AESIs are as follows:
    - Serious infections

- Meningococcal infection and other infections with encapsulated bacteria
- Development or worsening of any neurological condition (e.g., axonal neuropathy, multifocal mononeuropathy)
- Malignancies and hematologic abnormalities
- Serious hemolysis
- Transient immune complex reactions
- Infusion and injection-related reactions

- To characterize and estimate the frequency of AEs, SAEs, pregnancy outcomes, and infant outcomes in participants with PNH exposed to crovalimab during pregnancy and through breastfeeding. Specifically:
  - To estimate the frequency and further characterize all AEs, adverse pregnancy outcomes, and birth outcomes (during pregnancy until date of delivery), in pregnant female participants with PNH
  - To estimate the frequency and further characterize adverse fetal/neonatal/infant outcomes (e.g., major and minor congenital malformations, gestational age, postnatal growth and development) and SAEs at birth and through at least the first year of life of infants of mothers exposed to crovalimab during pregnancy
  - To estimate the frequency and further characterize all AEs for lactating females and infants exposed to crovalimab through breastfeeding

The secondary objectives for this study are as follows:

- To estimate the frequency and further characterize AEs and SAEs (not included as AESIs) in all participants with PNH exposed to crovalimab.
- To characterize clinical outcomes and laboratory test results relevant to PNH disease among participants with PNH who experienced an AESI
- To characterize patient-reported outcomes (PROs) among participants with PNH who experienced an AESI via a patient-reported fatigue assessment using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire

9. RESEARCH METHODS

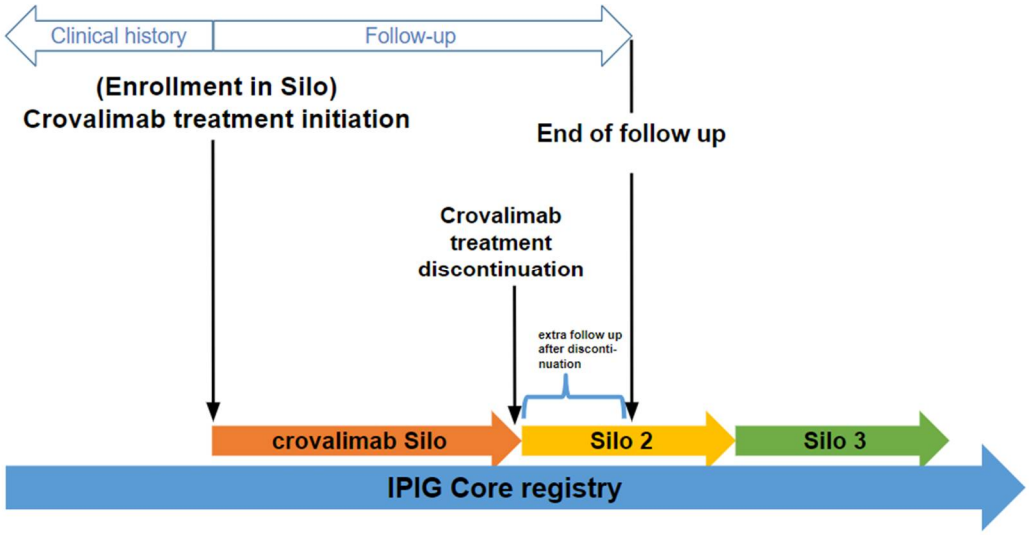
9.1 STUDY DESIGN

This study is a multi-center, multi-country, non-interventional, registry-based post-authorization safety study (PASS) using secondary data collected as part of the Crovalimab Silo registry (Study MO44987) of participants with PNH exposed to crovalimab, including pregnant women and their infants.

Product-specific silos initiated by the IPIG can be created on request by the respective Marketing Authorization Holders (MAHs) and will include participants treated with PNH-specific therapy from a single MAH. These silos will be established to collect specific data on treated participants with PNH and address research objectives, which are treatment-related, and/or requests from regulatory authorities. The Crovalimab Silo

is a product-specific registry enrolling participants with PNH treated with crovalimab (see Figure 1).

Figure 1 Schematic Representation of the Primary Data Collection in the Crovalimab Silo Registry, a Product-Specific Registry of the Core Registry



IPIG = International Paroxysmal Nocturnal Hemoglobinuria Interest Group.

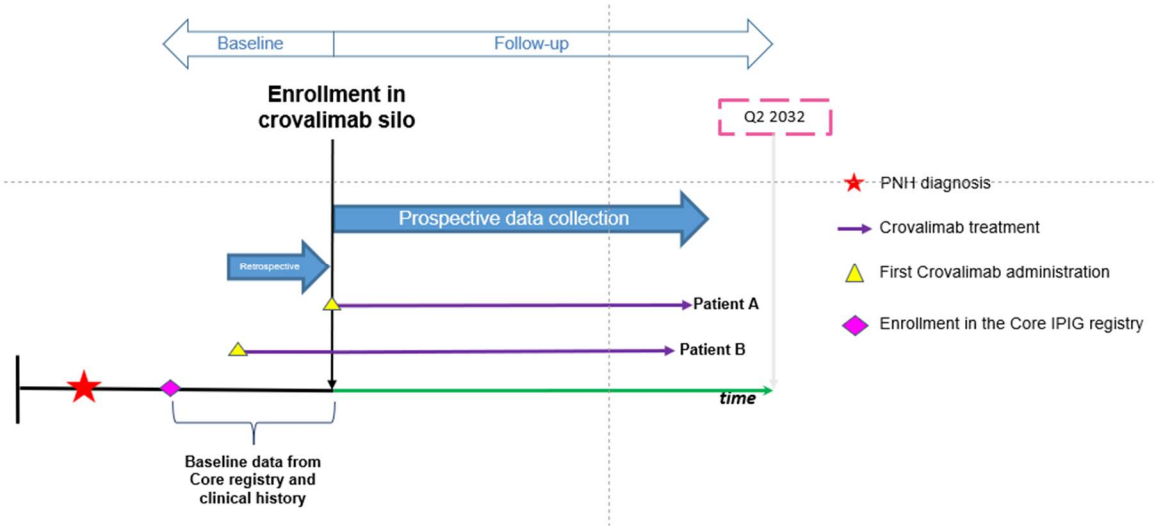
Participants enrolled in the Core Registry are expected to sign an Informed Consent Form for the purposes of that study. Following crovalimab treatment initiation, a separate privacy notice will be provided to the participants, which will explain in more detail how their data will be used, the specific data processing purposes, as well as the applicable legal bases for processing the data. Participants should acknowledge and receive the privacy notice to be part of the Crovalimab Silo.

The Crovalimab Silo will encompass retrospective and prospective data from all enrolled participants treated with crovalimab, including data from female pregnant patients and their infants. Patient demographics and medical history data will be collected at enrollment. Both prospective and retrospective data will cover participants' characteristics and clinical outcomes (including safety data, pregnancy and infant outcomes, and breastfeeding), and crovalimab exposure. For a visual representation of the data collection definitions for all participants with PNH, refer to Figure 2.

Prospective data collection will commence at the initiation of treatment for participants who began therapy with crovalimab on or after the start of the Crovalimab Silo registry (illustrated as Patient A in Figure 2). For participants who began treatment with crovalimab before the Crovalimab Silo was established, retrospective data will be collected from the Core Registry into the silo, if available; while prospective data

collection will begin from the time of silo enrollment (illustrated as Patient B in Figure 2). The MAH anticipates very few cases in this last scenario.

Figure 2 Study Design for PNH in the Crovalimab Silo



IPIG = International PNH Interest Group; PNH = paroxysmal nocturnal hemoglobinuria.

The planned start date for the Crovalimab Silo refers to the date when information about the first participant in the Crovalimab Silo will be recorded in the database, which is projected to be in Q1 2026. The last data extraction and planned end of the registry, based on a planned data collection in the Crovalimab Silo, is projected in Q2 2032.

Participants' visit schedules will follow SOC. Participants' data are expected to be entered in the electronic data capture (EDC) system by the clinicians and/or their qualified designee at the time of registry enrollment and approximately every 6 months thereafter. In addition, participants and/or their parents/legally authorized representatives have the option to complete electronic patient-reported outcome (ePRO) questionnaires (i.e., the FACIT-Fatigue questionnaire) at registry enrollment, and every 6 months thereafter.

If a participant withdraws from the IPIG registry, the date and reason will be recorded in the electronic Case Report Form (eCRF), with efforts made to obtain this information. Registry site termination may happen due to inadequate participant recruitment or non-compliance with protocols, guidelines, or regulatory requirements. If a clinician withdraws, the MAH should be notified in advance, and a new clinician will be trained and identified to take over patient referrals.

9.2 SETTING

This study will analyze individual patient-level data gathered from multiple countries within the Crovalimab Silo. To date, the Crovalimab Silo plans to enroll participants from

Belgium, Canada, France, Germany, Italy, Netherlands, South Korea, Spain, United Kingdom, and the United States. China is under feasibility.

Index Date

The index date is defined as follows:

- To evaluate AESIs and other SAEs and AEs for all participants with PNH, the index date will be defined as the date of enrollment in the Crovalimab Silo.
- To characterize SAEs and AEs for women who are pregnant and pregnancy outcomes, the index date for these outcomes will be defined based on the pregnancy status at the time of silo enrollment. If the participant with PNH is pregnant, the index date will be the date of the silo registry enrollment. If the participant with PNH becomes pregnant after enrollment, the index date will be defined as the date of conception (DOC).
- To assess adverse fetal/neonatal/infant outcomes, SAEs, and AEs at birth and through at least the first year of the infant's life, the index date will be defined as the date of infant birth.
- For breastfeeding-related safety events, the index date will be defined as the date of initiation of breastfeeding for women who are in the Crovalimab Silo before breastfeeding starts or as the date of enrollment for women who join the Crovalimab Silo while breastfeeding.

9.2.1 Study Population

This SDU study will include all participants with PNH who are treated with crovalimab and have available data from the Crovalimab Silo, including participants who are pregnant and information from their infants.

9.2.2 Inclusion/Exclusion Criteria

To evaluate AESIs and other SAEs and AEs for all participants with PNH:

Participants with PNH included in the SDU study will meet the same inclusion and exclusion criteria from the Crovalimab Silo listed below:

- Inclusion criteria:
  - Participants with PNH confirmed by flow cytometry.
  - Participant and/or parent/legally authorized representative provide written informed consent/assent to participate in the Core Registry and the Crovalimab Silo prior to any registry-related data collection, in a manner approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and local regulations.
  - Participants with PNH currently being treated with or who start crovalimab during the study period.
- Exclusion criteria:
  - Participants with PNH participating in an interventional PNH clinical trial while receiving crovalimab (i.e., in combination with other therapy), with exception of

participants with PNH participating in the extension period of COMMODORE/COMPOSER Roche studies and Post Trial Access Programs.

The exclusion criteria for all participants will also be applicable to assess crovalimab exposure during pregnancy, as well as pregnancy, infant, and breastfeeding outcomes.

To evaluate AEs and SAEs during pregnancy and pregnancy outcomes:
The following additional inclusion criteria will be applicable:

- Crovalimab exposure during pregnancy or 9 months before DOC

To evaluate infant AEs and SAEs and infant and breastfeeding outcomes:
The following additional inclusion criteria will be applicable:

- Breastfeeding infant
- Infant younger than 12 months of age

9.2.3 Participant Follow-up

The follow-up period will be the time period from index date (as defined in Section 9.2.1) until the end of the study or censoring, whichever comes first.

To evaluate AESIs and other AEs and SAEs for all participants with PNH, the date of censoring will be defined as the earliest occurrence of any of the following events:

- Consent withdrawal
- Site termination
- Crovalimab treatment discontinuation[1] (with an extra follow-up period after discontinuation)
- Enrollment into an interventional clinical trial[2]
- Death

To assess safety events during pregnancy and breastfeeding, including pregnancy and infant outcomes, additional censoring events will be defined:

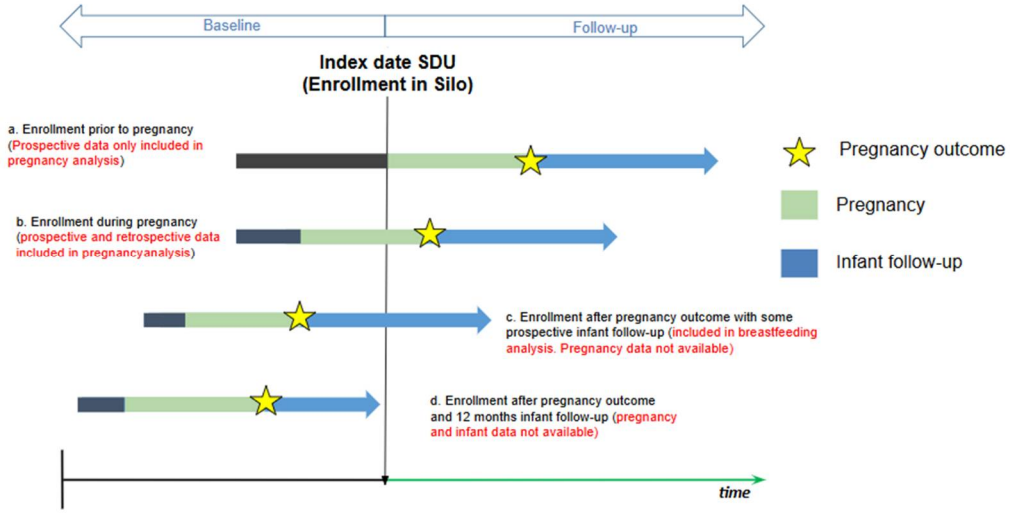
- Date of delivery (for pregnancy safety and outcomes)
- First year of the infant's life (for safety and infant outcomes)
- On the date when breastfeeding stops or first year of the infant's life (for breastfeeding)

[1] For participants with PNH censored due to crovalimab treatment discontinuation, follow-up will continue up to 12 months if the participant does not start a new complement inhibitor or for 12 weeks if the participant starts a new complement inhibitor.
[2] To preserve the integrity of data collected for any interventional therapy for PNH in clinical studies, as well as to avoid duplicate safety reporting, participant data collection will be paused from the Crovalimab Silo and the Core Registry when participants enroll in an interventional clinical study for a PNH therapy.

Note: Safety events from the mother will continue to be recorded even after pregnancy ends, delivery, or the cessation of breastfeeding. Similarly, infant safety events will also continue to be recorded through their first year of age if breastfeeding is suspended.

Evaluation of pregnancy and infant outcomes during crovalimab exposure will rely on prospectively collected data within the Crovalimab Silo only for participants who enroll into the silo before being pregnant. However, for participants who enroll into the Crovalimab Silo while being pregnant, retrospective data on crovalimab exposure and outcomes will be incorporated into the silo, if such data are available from the Core Registry. Data for participants whose pregnancy outcomes occur before their enrollment in the Crovalimab Silo will not be obtainable. Very few instances are expected in these latter two scenarios due to the timing of drug approvals and site initiations in the Core Registry (see Figure 3).

Figure 3 Identification of Prospective Data in The Silo Registry for Pregnancy and Infant Outcomes



SDU = secondary data use.

9.3 VARIABLES

9.3.1 Variables for All Participants with PNH

9.3.1.1 Crovalimab Exposure

The Crovalimab Silo is an observational study. No study medication will be provided as part of participation. Dosing and treatment duration of crovalimab are at the discretion of the physician in accordance with local clinical practice and local labeling.

Crovalimab exposure will be defined as the duration from the date of silo enrollment until crovalimab discontinuation date, plus 12 months if the participant with PNH does not start a new complement inhibitor or plus 12 weeks if the participant starts a new complement inhibitor. For participants with PNH who enroll into the silo under crovalimab treatment, additional time under crovalimab previous to enrollment will be

evaluated from available data requested at enrollment or from the Core Registry at baseline. Dates of exposure to crovalimab and doses administered will be collected and characterized.

For pregnancy and infant outcomes, exposure is defined as the period from 9 months (Based on the average estimated crovalimab terminal half-life of 53.1 days reported in the studies of crovalimab) prior to the DOC until the date of delivery. For breastfeeding outcomes, exposure is defined as the duration from 9 months previous the start of breastfeeding until the infant's first birthday or the date breastfeeding ends, whichever comes first.

9.3.1.2 Primary Safety Variables

9.3.1.2.1 Serious Infections

The presence, type, onset and resolution date and hospitalizations for the reason of serious infections will be described.

9.3.1.2.2 Meningococcal Infections and Other Infections with Encapsulated Bacteria

The presence, type, onset and resolution date and hospitalizations for the reason of Meningococcal and other infections with encapsulated bacteria will be described.

9.3.1.2.3 Development or Worsening of any Neurological Condition

Examples of neurological conditions include axonal neuropathy and multifactorial mononeuropathy will be described, including onset and resolution date.

9.3.1.2.4 Malignancies and Hematologic Abnormalities

The presence and type of malignancy, onset and resolution date will be described.

9.3.1.2.5 Serious Hemolysis

Serious hemolysis, onset and resolution date will be described. This event includes the following:

- New or worsening symptoms of PNH: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), dysphagia, backache, headache, erectile dysfunction, chest discomfort, jaundice and other symptoms with detailed specification. Onset and resolution dates, and duration of symptoms will also be collected.
- Serious hemolysis, identified by serum lactate dehydrogenase (LDH) levels greater than the pretreatment level, along with any of the following: greater than 25% absolute decrease in PNH clone size (in the absence of dilution due to transfusion) in ≤ 1 week; a hemoglobin level of ≤ 5 g/dL or a decrease of >4 g/dL in ≤ 1 week; angina; change in mental status; a 50% increase in serum creatinine level; or thrombosis.

Additionally, to contextualize hemolysis, the MAH will abstract the following:

- Possible alternative causes for the episode of hemolysis, including the presence of any complement-activating conditions.
- Proportion of PNH cells in granulocytes, monocytes, erythrocytes Type II/III, and reticulocytes.
- All medications used to treat or prevent the events of serious hemolysis.

9.3.1.2.6 Transient Immune Complex Reactions

All TICRs should be captured as a diagnosis of “transient immune complex reactions” in the AE eCRF, including the onset and resolution date. Associated signs and symptoms should be recorded in the dedicated TICR eCRF of the Crovalimab Silo.

9.3.1.2.7 Infusion- and Injection-related Reactions

All IRRs, occurring during or within 24 hours after crovalimab administration will be described. All reactions should also be evaluated to determine if they were related to studied medicinal product infusion or injection, and therefore, captured as a diagnosis (e.g., "infusion-related reaction", "injection-site reaction", or "anaphylactic reaction"). If possible, ambiguous terms such as "systemic reaction" should be avoided. Associated signs and symptoms should also be recorded. If a patient experiences both a local and systemic reaction to the same dose of studied medicinal product, each reaction will be recorded separately, with signs and symptoms also recorded separately on the dedicated Crovalimab Silo eCRF.

9.3.1.3 Secondary Variables

9.3.1.3.1 Adverse Events and SAEs (not included as AESI)

An adverse event is defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of this medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

Serious Adverse Events

The terms “serious” and “severe” are not synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event according to NCI CTCAE criteria; however, the event itself, may be of relatively minor medical significance (such as a severe headache). This is not the same as “serious”, which is based on event outcome or action criteria usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

An SAE is an AE that meets any of the following criteria:

- Results in **death** of a patient.
- Is **life-threatening**: This refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization**: An event/reaction that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
- Results in **prolongation of existing hospitalization**: An event/reaction that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
- Is a **congenital anomaly/birth defect**: An anomaly detected at or after birth, or any anomaly that results in fetal loss.
- Results in **persistent or significant disability/incapacity**: An event/reaction that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
- Is a **medically important event or reaction**: An important medical event/reaction that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly/birth defect, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- Any suspected transmission via a medicinal product of an infectious agent is also considered as a SAE.

All AESIs, AEs, and SAEs will be recorded, including their corresponding dates and characteristics such as outcome, treatment, hospitalization, severity, seriousness, and de-/rechallenge.

9.3.1.3.2 Clinical Outcomes and Laboratory Test Results Relevant to PNH Among Participants who Experienced an AESI

The following clinical outcomes and laboratory test results related to PNH will be recorded among participants with PNH who experience an AESI:

- Major adverse vascular events (MAVEs), including thrombosis
  - If yes, type of event
- Red blood cell transfusions
  - Yes/No
  - Number of units received
- Breakthrough hemolysis (BTH)
  - Physician-defined BTH
  - Protocol-defined BTH
    - ≥ 1 new or worsening sign or symptom of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [hemoglobin < 100 g/L], MAVE [including thrombosis], dysphagia, or erectile dysfunction) and elevated LDH ($\geq 2 \times$ the upper limit of normal [ULN]) after prior LDH reduction to $< 1.5 \times$ ULN on therapy
- High disease activity (HDA) status
  - Evidence of intravascular hemolysis (LDH $\geq 1.5 \times$ ULN) and any of the following symptoms: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin < 100 g/L), MAVE (including thrombosis), dysphagia, or erectile dysfunction
- Development or worsening of autoimmune disease
  - If yes, type of event
- Bone marrow pathology
  - If yes, type of bone marrow pathology or other hematological disorder, % hemoglobin, absolute reticulocyte count, LDH, LDH $\times$ ULN, LDH ratio, haptoglobin, indirect and total bilirubin, AST/ALT, direct antiglobulin test

9.3.1.4 Patient-reported Outcomes Among Participants with PNH who Experienced an AESI

The only PRO used during this study will be a patient-reported fatigue assessment using the FACIT-Fatigue questionnaire.

9.3.2 Variables Specific to Participants with PNH Who Are Pregnant or Breastfeeding and Their Infants

For the participants with PNH who are pregnant, and their infants, additional pregnancy and infant outcomes will be evaluated as described below. Data will be collected from the participant by their hematologist physician.

9.3.2.1 Primary Safety Variables

9.3.2.1.1 Ectopic Pregnancy

Any reported ectopic pregnancy will be sub-classified in the respective pregnancy outcome, including induced termination, maternal death, or spontaneous pregnancy loss.

9.3.2.1.2 Spontaneous Abortion

A spontaneous abortion is defined as loss of a fetus due to natural causes at $<$20 weeks of gestation. Information on malformations will be requested if available.

9.3.2.1.3 Pregnancy Terminations (with or without Presence of Fetal Defects)

Pregnancy terminations are defined as any induced or voluntary fetal loss during pregnancy. Information on malformations will be requested if available. The reason for elective or therapeutic termination will be recorded.

9.3.2.1.4 Fetal Death or Stillbirth (with or without Fetal Defects)

Fetal death or stillbirth refers to fetuses born dead $\geq$20 weeks gestation or weighing $\geq$350 grams ([ACOG] American College of Obstetricians and Gynecologists Obstetric Care Consensus No 2020). Fetal death occurring $\geq$20 weeks but $\leq$28 weeks gestation is considered an early fetal loss. Fetal death occurring $>$28 weeks is considered a late fetal loss ([ACOG] American College of Obstetricians and Gynecologists Obstetric Care Consensus No 2020). If gestational age is unknown, stillbirth refers to a fetus weighing $>$350 g.

Data from gross or pathological examinations of the abortus or fetus will not be available; however, presence of abnormalities will be recorded.

9.3.2.1.5 Live Birth (with or without Congenital Anomaly)

A live birth refers to a complete expulsion or extraction from its mother of a surviving neonate. Information on malformations will be requested, if available.

9.3.2.1.6 Preterm Birth

According to the U.S Centers for Disease Control and Prevention (CDC), a live birth is classified as preterm prior to 37 weeks of gestation ([CDC] 2024a) as follows: early preterm ($<$34 weeks), late preterm (34–36 weeks), early term (37–38 weeks).

In the E.U, the classification of preterm birth aligns with definitions provided by the WHO and other medical guidelines as follows ([WHO] World Health Organization 2023): extremely preterm ($<$28 weeks gestation), very preterm (28–31 weeks gestation), moderate to late preterm (32–36 weeks gestation).

9.3.2.1.7 Size for Gestational Age

All live births will be classified as small, appropriate, or large for gestational age using the U.S. CDC definition of birth weight below the 10th percentile, between the 10th and

90th, and above the 90th percentile for age, respectively ([CDC] 2024b [WHO] World Health Organization 2006).

9.3.2.1.8 Low Birth Weight

An infant with low birth weight is classified as weighing under 2500 grams ([CDC] 1984, WHO 2011). Infants with very low birth weight are defined as infants who weigh < 1500 grams, while moderate low birth weight ranges between 1500 grams and 2499 grams.

9.3.2.1.9 Postnatal growth deficiency or failure to thrive (FTT):

Defined as weight below the 10th percentile for sex and chronological age using standard growth charts. Postnatal growth deficiency (or FTT) evaluation utilizes the sex-specific international growth reference standards from the World Health Organization (WHO) for children aged 0 to 24 months. Data on FTT will be collected during maternal hematologist follow-ups, and when feasible, FTT will be characterized retrospectively at 3, 6, 9, and 12 months of infant age.

9.3.2.1.10 Infant developmental deficiency:

Failure to achieve the developmental milestones for chronological age, as defined using CDC milestones across social/emotional, language/communication, cognitive, and movement/physical development categories, assessed separately for each. Similar to postnatal growth deficiency evaluation, developmental deficiency data will be collected during maternal hematologist follow-ups and characterized retrospectively at 3, 6, 9, and 12 months of infant age when feasible.

9.3.2.1.11 Congenital Malformations

Major malformations are those that have significant medical, social or cosmetic consequences, and typically require surgical intervention or are life-threatening (e.g., cleft lip, spina bifida). Minor malformations pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences, rarely requiring surgical intervention (e.g., single palmar crease, clinodactyly). Both major and minor congenital malformations reported up to 1 year of age by the mother will be included in the analysis.

9.3.2.1.12 Serious and Severe Infections and Hospitalization of Infants

A serious infection will be defined as any infection in the infant that fulfills the definition of an SAE outlined in Section 9.3.1.3.1. Information on infant hospitalization will be requested if available.

9.3.2.1.13 Neonatal Death

A neonatal death is defined as a death occurring in a neonate prior to 28 days of life. In the event of a neonatal death, existence of fetal malformations will be requested.

9.3.2.1.14 Perinatal Death

Perinatal death is defined as the death of an infant between 28 days of life and 12 weeks of life. In the event of a perinatal death, existence of fetal malformations will be requested.

9.3.2.1.15 Infant Death

Infant death is defined as the death of an infant occurring between 12 and 52 weeks of life. In the event of an infant death, existence of fetal malformations will be requested.

9.3.2.1.16 Preeclampsia

A disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term, and proteinuria ([ACOG] American College of Obstetricians and Gynecologists 2020, [WHO] World Health Organization 2011). Or, in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

- Thrombocytopenia: Platelet count less than $100{,}000 \times 10^9$/L
- Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
- Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

9.3.2.1.17 Eclampsia

The convulsive manifestation of the hypertensive disorders of pregnancy and is among the more severe manifestations of the disease. Eclampsia is defined by new–onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions, such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use ([ACOG] American College of Obstetricians and Gynecologists 2020, [WHO] World Health Organization 2011).

9.3.2.1.18 Preterm Prelabor Rupture of Membrane:

Membrane rupture before labor that occurs before 37 weeks of gestation ([ACOG] American College of Obstetricians and Gynecologists 2020, [WHO] World Health Organization 2015).

9.3.2.1.19 Maternal Death

Maternal death is defined as the death of a pregnant woman during pregnancy, labor, or delivery. Maternal deaths for up to 12 weeks after delivery will also be reported.

9.3.2.1.20 Any Adverse Events during Pregnancy

Includes all variables from Section 9.3.1.3.1.

9.3.2.1.21 Any Adverse Events Experienced by the Infant

Includes all variables from Section 9.3.1.3.1 from birth up the first year of life.

9.3.2.1.22 Any adverse events for lactating females and infants through breastfeeding

Includes all variables from Section 9.3.1.3.1.

9.3.3 Baseline and Follow-up Variables

The following baseline and follow-up variables will be collected at enrollment for all participants with PNH and during pregnancy and infant birth:

- Participant characteristics and demographics: Date of birth or age in years (where allowed), sex, race/ethnicity (where allowed), country of residence
- Vaccination: for meningococcal (group C, AC, ACWY, and B), Hemophilus influenzae type b, pneumococcal, COVID and other. Dates of vaccinations and vaccination brands where possible
- Clinical history relevant for PNH, including previous PNH treatment and date of last administration
- Any concomitant medication
- Breastfeeding:
    - Yes/No
    - Duration of breastfeeding (in weeks or months during the first year of age of the infant)
    - Exclusively breastfeeding (Yes/No)
    - Supplementing with formula (Yes/No)
    - The ages of infants when formula supplementation began
    - Reasons for any cessation of breastfeeding
- Potential confounding factors affecting safety, pregnancy, and infant outcomes
    - Maternal medical history (e.g., hypertension, diabetes, seizure disorder, autoimmune disease, known risk factors for adverse pregnancy outcomes including environmental or occupational exposures)
    - Obstetric history: Number of pregnancies and outcome of each (live birth, miscarriage, pregnancy termination [elective or therapeutic], ectopic pregnancy), previous maternal pregnancy complications, previous fetal/neonatal abnormalities and type
    - Family history (specify type, maternal or paternal, among others): Malformations, genetic disorders, multiple fetuses/births

Participant data will be collected in the Crovalimab Silo by the clinician and/or qualified designee in accordance with routine clinical practice according to Table 1.

Table 1 Crovalimab Silo Data Collection Schedule

Data	Baseline (Enrollment Visit) [a]	Follow-up [b]	Participant Discontinuation of Crovalimab/Registry Completion [c]
Crovalimab exposure (including dates and doses)	X	X	
Participant characteristics, demographics, clinical history, potential confounding factors, any ongoing safety events and concomitant medication	X		
Last PNH treatment (including date and dose, except for previous silo drug)	X		
Proportion of PNH cells (as measured by flow cytometry of granulocytes, monocytes, and erythrocytes)	X	X	X
AESIs, AEs, SAEs (including dates) [d]	X	X	X
Clinical events and outcomes [e]	X	X	X
Clinical laboratory test results related to PNH [f]	X	X	X
Obstetric history [g]	X		
Pregnancy status, outcome and maternal complications	X	X	X
AEs, adverse fetal/neonatal/infant outcomes and baby complications, including growth and development deficiency [h]		X	X
Breastfeeding information	X	X	X
Vaccination	X	X	X
Fatigue questionnaire [i]	X	X	

Data	Baseline (Enrollment Visit) [a]	Follow-up [b]	Participant Discontinuation of Crovalimab/Registry Completion [c]

AE = adverse event; ASEI = adverse event of special interest; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; MAVE = major adverse vascular event; PNH = paroxysmal nocturnal hemoglobinuria; SAE = serious adverse event; ULN = upper limit of normal.

[a] Data from baseline will include information collected in the core and at the enrollment visit.

[b] Data are expected to be entered in the electronic data capture system approximately every 6 months post-enrollment. Every participant will be followed up during their entire crovalimab treatment and up to 12 months after discontinuation of crovalimab, if they do not start a new complement inhibitor (or 12 weeks if they start a new complement inhibitor).

[c] After discontinuation from crovalimab, participants with PNH would be followed up for 12 months from the discontinuation date of crovalimab (if they do not start a new complement inhibitor) or up to 12 weeks after discontinuation (if they start a new complement inhibitor).

[d] Including serious infections, Meningococcal infection, development or worsening of any neurological condition (e.g., axonal neuropathy, multifocal mononeuropathy, etc.), malignancies and hematologic abnormalities, serious hemolysis in participants with PNH who discontinue crovalimab, transient immune complex reactions, and infusion and injection related reactions. Treatment, hospitalizations, outcomes and causality for AESIs, AEs, and SAEs will be also collected.

[e] Including, but not limited to MAVEs (including thrombosis), packed red blood cell transfusions, breakthrough hemolysis, high disease activity status (evidence of LDH $\geq 1.5 \times$ ULN with any of the following symptoms: fatigue, hemoglobinuria, abdominal pain, shortness of breath, anemia (hemoglobin $<$ 100 g/L), dysphagia, erectile dysfunction, development or worsening of autoimmune disease, bone marrow pathology and hematological disorders, impaired renal function, impaired hepatic function, and death.

[f] Including, but not limited to hemoglobin, absolute reticulocyte count, LDH, LDH $\times$ ULN, LDH ratio, haptoglobin, indirect and total bilirubin, AST/ALT, direct antiglobulin test.

[g] Obstetric history (females): pregnancies, live births, miscarriages, and stillbirths, pregnancy or delivery complications, etc.

[h] Serious safety events, baby complications, and postnatal growth of the infant through at least their first year of age. When possible, information will be categorized by intervals of 3, 6, 9, and 12 months of infant age.

[l] Patient-reported fatigue assessment using the FACIT-Fatigue questionnaire.

9.4 DATA SOURCE

This study will analyze individual patient-level data collected from the Crovalimab Silo registry. A description of the Crovalimab Silo can be found in Section 9.1.

9.5 STUDY SIZE

Enrollment will depend on the approval timelines, uptake and treatment course in each country where the sites are open, as well as the total number of evaluable participants with PNH for AESIs (described in Section 9.3.1.2). However, based on patient projections in selected countries, the MAH expects 300 participants with PNH to be enrolled with up to 7 years of follow-up during the duration of the Crovalimab Silo registry (7 years).

Table 2 provides probabilities (and associated 2-sided 95% CIs) to observe at least one event for AESIs with assumed prevalence ranging from 0.5%–20% in a population of 300 participants with PNH. For example, in the crovalimab trials, 6% of patients had a serious infection, 6.4% had an injection-related reaction, and 17.8% had a TICR, while no patients presented with a meningococcal infection or a serious hemolysis (Crovalimab E.U. Risk Management Plan [RMP] Version 1.0, 28 June 2024).

Table 2 Probability to Observe at least one Event for AESIs with Varying Prevalence

Assumed Prevalence [a]	Probability to Observe at least One AESI (95% CI)
0.5%	77.8% (10.2%–99.8%)
1.0%	95.1% (46.2%–100.0%)
1.5%	98.9% (74.3%–100.0%)
2.0%	99.8% (89.1%–100.0%)
5.0%	100.0% (100.0%–100.0%)
7.0%	100.0% (100.0%–100.0%)
10.0%	100.0% (100.0%–100.0%)
15.0%	100.0% (100.0%–100.0%)
20.0%	100.0% (100.0%–100.0%)

AESI = adverse event of special interest.

Note: 95% CIs are 2-sided and were calculated using Clopper-Pearson method (Clopper and Pearson 1934).

[a] Assumed prevalence obtained during whole follow-up period.

In addition, the MAH aims to enroll approximately 25 participants with PNH who are pregnant in the Crovalimab Silo registry. Nevertheless, since the management of PNH during pregnancy has been challenging and pregnancy has been discouraged in participants with PNH, there are very few reported cases of pregnant participants with PNH treated with C5 inhibitors. For example, in a similar registry, there were only 94 pregnancies in fewer than 1,086 females treated with eculizumab from June 2006 to November 2014 (Kelly et al. 2015; Höchsmann et al. 2022).

In real-world clinical practice, treatment switching is common for various personal or medical reasons. Furthermore, the potential for loss to follow-up (including death, registry participation or consent withdrawal) and variations in the standard of care (SOC) across different countries can also preclude the possibility of maintaining a minimum 5 –year follow-up for all participants with PNH.

The MAH will proactively consider renegotiation with the IPG registry if required to extend the Crovalimab Silo primary data collection study duration, depending on enrollment of pregnant participants with PNH and participant follow up. Consistent with the commitment to obtaining pregnancy safety data, participant recruitment and follow-

up progress will be closely monitored, and updates will be provided as part of interim reports. In parallel, the MAH will investigate alternative approaches for data collection to supplement enrollment, if needed.

9.6 DATA MANAGEMENT

Data management information is as follows:

- The primary data collection of the Crovalimab Silo is coordinated by IPIG and the clinical research organization ICON.
- The data transfer process is described in the Crovalimab Silo data transfer agreement.
- The MAH will approve the eCRF specifications for this study. Source data will be entered into the EDC system built by ICON and the IPIG Registry.
- ICON and the IPIG Registry will produce a Data Quality Plan that is approved by the MAH, which describes the quality checking to be performed on the collected data points by ICON.
- The eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at ICON and the IPIG Registry and records retention for the study data will be consistent with ICON and the IPIG Registry standard procedures.
- Pseudonymized data will be transferred electronically as described in the Crovalimab Silo data transfer agreement from ICON/IPIG Registry to the MAH. The MAH standard procedures will be used to handle and process the electronic transfer of these data.
- ICON/IPIG Registry will comply with the MAH procedures regarding content, archiving and records management of process documents defined in MAH reference model (RRM).

Following the extraction from the data source, pseudonymized data will be stored at ICON/IPIG Registry. Access to the data will be restricted to MAH. Only pseudonymized individual patient data will be provided to Roche/Genentech.

9.7 DATA ANALYSIS

Patient demographic and clinical characteristics will be described separately for all participants with PNH, participants who experience an AESI, and participants with PNH who are pregnant and their infants.

The number of participants with PNH included in the study and the number of participants with PNH who complete the study and discontinue early will be summarized. The reasons for study discontinuation will also be summarized. Characteristics of these discontinued study participants will be compared with those who complete the registry.

9.7.1 Safety Analyses

No formal statistical testing will be performed. Descriptive statistics will be reported using summary tables and figures (where appropriate). Continuous variables will be summarized using mean, standard deviation, median, range (min–max) and interquartile range. Categorical variables will be summarized using counts and proportions (%).

Additionally, incidence and incidence rate (IRs; in person-years) and their 95% CIs of AESIs, SAEs and AEs will be calculated. The exact 95% CIs will be computed using the Clopper-Pearson method (Clopper and Pearson 1934). For the calculation of IRs, the denominator will be the pooled person-time of all the participants within the cohort. The patient time–at-risk will be calculated from index date until the date of an incident event or censoring, whichever occurs first. All first events occurring during follow-up period will be counted in the total number of events (thus, for each participant, only the first event will be counted) and divided by the total patient-years at risk. In addition, to IRs, incidence proportions will be calculated as proportion of participants with PNH afflicted with each of the AESIs, SAEs, and AEs up to the data extraction date.

9.7.2 Subgroup and Sensitivity Analyses

Subgroup and sensitivity analyses will be implemented when sample size allows.

Analyses will be presented separately for all participants with PNH, for pregnant female participants with PNH, for all infants, and for infants sub-grouped by breastfeeding status (yes/no).

When feasible, analyses will be further detailed according to each trimester of pregnancy and each quarter within the infant's first year of development.

To account for previous complement inhibitor exposure, subgroup analyses will be also based on previous PNH treatment exposure, using the following definitions: "naïve new users" when individuals initiate crovalimab without prior exposure to C5 inhibitors, and “Prevalent new users" when individuals initiate crovalimab after having received at least one C5 inhibitor any time prior to crovalimab treatment start. Safety events will be also described by causality.

Potential confounding factors influencing safety and pregnancy outcomes, such as demographic information (e.g., age, race/ethnicity), clinical characteristics, maternal medical history, obstetrical history, comorbidities, and concomitant medications will be described among participants with PNH who experience an AESI, as well as for pregnancy or infant outcomes. If needed, subgroup analysis will be performed and AESIs proportions and incidence rates will be compared between subgroups.

Similarly, subgroup analysis may include clinical and laboratory test outcomes for PNH (e.g., MAVEs, HDA, BTH, etc.) and previous PNH treatment.

Sensitivity analysis will be performed restricting the data to safety events and crovalimab exposure that was collected prospectively only. The effects of the timing of crovalimab exposure before and during pregnancy and cumulative exposure periods on each outcome will be also evaluated as sensitivity analysis. Sensitivity analysis may also include timing variations of FTT and development deficiency outcomes, when available.

Full details on all statistical analyses, including other subgroup and sensitivity analyses, will be described in the Statistical Analysis Plan (SAP).

9.8 QUALITY CONTROL

ICON/IPIG Registry must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms (if applicable), and documentation of IRB/IEC and governmental approval (if required).

The MAH shall ensure that the datasets and statistical programs that are held within MAH systems and used for generating the analysis results included in all interim reports and the final study report are kept in electronic format and are available for auditing and inspection.

Data not held within MAH systems will be periodically transferred electronically from ICON/IPIG Registry to the MAH. ICON/IPIG Registry will comply with the MAH procedures regarding content, archiving and records management of process documents, as described in the data transfer agreement.

Retention of Records

Archiving at the study site has to be for at least five years after final study report or first publication of study results, whichever comes later; or according to local regulation.

Records and documents pertaining to the conduct of this SDU study must be retained by the MAH for at least 25 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the MAH.
Written notification should be provided to the MAH prior to transferring any records to another party or moving them to another location.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This study is a long-term, non-interventional investigation where data collection mirrors routine clinical practice rather than adhering to mandatory assessments at pre-specified intervals. Given the nature of non-interventional studies, long-term follow-up, and the focus on rare diseases, certain limitations are intrinsic to this study design. The IPIG registry incorporates potential mitigation strategies, which are described below.

9.9.1 Selection Bias

To minimize selection bias, clinicians will be instructed to consecutively enroll all consenting participants with PNH who meet the selection criteria, regardless of other factors. However, since participation in the registry is voluntary for both sites and participants, common non-response selection and participation biases may occur, which is typical for this type of observational registry.

9.9.2 Data Collection Bias

The quality of patient data collected in the registry will depend on the source documentation at the sites. To address this, site training and continuous monitoring will be conducted to minimize missing data and enhance the quality of documentation practices. Additionally, automated edit checks and queries in the EDC system will help minimize missing or incorrect data.

9.9.3 Confounding

Confounding arises when treatment effects or disease exposures vary due to another factor. This can be managed using stratification or subgroup analyses in the statistical evaluation.

9.9.4 Loss to Follow-up

Given the maximum follow-up duration of 7 years, the study may experience a significant proportion of discontinued participants. To detect potential biases, the characteristics of these discontinued participants will be compared with those who complete the registry. Specific Concerns for PNH and Pregnancy In parallel, the MAH will explore options to renegotiate with the IPIG registry if needed to extend the study duration, ensuring a minimum five-year follow-up is met for all enrolled participants with PNH and pregnant participants with PNH are included. Likewise, the MAH will investigate alternative approaches for data collection to supplement enrollment if necessary.

Potential confounding factors affecting pregnancy outcomes will be assessed and contextualized, particularly those related to PNH treatment. It is unlikely that participants with PNH who are pregnant will stop crovalimab therapy entirely due to the severity of PNH relapses.

Moreover, existing evidence suggests PNH is associated with certain pregnancy complications and adverse outcomes, indicating that PNH itself may act as a confounder in the relationship between crovalimab and pregnancy-related outcomes evaluated in this study. Residual confounding from unmeasured factors is anticipated, and its impact on study outcomes cannot be predicted.

9.9.5 Data Collection Procedures

Pregnancy, infant, and breastfeeding outcomes will be collected through a passive reporting system during each follow-up visit by the nurse or hematologist.

Consequently, there exists the potential for underreporting, incomplete reporting, and missing data on pregnancy and infant outcomes. With regards to inconsistent, erroneous, or missing data, queries will be generated electronically and sent to the site staff for correction. The identifying information (assigned username, date, and time) will be collected for both the originator of the query and the originator of the data change (if applicable). An audit trail within the system will track all changes made to the data.

As specific interval data collection for pregnancy and infant outcomes is not feasible in a prospective manner, the MAH will ensure that the exact timing of each data point is documented retrospectively and reported, when feasible, for each trimester of pregnancy and each quarter during the infant's first year of development, to enable subgroup analyses.

Additionally, obstetric and neonatal outcome adjudication is not feasible due to the IPIG collaboration's structure, which relies on hematologists for data collection, without teratologist/obstetric/pediatrician involvement.

9.9.6 Size of Target Populations

Given that PNH is linked to certain pregnancy complications and adverse outcomes, the final sample size of the target population for characterizing pregnant and infant outcomes may be small and therefore could pose a limitation. If low sample size is an issue, alternative PNH data sources may be considered for evaluation.

9.9.7 Representativeness

The latest country feasibility assessment indicates that approximately 50% of the planned 300 participants with PNH are expected to be sourced from selected EU countries, with the remaining approximately 50% from non-EU countries (including United States). The inclusion of these countries is intended to contribute to the overall representativeness of the study population for participants with PNH within the EU and other geographical areas.

Importantly, available evidence suggests that the clinical presentation, pathophysiology, and disease course of PNH are largely consistent across geographic regions. Studies such as Hillmen et al. 2006, Risitano et al. 2014, and Brodsky 2020 have shown that participants with PNH globally exhibit comparable disease characteristics, including complement-mediated hemolysis, risk of thrombosis, and bone marrow failure syndromes. While minor regional or ethnic variations in incidence or specific complications exist (e.g., differences in thrombosis rates between Western and Asian populations (Brodsky 2020; Sakurai et al. 2019)), the fundamental disease process remains consistent.

Moreover, the standard of care, including the use of complement inhibitors, is harmonized in many regions due to international clinical guidelines and shared clinical

practices (Risitano et al. 2014), further supporting the extrapolation of study results across countries.

Consequently, it is expected that participants with PNH receiving crovalimab will share broadly similar demographic and clinical profiles regardless of country of origin (Dingli et al. 2023). Nonetheless, the MAH acknowledges that enrolling participants with PNH from a limited number of countries within each region may present some limitations in terms of generalizability to the entire EU or global PNH population. These limitations will be carefully considered in the analysis and interpretation of the study results.

9.9.8 Lack of comparator safety data

A key limitation of this observational study is our inability to compare crovalimab's safety data directly with the safety data from other complement inhibitors within the IPIG registry. This is due to the study's design and the restrictions of the IPIG registry's data-sharing agreements, which prevent access to and comparison with data from different silos and therefore the inclusion of a dedicated comparator arm.

9.10 OTHER ASPECTS

As the current study is observational, Awareness and Outreach Strategy and Retention Plans are not being implemented by the MAH. Instead, the International PNH Interest Group (IPIG) will manage these activities for the primary data collection on the Silo and Core registries. IPIG is actively promoting the IPIG PNH Registry at the IPIG annual conferences to reach a broad audience of hematologists. Additionally, hematologists will be directly contacted to encourage their participation in the registry and subsequent enrollment of eligible participants with PNH. To support this primary data collection, a comprehensive retention plan will be developed and implemented. This plan will ensure ongoing site and patient engagement through regular communication, provision of study updates, and facilitated data submission, thereby minimizing attrition and maximizing data completeness.

10. PROTECTION OF HUMAN SUBJECTS

10.1 INFORMED CONSENT

The IPIG sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site in the Crovalimab Silo. If applicable, it will be provided in a certified translation to the local language. The MAH must review and approve any proposed deviations from the IPIG 's sample Informed Consent Forms or any alternate Consent Forms proposed by the site (collectively, the “Consent Forms”) before IRB/IEC submission. The final Consent Forms approved by the IRB/IEC must be provided to the marketing authorization holder for archiving and for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before the start of extraction of his or her data in the eCRF.

By signing the form, the patient confirms that he/she has been informed about the study and agrees to the secondary use of his/her data, pooling of data with similar scientific data (if applicable), and the possibility of monitoring activities. It is the accountability of the physician for ascertaining that the subject has comprehended the information and to obtain written informed consent from each patient participating in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by Site Operations Representative at any time.

The participants have explicitly agreed to any secondary use of their data.

For this study, it is not necessary, or possible/practical to obtain informed consent for use of secondary data. However certain precautions will be taken, including:

- Ensuring data are pseudonymized
- Ensuring final analysis data are pseudonymized
- Ensuring possibility of linkage back to individual identified participants is impossible or tightly controlled
- Obtaining ethical committee approval for use of data as proposed (e.g., the review of and extraction of information from individual medical charts) for the proposed use ahead of study initiation

10.2 CONFIDENTIALITY

ICON/IPIG Registry maintains confidentiality standards by coding each participant enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any IPIG location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, IPIG monitors, representatives, and collaborators, and the IRB/IEC for each study site, as appropriate.

10.3 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiological Practice (GPP) published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted. The study will comply with national and E.U. requirements for ensuring the well-being and rights of participants in non-interventional PASS.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional PASS involving the use of secondary data and the reporting of adverse reactions in the form of individual Case Safety Reports (ICSRs) is not required.

Medical history and clinical outcomes, including adverse events, will be coded by System Organ Class and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®, the most recent version) lowest level term (LLT). Medications and vaccinations will be coded with the most recent edition of the WHO Drug Dictionary.

All adverse events extracted from the data source for the study as specified in the protocol will be summarized as part of any interim safety analyses and in the final study report and final publication.

11.1 CAUSALITY ASSESSMENT OF ADVERSE EVENTS

The following definitions of relationship to crovalimab should be used by clinicians during the data collection to characterize the suspected causality of each AE. This will be performed based on their consideration of all available information about the AE, including temporal relationship to crovalimab administration, pharmacological plausibility, and alternative etiology (e.g., underlying illness, concurrent conditions, concomitant treatments):

- **Related:** There is a reasonable possibility that the administration of crovalimab caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.
- **Not Related:** A causal relationship of the AE to crovalimab administration is unlikely, or underlying diseases, complications, concomitant drugs, and concurrent treatments provide a sufficient explanation for the observed AE.

12. PLANS FOR DISSEMINATION AND COMMUNICATING STUDY RESULTS

Regardless of the outcome of non-interventional PASS, the MAH is dedicated to openly providing information on the non-interventional PASS to healthcare professionals and to

the public, both at scientific congresses and in peer-reviewed journals. The MAH will comply with all requirements for publication of study results.

In accordance with the 2010 E.U. pharmacovigilance legislation, information about this PASS will be entered into the publicly available EMA Catalogue of RWD Studies (https://catalogues.ema.europa.eu/catalogue-rwd-studies). The study protocol will be entered into the register before the start of data collection. Updates to the study protocol in case of substantial amendments, interim reports where applicable, and the final study report will also be entered in the register as appropriate.

The results of this study may be published or presented at scientific meetings. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements.

13. REFERENCES

[ACOG] American College of Obstetricians and Gynecologists Obstetric Care Consensus No 10, 2020. Management of Stillbirth. [resource on the Internet]. 2020. Available from: https://www.acog.org/clinical/clinical-guidance/obstetric-care-consensus/articles/2020/03/management-of-stillbirth.

[ACOG] American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia. Obstet Gynecol. 2020;135:e237-e260.

Alashkar F, Saner FH, Vance C, et al. Pregnancy in classical paroxysmal nocturnal hemoglobinuria and aplastic anemia-paroxysmal nocturnal hemoglobinuria: a high-risk constellation. Front Med (Lausanne) 2020;7:543372.

Brodsky RA. A complementary new drug for PNH. Blood. 2020;135:884-88.

Cançado RD, Araújo ADS, Sandes AF, et al. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. Hematol Transfus Cell Ther 2021;43:341–8.

[CDC] U.S. Centers for Disease Control and Prevention. International Notes Update: Incidence of low birth weight. MMWR 1984;33:459–60, 465–70.

[CDC] U.S. Centers for Disease Control and Prevention. Maternal Infant Health: Pretern Birth [resource on the Internet]. 2024a [updated 15 May 2024]. Available from https://www.cdc.gov/maternal-infant-health/preterm-birth/index.html.

[CDC] U.S. Centers for Disease Control and Prevention. Growth Charts: What to Know [resource on the Internet]. 2024b [updated 2 Septmeber 2024]. Available from https://www.cdc.gov/growthcharts/information-for-healthcare-professionals.html.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404–13.

Curran KJ, Kernan NA, Prockop SE, et al. Paroxysmal nocturnal hemoglobinuria in pediatric patients. Pediatr Blood Cancer 2012;59:525–9.

Dingli D, Maciejewski JP, Larratt L et al. Relationship of paroxysmal nocturnal hemoglobinuria (PNH) granulocyte clone size to disease burden and risk of major vascular events in untreated patients: results from the International PNH Registry. Ann Hematol. 2023;102:1637-1644.

Farooq Q, Saleem MW, Khan ZU, et al. Paroxysmal nocturnal hemoglobinuria: a diagnostic “zero-sum-game”. Cureus 2020;12:e11956.

Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006;355:1233-43.

Höchsmann B, de Fontbrune FS, Lee JW, et al. Effect of eculizumab treatment in patients with paroxysmal nocturnal hemoglobinuria with or without high disease activity: Real-world findings from the International Paroxysmal Nocturnal Hemoglobinuria Registry. Eur J Haematol 2022;109:197–204.

Kelly RJ, Höchsmann B, Szer J, et al. Eculizumab in pregnant patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 2015;373:1032–9.

Mandala E, Lafaras C, Goulis I, et al. reatment of a patient with classical paroxysmal nocturnal hemoglobinuria and Budd-Chiari syndrome, with complement inhibitor eculizumab: Case Report. Hippokratia 2013;17:81–4.

Ninomiya K, Okura M. Nationwide comprehensive epidemiological study of rare diseases in Japan using a health insurance claims database. Orphanet J Rare Dis 2022;17:140.

[NORD] National Organization for Rare Disorders. Paroxysmal Nocturnal Hemoglobinuria [resource on the Internet] 2024 [last updated 2024 May 29]. Available from: https://rarediseases.org/rare-diseases/paroxysmal-nocturnal-hemoglobinuria/.

Risitano AM, Ricklin D, Huang Y, et al. Peptide inhibitors of C3 activation as a novel strategy of complement inhibition for the treatment of paroxysmal nocturnal hemoglobinuria. Blood. 2014;123:2094-101.

Roth A, Fu R, He G, et al. Safety of Crovalimab Versus Eculizumab in Patients With Paroxysmal Nocturnal Haemoglobinuria (PNH): Pooled Results From the Phase 3 COMMODORE Studies. Eur J Haematol. 2025;114:373-382.

Roth A, He G, Tong H, et al. Phase 3 randomized COMMODORE 2 trial: Crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibition. Am J Hematol 2024;99:1768–77.

Sakurai M, Jang JH, Chou WC et al. Comparative study on baseline clinical characteristics of Asian versus non-Asian patients with paroxysmal nocturnal hemoglobinuria. Int. J. Hematol. 2019;110:411-418.

Shah N, Bhatt H. Paroxysmal nocturnal hemoglobinuria.StatPearls [resource on the Internet] 2023 [last updtaed 2023 July 31]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562292/.

[WHO] World Health Organization. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. [resource on the Internet]. 2006. Available from: https://www.who.int/publications/i/item/924154693X.

[WHO] World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia [resource on the Internet]. 2011. Available from: https://www.who.int/publications/i/item/9789241548335.

[WHO] World Health Organization. Guidelines on optimal feeding of low birth-weight infants in low- and middle-income countries [resource on the Internet]. 2011. Available from: https://iris.who.int/handle/10665/85670.

[WHO] World Health Organization. WHO recommendations on interventions to improve preterm birth outcomes [resource on the Internet]. 2015. Available from: https://iris.who.int/bitstream/handle/10665/183037/9789241508988_eng.pdf.

[WHO] World Health Organization. Preterm Birth [resource on the Internet]. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/preterm-birth.

Annexe 1
List of Stand-Alone Documents Not Included in the Protocol

- The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols (Revision 4)

Annexe 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 it has been addressed in the study protocol or not. 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 authorization holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization 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: A POST-AUTHORIZATION SAFETY STUDY (PASS) TO CHARACTERIZE SAFETY EVENTS AND SPECIAL CONDITIONS, SUCH AS PREGNANCY AND INFANT OUTCOMES, IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) PATIENTS TREATED WITH CROVALIMAB WITHIN THE IPIG REGISTRY

EU PAS Register® number: To be registered. **Study reference number (if applicable):** Not applicable

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[3]	☒	☐	☐	9.1
1.1.2 End of data collection[4]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8.2
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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7

[3] 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.
[4] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
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 recorded in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1
	4.2.2 Age and sex	☐	☐	☒	
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.5
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

Comments:

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 categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1.1
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 categorized according to time windows?	☒	☐	☐	9.3.1.1
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.3.1.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

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?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
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)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	9.7, 9.9
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

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, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.7.2

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:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates and other characteristics?	☐	☐	☒	
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)	☐	☐	☒	
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	11
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☒	☐	

Comments:

The study will be based on secondary data from the Crovalimab Silo a product-specific registry of the IPIG core registry. Details on data source are described in Section 8.1.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7, 9.9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	9.7, 9.9
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	

Comments:

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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
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)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

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?	☒	☐	☐	5

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Date: 19/Jun/2025

Signature: _____

Annex 3. Additional information

Not applicable