Official Title: A Phase III, Randomized, Open-Label Active-controlled, Multicenter Study Evaluating the Efficacy and Safety of Crovalimab Versus Eculizumab in Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) not Previously Treated With Complement Inhibitors

NCT Number: NCT04434092

Document Date: Protocol Amendment 7: 15-September-2023

PROTOCOL

PROTOCOL **TITLE:**	**A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS**
PROTOCOL NUMBER:	BO42162
VERSION NUMBER:	7
TEST PRODUCT:	Crovalimab (RO7112689)
STUDY PHASE:	*Phase III*
REGULATORY AGENCY IDENTIFIERS:	IND Number: 131343 EudraCT Number: 2019-004931-21 *EU CT Number: 2023-506498-36-00* NCT Number: NCT04434092
*CO-***SPONSOR** *NAMES AND LEGAL REGISTERED ADDRESSES:*	F. Hoffmann-La Roche Ltd *Grenzacherstrasse 124* *4070 Basel, Switzerland* Chugai Pharmaceutical Co. Ltd *1-1 Nihonbashi-Muromachi 2-chome* *Chuo-ku, Tokyo 103-8324, Japan*
APPROVAL FINAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
7	See electronic date stamp on the final page of this document.	South Korea	8	To be determined
6	30 September 2022	South Korea	7	13 October 2022
5	24 January 2022	South Korea	6	4 February 2022
4	16 July 2021	South Korea	5	20 August 2021
3	20 November 2020	Colombia	4	25 February 2022
		South Korea	4	7 May 2021
		United Kingdom and Northern Ireland	3	13 May 2021
2	8 May 2020	France	2	17 November 2020
		Sweden	2	14 August 2020
1	13 March 2020	—	—	—

PROTOCOL AMENDMENT, VERSION 7
RATIONALE

Protocol BO42162 has been amended to align with the Clinical Trials Regulation (CTR) requirements and to introduce patient injection site flexibility. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- The following changes have been made to align with CTR and other guidelines:
  - The synopsis has been simplified.
  - A section describing the duration of participation has been added (Section 3.3).
  - Personal identifiable information (i.e., name and telephone number) and related language for the Medical Monitors has been removed from the protocol (Sections 5.4.1 and 9.7).
  - It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The following changes have been made to allow patients to inject subcutaneous crovalimab at additional (alternative) injection sites:
  - Language has been updated to specify that pharmacokinetic and safety data comparing injection sites will be analyzed as an exploratory endpoint on a descriptive basis (Sections 2.1 and 2.2).
  - It has been clarified that the abdomen must be used as the injection site during the first 24 weeks of crovalimab treatment (Section 4.3.2.1).
  - Language has been added to allow patients and/or caregivers to use an alternative injection site on the upper arm or thigh following at least 24 weeks of crovalimab treatment (Section 4.3.2.1).
- Language has been added to clarify that drug-target-drug complex samples should not be collected for follow-up assessments that occur after Week 25 post crovalimab treatment initiation in switch patients (Appendix 1).
- Language has been added to clarify timing of vital signs assessment (Appendix 1).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

***PROTOCOL* TITLE:**	**A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS**
PROTOCOL NUMBER:	BO42162
VERSION NUMBER:	7
TEST PRODUCT:	Crovalimab (RO7112689)
SPONSOR *NAMES*:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to your local study monitor.

PROTOCOL SYNOPSIS

PROTOCOL **TITLE:**	**A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS**
PROTOCOL NUMBER:	BO42162
VERSION NUMBER:	7
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 131343 EudraCT Number: 2019-004931-21 *EU CT Number: 2023-506498-36-00* NCT Number: NCT04434092

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy and safety of crovalimab, a novel humanized anti-C5 monoclonal antibody, compared to eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PNH) who have not been previously treated with a complement inhibitor therapy. The current standard of care for treatment of patients with PNH with symptomatic hemolysis or thrombosis is C5 inhibition with eculizumab or ravulizumab. Treatment with C5 inhibitors is highly effective in the majority of patients in decreasing symptoms and complications of PNH. Despite significant improvements in the treatment of PNH, there remains a high unmet medical need.

Based on clinical data, nonclinical pharmacology, and pharmacodynamic data, crovalimab is expected to lead to consistent and complete complement protein C5 inhibition resulting in suppression of intravascular hemolysis at the targeted dosing regimens.

Additionally, crovalimab has been shown to block hemolysis in patients with C5 R885 single nucleotide polymorphisms (and other C5 variants) who are unresponsive to currently available complement inhibitors and may be an effective treatment option in these patients who experience a very high unmet medical need.

OBJECTIVES AND ENDPOINTS

Primary Objective	*Corresponding Endpoints*
• *To evaluate the efficacy of crovalimab compared to eculizumab, based on the non-inferiority assessment of the co-primary endpoints*	• *Proportion of patients who achieve transfusion avoidance (TA) from baseline through Week 25 (after 24 weeks on treatment)* *TA is defined as patients who are packed red blood cells (RBC) transfusion-free and do not require transfusion per protocol-specified guidelines.* • *Proportion of patients with hemolysis control, measured by lactate dehydrogenase (LDH) ≤1.5 × ULN from Week 5 through Week 25 (as measured at the central laboratory)*

Secondary Objectives	*Corresponding Endpoints*
• *To evaluate efficacy of crovalimab compared with eculizumab, based on the non-inferiority assessment of the endpoints*	• *Proportion of patients with breakthrough hemolysis (BTH) from baseline through Week 25* *BTH is defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin <10 g/dL], a major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥2 × upper limit of normal (ULN) after prior reduction of LDH to ≤1.5 × ULN on treatment.* • *Proportion of patients with stabilization of hemoglobin from baseline through Week 25* • *Mean change from baseline to Week 25 in fatigue, as assessed by the FACIT–Fatigue*
• *To evaluate the overall safety of crovalimab compared to eculizumab*	• *Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5* • *Change from baseline in targeted vital signs* • *Change from baseline in targeted clinical laboratory test results* • *Incidence and severity of injection-site reactions, infusion-related reactions, hypersensitivity, and infections (including meningococcal meningitis)* • *Incidence of adverse events leading to study drug discontinuation* • *Incidence and severity of clinical manifestations of drug-target drug complex formation in patients who switched to crovalimab treatment from eculizumab treatment*
• *To evaluate the pharmacokinetics of crovalimab and eculizumab*	• *Serum concentrations of crovalimab and eculizumab over time*
• *To evaluate the immune response to crovalimab*	• *Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study*
• *To identify and/or evaluate biomarkers that can potentially provide evidence of crovalimab and eculizumab activity (i.e., pharmacodynamic [PD] biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), or can increase the*	• *Change over time in PD biomarkers, including complement activity (CH50) measured by a liposome immunoassay and total C5 concentration* • *Change over time in free C5 concentration in crovalimab-treated patients.* • *Observed value and absolute change from baseline to Week 25 in parameters reflecting hemolysis (e.g., reticulocyte count, free hemoglobin, haptoglobin).* • *Change over time in additional exploratory biomarkers, including but not limited to PNH clone*

knowledge and understanding of disease biology and drug safety	*size, markers from the complement system, and markers for intra- and extra-vascular hemolysis (e.g., C3, C4, C3d on RBCs, and sC5b9 complex), as well as markers of endothelial cell activation and markers from the coagulation system (e.g., von Willebrand factor, P selectin, D-dimer, thrombin-anti-thrombin complexes, thrombin generation) may also be evaluated.* • *To investigate potential treatment resistance mechanisms, Arg885 and additional polymorphisms in C5 and in other complement-related genes may be analyzed. Human leukocyte antigen typing to investigate potential mechanisms of immunogenicity may also be performed.*

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 2.

OVERALL DESIGN AND STUDY POPULATION

This randomized, multicenter, open-label, active-controlled Phase III clinical study will enroll patients who have a body weight ≥40 kg, have been diagnosed with PNH, and have not been previously treated with a complement-inhibitor therapy.

Several key aspects of the study design and study population are summarized below.

Phase:	*Phase III*	***Population Type:***	*Adult and/or pediatric patients, as applicable*
Control Method:	*Active comparator*	***Population Diagnosis or Condition:***	*PNH*
Interventional Model:	*Parallel group*	***Population Age:***	*≥18 years (Arm A & B)* *<18 years (Arm C)*
Test Product{s}:	*Crovalimab*	***Site Distribution:***	*Multi-site and multi-region*
Active Comparator:	*Eculizumab*	***Study Treatment Assignment Method:***	*Randomization and stratification*
Number of Arms:	*3*	***Number of Participants to Be Enrolled:***	*Approximately 200 total*

STUDY TREATMENT

For patients who are randomized to crovalimab, an initial IV loading dose will be administered on Week 1 Day 1, followed by four weekly crovalimab SC doses on Week 1 Day 2, then on Weeks 2, 3, and 4. Maintenance dosing will begin at Week 5 and will continue every 4 weeks thereafter, for a total of at least 24 weeks of primary treatment period, followed by the treatment extension period of no more than 5 years. All patients who receive crovalimab as part of this study will do so according to a weight-based tiered dosing approach schedule.

For patients who are randomized to eculizumab, dosing will follow local prescribing information or, if enrolled in a country without access to commercial eculizumab, the pharmacy manual. Initial weekly doses for 4 weeks will be followed by every 2-week administrations starting on Week 5. To obtain additional efficacy and safety data, patients who are randomized to eculizumab will have the opportunity to switch to crovalimab as part of the extension period of

the study, once they have completed 24 weeks of treatment with eculizumab, if the treating physician determines that this is in their best interest.

All patients who receive crovalimab (those randomized to crovalimab and those who opt to switch to crovalimab after completing the 24 weeks of the primary treatment period) will continue to do so during the extension period for a maximum of 5 years and then according to the Roche Global Policy on Continued Access to Investigational Medicinal Products.

Treatment discontinuation date is defined as the last day the patient receives a dose of medication on the study. All patients who discontinue from crovalimab treatment while on the study will return for a safety follow-up site visit 24 weeks after treatment discontinuation and a safety telephone call 46 weeks (approximately 10.5 months) after treatment discontinuation, unless they continue crovalimab outside the study. If patients discontinue and switch to a different C5 inhibitor, they should remain in safety follow-up and be monitored. Patients who discontinue from study eculizumab treatment will return for a safety follow-up visit 10 weeks after treatment discontinuation date. For all patients who discontinue study treatment, the day of the safety follow-up visit represents the end of study.

Descriptive Analysis Arm (Arm C)

The descriptive analysis arm will consist of pediatric patients (< 18 years old) and body weight ≥ 40 kg who meet all the other inclusion and exclusion criteria for the study.

If necessary, patients may receive a blood transfusion prior to enrollment to reach a hemoglobin level above the protocol-specified transfusion threshold. The patient's post-transfusion hemoglobin value should be confirmed before enrollment by local laboratory to be above the protocol-specified transfusion threshold for eligibility.

Patients in Arm C will receive a loading series of crovalimab doses comprised of an IV dose on Day 1 of Week 1, followed by weekly crovalimab SC doses for 4 weeks at Week 1 (Day 2) and then at Weeks 2, 3, and 4. Maintenance doses will begin at Week 5 and will be administered Q4W thereafter.

After 24 weeks of crovalimab treatment, patients who derive benefit from treatment may continue to receive crovalimab for a maximum of 5 years in the extension period and then according to Roche Global Policy on Continued Access to Investigational Medicinal Products.

TEST PRODUCT (INVESTIGATIONAL DRUG).

The investigational medicinal products (IMPs) for this study are crovalimab and eculizumab.

CROVALIMAB FOR IV INFUSION AND SC ADMINISTRATION

Crovalimab will be supplied by the Sponsor as a single-use vial formulation that is suitable for IV or SC administration. For information on the formulation and handling of crovalimab, see the pharmacy manual and the Crovalimab Investigator's Brochure.

Each crovalimab vial will contain an extractable volume of 1 mL (170 mg [nominal]) crovalimab or an extractable volume of 2 mL (340 mg [nominal]) crovalimab.

For IV infusion, crovalimab solution for infusion is diluted in 0.9% (w/v) sodium chloride solution prior to administration.

For SC administration, crovalimab solution for injection is used undiluted. In order to minimize the number of SC injections for patients, the administration per single injection of up to 2 mL drug product solution is permitted. Considerations for vial pooling are as follows:

- The 1 mL (170 mg) configuration will require combining of crovalimab drug product solution (vial pooling) from two 1-mL vials into a single syringe, as described in the Instruction for use.
- The 2 mL (340 mg) configuration will not require the vial-pooling step. The Instruction for Use will be adapted accordingly.

ECULIZUMAB

Eculizumab will be provided by the Sponsor to investigator sites as an IMP for IV infusion. For information on the formulation, packaging, and handling of eculizumab, see the local prescribing information for eculizumab or, if treated in a country without access to commercial eculizumab, information in the pharmacy manual.

DURATION OF PARTICIPATION

The total duration of study participation for each individual who continues in the extension period is expected to be approximately 6 years. The total duration of study participation for each individual who does not continue in the extension period is expected to be approximately 6 months.

COMMITTEES

Independent Committees:	*independent Data Monitoring Committee*
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AUC_{SS}	area under the concentration-time curve at steady state
BTH	breakthrough hemolysis
C5	component 5
CBC	complete blood count
CCOD	clinical cutoff date
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	lowest concentration reached by drug before the next dose is administered
$C_{trough, SS}$	steady state C_{trough}
DTDC	drug-target-drug complex
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	*European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire*
EQ-5D-5L	EuroQol 5-Dimension Questionnaire
FACIT	Functional Assessment of Chronic Illness Therapy
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GEE	generalized estimating equation
GPI	glycosylphosphatidylinositol
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care provider
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	*health-related quality of life*
ICE	intercurrent event
ICH	International Council for Harmonisation

Abbreviation	Definition
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LDH	lactate dehydrogenase
LIA	liposome immunoassay
LL	lower limit
LPLV	last patient, last visit
MAC	membrane attack complex
MAVE	major adverse vascular event
MFS	Multidimensional Fatigue Scale
MMRM	mixed model for repeated measures
MN	mobile nurse
NCI	National Cancer Institute
NIM	non-inferiority margin
NSDR	non-study drug−related
OLE	open-label extension
PD	pharmacodynamic
PedsQL™	Pediatric Quality of Life™
PK	pharmacokinetic
PNH	paroxysmal nocturnal hemoglobinuria
popPK	population pharmacokinetic
pRBC	packed RBC
PRO	patient-reported outcome
QoL	quality of life
QTcF	QT interval corrected through use of Fridericia's formula
QW	every week
Q2W, Q4W, Q8W, Q12W	every 2, 4, 8, 12 weeks (respectively)
RBR	Research Biosample Repository
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDR	study drug−related
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism

Abbreviation	Definition
SOC	standard of care
TA	transfusion avoidance
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
ULN	upper limit of normal
VAS	*visual analog scale*
vWF	*von Willebrand factor*
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare, acquired, clonal, hematopoietic stem cell disorder. In PNH, hematopoietic cells acquire a somatic mutation in the gene encoding phosphatidylinositol glycan anchor biosynthesis class A located on chromosome X. Consequently, progeny of affected stem cells (erythrocytes, granulocytes, monocytes, platelets, and lymphocytes) are deficient in all glycosylphosphatidylinositol (GPI)-anchored proteins that are normally expressed on hematopoietic cells, including the complement regulatory proteins CD55 and CD59. CD59 blocks the formation of the terminal complement complex (also known as the membrane attack complex [MAC]) on the cell surface, thereby preventing complement-mediated damage to erythrocyte and platelets. Therefore, the absence of CD59 on erythrocytes or platelets leads to intravascular hemolysis resulting in anemia and hemoglobinuria or the risk of potentially life-threatening thromboembolic events.

The hallmark of classic PNH is intravascular hemolysis. While there are no certain predictors of clinical manifestations, clone size (i.e., the proportion of circulating cells that arise from the GPI-anchored protein deficient clone) correlates with severity of symptoms (Parker 2016). Survival appears to be related to severity of symptoms, including anemia, impaired renal function, dyspnea, and thromboembolic events; bone marrow failure may dominate the course of the disease (Nishimura et al. 2004; de Latour et al. 2008; Jang et al. 2016). In general, a larger clone size suggests that there is a large enough population of hematopoietic cells lacking functional GPI, which are susceptible to complement-mediated injury. Moreover, clone size combined with symptomatology may guide initiation of treatment for the disease (Brodsky 2009).

Data from the international PNH registry suggest that thrombotic events and impaired renal function are major complications of the disease. Prior to the introduction of eculizumab, PNH had been fatal in about 35% of patients within 5 years of diagnosis. Thromboembolic events were the leading cause of death in patients with PNH (40%–67% of deaths with known cause) (Hillmen et al. 2007) and were reported in patients despite prophylactic anticoagulation therapy. Quality of life, as well as the ability to work, are impaired in many patients with PNH without treatment of component 5 (C5) inhibitor (Hill et al. 2017). The only curative treatment for PNH remains bone marrow transplantation, which is associated with significant morbidity and mortality (de Latour et al. 2012)

Data on prevalence are scarce, but it is estimated that overall in the United States, Europe, and Japan, there are about 10,000 patients with this disease. Data from the international PNH registry suggest that the median age of disease onset is 32 years (range: 3–87 years) (Schrezenmeier et al. 2014).

Inhibition of the complement C5 has been proven to be a successful therapeutic intervention in patients with PNH. The current standard of care (SOC) for treatment of patients with PNH with symptomatic hemolysis or thrombosis is C5 inhibition with eculizumab or ravulizumab. Eculizumab significantly reduces intravascular hemolysis as measured by serum lactate dehydrogenase (LDH), stabilizes hemoglobin, reduces the need for RBC transfusions, and improves fatigue (Functional Assessment of Chronic Illness Therapy [FACIT]) and health-related quality of life (HRQoL) (European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire [EORTC QLQ-C30]). In addition, long-term data show a significant reduction of thromboembolic events and a reduced mortality rate with chronic eculizumab treatment (Hillmen et al. 2013). Ravulizumab is a longer acting humanized anti-C5 antibody that was approved by the U.S. Food and Drug Administration (FDA; December 2018) and recently received a positive European Commission Decision (July 2019). Both approved C5 inhibitors target the same epitope on C5 and demonstrate similar efficacy in complement inhibition, but ravulizumab is engineered with amino acid substitutions resulting in a terminal half-life of approximately four times that of eculizumab and favorable pharmacokinetics (Hill et al. 2017).

Treatment with C5 inhibitors is highly effective in the majority of patients in decreasing symptoms and complications of PNH. Importantly, it does not affect the natural history of the disease because C5 inhibition does not affect the PNH clone (Brodsky et al. 2008; Brodsky 2009). Rather, the clonally derived cells survive longer with C5 inhibitors due to reduced complement-mediated injury, while the phosphatidylinositol glycan anchor biosynthesis class A-mutated hematopoietic stem cell is not affected. Therefore, patients with PNH require lifelong treatment to prevent complications and symptoms. Continuous treatment with C5 inhibitors for patients with PNH results in similar life expectancy compared with age-matched controls (Kelly et al. 2011).

Despite these significant improvements in the treatment of PNH, there remains a high unmet medical need. Approximately 35% to 50% of patients continue to require regular transfusions despite eculizumab treatment (Brodsky et al. 2008). Reasons for the continued need for transfusion include breakthrough hemolysis (BTH) caused by the following: infections, inadequate C5 inhibition by eculizumab, surgery, pregnancy, and underlying bone marrow failure or extravascular hemolysis. Hemolytic activity remains detectable in many patients during treatment with eculizumab, which may be related to incomplete C5 blockage and extravascular hemolysis (de Latour et al. 2015). Higher LDH, lower hemoglobin levels, higher bilirubin levels, and higher reticulocyte counts were noted in cases of incomplete blockage. In ex vivo studies using plasma from healthy donors and patients with PNH, eculizumab concentrations of 40 μg/mL and higher resulted in C5 inhibition. In clinical practice, some patients with PNH require either a higher dose of eculizumab than is approved or need to be dosed more frequently to control BTH (Kelly et al. 2011). In addition, approximately 3% of Japanese patients (lower in other ethnicities) with PNH have a C5 polymorphism (c.2654G to A),

which predicts the amino acid substitution pArg885His (Nishimura et al. 2014) that precludes eculizumab binding to C5 resulting in no response to eculizumab treatment (Karczewski et al. 2019).

1.2 BACKGROUND ON CROVALIMAB

1.2.1 Molecule and Nonclinical Data

Crovalimab is a novel humanized anti-C5 monoclonal antibody. Crovalimab binds to complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9 (MAC). It inhibits terminal complement-mediated intravascular hemolysis in patients with PNH. Crovalimab is based on SMART-Ig (Recycling Antibody®) (Fukuzawa et al. 2017) with pH-dependent antigen binding allowing for efficient target disposal, and enhancement of neonatal fragment crystallizable receptor (FcRn) binding to improve antibody recycling efficiency, which results in a prolonged half-life and prolonged complement inhibition. The physicochemical properties of crovalimab support the development of high concentration formulation. The combination of the SMART-Ig and the high concentrated formulation enable every 4-week (Q4W) SC dosing. Based on clinical data, nonclinical pharmacology, and pharmacodynamic (PD) data, crovalimab is expected to lead to consistent and complete complement protein C5 inhibition resulting in suppression of intravascular hemolysis at the targeted dosing regimens.

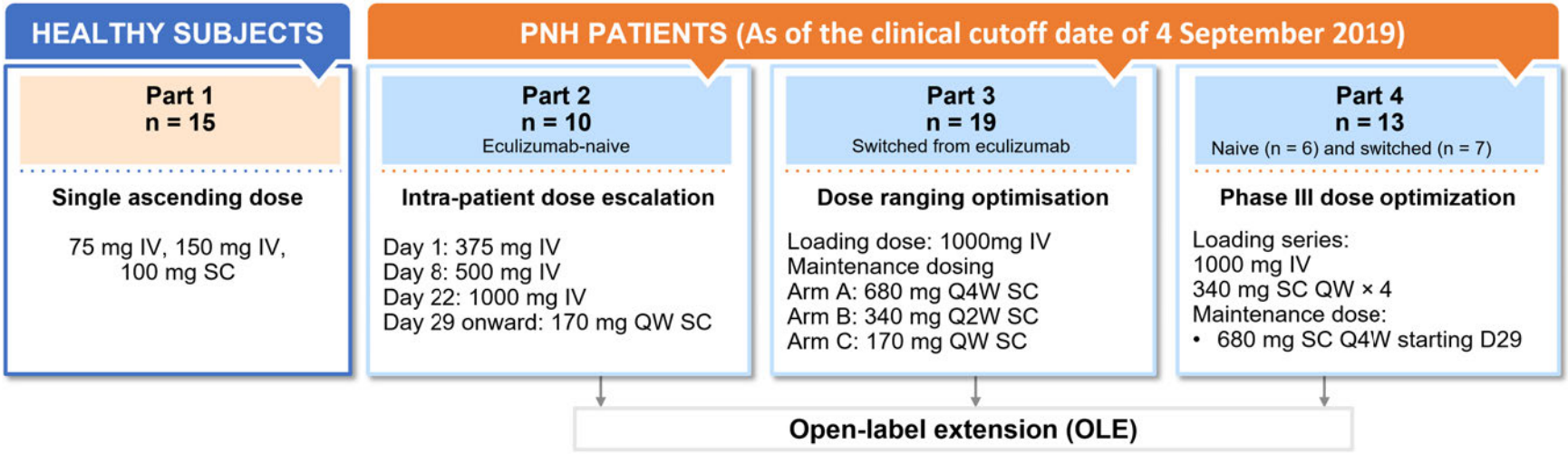
Additionally, crovalimab binds to a different C5 epitope than eculizumab or ravulizumab. In vitro studies with C5 variants (including Arg885His and also V145I, R449G, V802I, R928Q, D966Y, S1310N, and E1437D) have shown that crovalimab binds comparably with these as to wild-type C5 (Fukuzawa et al. 2017). Crovalimab has been shown in ex vivo experiments to block hemolysis in patients who have a single missense C5 heterozygous mutation that predicts an arginine at 885 (*Arg885His* missense mutation). In Study BP39144, 4 patients with PNH who have a single missense C5 heterozygous mutation were enrolled in the BP39144 study. Complement inhibition was achieved and generally maintained throughout the observation period for all 4 patients. Therefore, crovalimab may be an effective complement inhibitor for patients with C5 *R885* single nucleotide polymorphisms (SNPs) (and similar C5 variants) who are failed by currently available complement inhibitors and therefore have a very high unmet medical need.

Refer to the Crovalimab Investigator's Brochure for details on most updated nonclinical and clinical studies.

1.2.2 Clinical Experience with Crovalimab

The clinical data obtained for crovalimab to date are from Study BP39144. Study BP39144 is an ongoing Phase I/II study designed to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of crovalimab in healthy volunteers and patients with PNH. Study BP39144 consists of four sequential parts and an open-label extension (OLE) for patients with PNH, as shown in Figure 1.

Figure 1 Study BP39144 Schema



D = day; PNH = paroxysmal nocturnal hemoglobinuria; Q2W = every 2 weeks; Q4W = every 4 weeks; QW = once a week.

As of the clinical cutoff date (CCOD) of 4 September 2019, a total of 42 patients with PNH had been treated with crovalimab, including 16 treatment-naive (C5 inhibitors) patients and 26 patients who switched from eculizumab to crovalimab. Please refer to the Crovalimab Investigator's Brochure for the most updated information on the completed enrollment for Study BP39144.

Based on the healthy volunteer data from Part 1, patients naive to C5 inhibitor or who switched from eculizumab were treated with crovalimab in Part 2 or 3, respectively. Part 4 evaluated an optimized dosing regimen. All patients were offered to continue crovalimab treatment in an OLE phase.

Additional clinical data are also available from Study YO42311, a Phase III, single-arm study of crovalimab in patients with PNH, not previously treated with a complement inhibitor (China only).

Updated pharmacokinetic (PK) and PD data from Study BP39144 and Study YO42311 were analyzed, and relevant results were included in Section 1.2.2.2.

Refer to the Crovalimab Investigator's Brochure for details on clinical studies, including the most updated clinical efficacy and safety data.

1.2.2.1 Safety Data from Study BP39144

Crovalimab was safe and well-tolerated at all dose levels evaluated in Study BP39144. There were no deaths or meningococcal infections, and no adverse events resulted in withdrawal from the study or dose modification/interruption.

Out of 16 treatment-naive patients (10 patients from Part 2 and 6 patients from Part 4) with PNH who were treated with crovalimab, 3 patients experienced five serious adverse events; 1 patient experienced coronary artery stenosis, 1 patient experienced bile duct stone and cholelithiasis, and 1 patient experienced atrial fibrillation and abdominal pain (CCOD: 4 September 2019). All serious adverse events were assessed by the investigators as not related to crovalimab. All serious adverse events had resolved completely, apart from atrial fibrillation, which had resolved with sequelae.

Out of 26 patients (19 patients from Part 3 and 7 patients from Part 4) with PNH who had switched from eculizumab to crovalimab, 4 patients experienced four serious adverse events: BTH, nephrolithiasis, erysipelas, and upper respiratory tract infection (1 patient each) (CCOD: 4 September 2019). All serious adverse events were assessed by the investigators as not related to crovalimab except upper respiratory tract infection. At the time of the CCOD, all serious adverse events had resolved.

Refer to the Crovalimab Investigator's Brochure for the most updated clinical safety data.

Drug-Target-Drug Complexes

Crovalimab and eculizumab bind different epitopes on C5. This was identified early in the clinical development program as a potential safety concern due to formation of drug-target-drug complexes (DTDCs). When both are present in the circulation, complexes comprised of the two antibodies bridged by C5 are formed. These DTDCs comprise of one or more crovalimab-C5-eculizumab units. Large DTDCs are of particular clinical importance as they clear more slowly than small complexes, and in general, small immune complexes tend to be inert and are less likely to trigger a Type III hypersensitivity reaction (Nangaku and Couser 2005). Larger DTDCs (i.e., DTDCs constituted of more than a single motif) are expected to be cleared within approximately 7 to 8 weeks, while smaller DTDCs (i.e., single motif) are expected to be cleared within hours.

Formation of DTDCs has two main consequences: 1) transient enhancement of crovalimab clearance resulting in a transient exposure drop and 2) potential for development of Type III hypersensitivity.

The goal of the dosing regimen for patients switching from eculizumab to crovalimab is to maintain crovalimab trough concentrations above approximately 100 μg/mL associated with complete complement activity inhibition despite the transient formation of DTDCs.

Part 3 of Study BP39144 (CCOD: 4 September 2019) included patients who were previously treated with eculizumab and switched to treatment with crovalimab. The dosing regimen included a loading dose of crovalimab 1000 mg IV and maintenance doses of 680 mg Q4W SC or 340 mg every 2 weeks (Q2W) SC or 170 mg once a week (QW) SC.

Two out of 19 patients in Part 3 had developed events of mild to moderate severity compatible with a Type III hypersensitivity reactions.

One patient experienced a mild urticaria of the right palm that started on study Day 6 and resolved on Day 10. The patient also developed mild purpura involving the lower extremities that starting on Day 10 and resolved on Day 21 without sequelae.

A second patient with a history of hepatitis C and hepatitis B experienced a moderate small vessel vasculitis that started on Day 9 and resolved on Day 31 and an event of mild joint pain (with associated fatigue and headache) that started on Day 13 and resolved on Day 29. All events resolved without sequelae.

Both patients were treated with topical steroids and with antihistamine medications for symptoms. Importantly, they continued crovalimab without modification or interruption of dosing, or reoccurrence of the clinical manifestation described above. Neither patient

had evidence of associated organ dysfunction. Specifically, no change was observed in creatinine levels, and neither developed hematuria, proteinuria, or hypertension.

As expected, DTDCs were transiently detected in all patients switching from eculizumab to crovalimab in Study BP39144. Their amount and size distribution were indistinguishable between asymptomatic patients and the 2 individuals with Type III hypersensitivity reaction. All complexes cleared within approximately 10 weeks.

To minimize the risk for patients, enhanced monitoring during study and proper management of clinical manifestations of DTDCs were implemented (see Section 5.1.1.2 for details).

Due to the potential risk of DTDC-mediated Type III hypersensitivity reactions, it is recommended that patients who discontinue from the study and switch to another C5 inhibitor also be monitored, and guidelines have been incorporated into this Phase III protocol.

Based on the results of Part 3 of Study BP39144, dose and dosing regimen were further optimized to ensure maintaining crovalimab trough concentrations above concentration associated to full complement activity inhibition throughout the dosing interval in the majority of the patients despite the initial concentration drop triggered by DTDCs formation and variability between patients while reducing the formation of large DTDCs using a dual modeling approach (see Section 3.4.1.1 for details).

The identified dose and dosing regimen were investigated in Study BP39144 Part 4 (CCOD: 4 September 2019). Preliminary data from Study BP39144, Part 4 indicate that the exposure of crovalimab was maintained over 100 μg/mL, a concentration associated with complement activity inhibition. Complement inhibition was generally maintained in all patients over time.

In addition, available DTDC data show a reduced proportion of large DTDCs and faster clearance in patients from Part 4 compared with patients from Part 3, as predicted by the model. The median percentage of the large DTDCs (the sum of Fraction 1 to 4) was reduced by 67% in patients switching from eculizumab in Part 4 who received the optimized crovalimab dose and dosing regimen as compared with data from patients in Part 3.

None of the 7 patients who switched from eculizumab to crovalimab in Part 4 had clinical manifestations suggestive of Type III hypersensitivity reaction or other adverse consequences.

Refer to the Crovalimab Investigator's Brochure for the most updated clinical safety data.

Conclusion

Based on the preliminary data from Study BP39144 Part 4, the proposed dose and dosing regimen for patients switching from eculizumab to crovalimab will maintain crovalimab concentrations above approximately 100 μg/mL while minimizing the formation of large DTDCs.

Optimized dosing along with risk minimization strategies (including patient selection, monitoring, and management of clinical manifestation of DTDCs) outlined in the Phase III studies will ensure that the risk of DTDCs during switching is minimized and properly managed.

1.2.2.2 Pharmacokinetic and Pharmacodynamic Data from Study BP39144 and YO42311

A population PK (popPK) model (legacy popPK model) was initially developed based on data from Study BP39144 including healthy volunteers, treatment-naive patients with PNH, and patients with PNH switching from eculizumab to crovalimab (CCOD: 29 January 2020). At the time of the primary analysis of Study YO42311, the legacy popPK model was updated by pooling data from the Phase III study YO42311 (up to the CCOD: 10 February 2022) and data from Study BP39144 (Part 1, Part 2, and Part 4A, up to the CCOD: 01 November 2021) in treatment-naive patients with PNH only. Patients switching from eculizumab to crovalimab in Study BP39144 (Parts 3 and 4B) were excluded from the updated popPK analysis. This was done in order to support the regulatory submission of Study YO42311 in treatment-naive patients with PNH.

For both the legacy and updated popPK models, the concentration–time profile of crovalimab is best described by a two compartment model with first-order elimination and first-order absorption to describe SC absorption.

Body weight was a significant covariate on the clearance and volume of distribution; and was introduced using allometric scaling. Consequently, for a given dose, crovalimab systemic exposure is expected to vary with patients' body weight, with lower systemic exposure in patients with higher body weight. To compensate for the effect of body weight on the disposition parameters, a body weight tiered dosing was used (see Section 3.4.1). Age was also found as a significant covariate on the absorption rate constant. Simulations showed that exposure was similar across age groups, and no dose adaptation was required to compensate for the effect of age. Anti-drug antibody (ADA) was also tested as a covariate for clearance but had no significant impact. Based on the updated popPK model, bioavailability after SC administration is estimated to be 73.5%. The terminal half-life is estimated at approximately 59 days.

PD data indicate that crovalimab can potently inhibit terminal complement activity in healthy volunteers and patients with PNH, inducing a concentration-dependent inhibition of serum hemolytic activity as measured by an ex vivo liposome immunoassay (LIA).

A preliminary assessment of the exposure–response relationship suggests that approximately 100 μg/mL of crovalimab achieves complement inhibition that reduces hemolytic activity to <10 U/mL (limit of quantification of the assay).

1.2.2.3 Immunogenicity and Anti-Drug Antibody from Study BP39144

As of the CCOD of 4 September 2019, anti-crovalimab antibodies were detected in 2 of 9 healthy volunteers and 9 of the 37 crovalimab-treated patients (Parts 2, 3, and 4 combined; 5 patients with no data available). In the majority of patients with detectable anti-crovalimab antibodies, there is no evidence of exposure loss, PD-effect loss, or correlation with observed adverse events. One patient with anti-drug antibodies (ADAs) had a decrease in complement inhibition concomitant to a decrease in drug exposure from Weeks 12 to 36 and then achieved complement inhibition again at Week 52 concomitant to a drug exposure normalization. This patient had positive ADA starting at Week 8. The ADA titer started to decrease at Week 52.

Refer to the Crovalimab Investigator's Brochure for the most updated immunogenicity data.

1.2.2.4 Efficacy Results from Study BP39144

The following results are as of the CCOD of 4 September 2019:

LDH: In Part 2 of the study (C5-inhibitor treatment-naive patients), mean LDH levels reached ≤1.5×upper limit of normal (ULN) by Day 15 and remained 1–1.5×ULN throughout the remainder of the study. Seventy percent of the patients reached LDH <1.5×ULN by Day 22, and LDH levels remained relatively stable through the open-label treatment and OLE. Similarly, in patients enrolled in Part 3 (switching from eculizumab therapy), the mean LDH levels remained 1–1.5×ULN throughout the duration of the study. Seventy-five percent of the patients enrolled in Part 3 had reached LDH <1.5×ULN.

By Day 15, mean LDH levels in both arms of Part 4 (C5-inhibitor treatment-naive and eculizumab-pretreated patients, respectively) were stable at 1–1.5×ULN. All 6 treatment-naive patients in Arm A had reached LDH levels ≤1.5×ULN by Day 22 and maintained them through the end of the observation period. Among the 7 pretreated patients in Arm B, LDH <1.5×ULN was maintained throughout the duration of the observation period, with the exception of 2 patients whose LDH rose above 1.5×ULN at Days 15 and 29. One patient had an increase in hemolysis parameters in the context of febrile syndrome; a second patient had an adverse event of hemolytic crisis with concurrent adverse event bronchitis. At the time of the CCOD, 30% of the treatment-naive patients and 50% of the patients who switched from eculizumab had achieved an LDH ≤1×ULN.

Transfusions: Among patients in Part 4 who completed at least 4 weeks of study treatment, transfusion avoidance (TA) was achieved in 3 of 5 treatment-naive

patients and in 3 of 4 eculizumab-pretreated patients. Similarly, TA through Week 28 was achieved in 8 of 10 treatment-naive patients in Part 2 and 13 of 19 eculizumab-pretreated patients in Part 3.

Breakthrough hemolysis: The analysis of BTH was post hoc, and BTH was defined as the presence of elevated LDH $\geq 2 \times$ ULN after a prior decrease to LDH $< 1.5 \times$ ULN from the start of study treatment, with either concurrent drop in hemoglobin $<$10 g/dL OR at least one new or worsening clinical symptom or sign of intravascular hemolysis. A total of four BTH events meeting the criteria above occurred in eculizumab-pretreated patients (Part 3); three of these events were an elevated LDH with concurrent drop in hemoglobin $<$10 g/dL (at Days 15, 223, and 403 on crovalimab treatment) and one event was an elevated LDH with at least one clinical symptom of intravascular hemolysis (dark urine and fatigue, on Day 181). The BTH rate in patient-years was 0.18 (95% CI: 0.05 to 0.47). No BTH events were observed in Parts 2 and 4 of the study, although 1 patient enrolled in Part 4 is reported to have experienced an adverse event of hemolytic crisis which did not meet the criteria for LDH elevation (Day 43).

Hemoglobin stabilization: Of the 9 patients who completed 5 weeks of treatment in Part 4 of the study, hemoglobin stabilization from baseline to Day 29 of treatment was observed in 3 of 5 treatment-naive patients and in 3 of 4 eculizumab-pretreated patients. Similar results were observed in Parts 2 and 3 of the study among patients who completed at least 28 weeks of treatment: 8 of 10 treatment-naive patients (Part 2) and 14 of 19 eculizumab-pretreated patients achieved or maintained hemoglobin stabilization within the first 4 weeks of crovalimab treatment.

Four patients with PNH who have a single missense C5 heterozygous mutation and whose hemolysis was not controlled by previous eculizumab treatment were enrolled in Study BP39144. Complement inhibition was achieved and generally maintained throughout the observation period for all 4 patients; accordingly, all 4 patients achieved and maintained control of intravascular hemolysis.

Refer to the Crovalimab Investigator's Brochure for the most updated details on clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale and Benefit

The main objective of effective PNH treatment is to provide immediate, complete, and sustained inhibition of terminal complement activity to block hemolysis and prevent thrombotic events. The current SOC for adult and pediatric patients with PNH is chronic, continuous C5-inhibitor therapy.

Patients treated with eculizumab are required to receive maintenance infusions Q2W, and patients treated with ravulizumab are required to receive maintenance infusions every 8 weeks. Approximately 10% to 15% of patients treated with the labeled dose of

eculizumab experience an increase in hemolysis near the end of the dosing interval and may require either a higher-than-approved dose of eculizumab or more frequent dosing to control BTH (Kelly et al. 2011; Hillmen et al. 2013).

Crovalimab binds with high affinity to complement protein C5, preventing generation of the terminal complement complex C5b-9 (MAC) and inhibiting terminal complement-mediated intravascular hemolysis in patients with PNH. Its high SC bioavailability, prolonged half-life, and extended complement inhibition through reduced target (C5) accumulation, coupled with physiochemical properties that support the development of a high-concentration formulation, allow for SC, low-volume dosing every 4 weeks, with the potential to substantially reduce treatment burden, offering a meaningful potential benefit to individuals with PNH.

Additionally, crovalimab has been shown to block hemolysis in patients with C5 *R885* SNPs (and other C5 variants) who are unresponsive to currently available complement inhibitors and may be an effective treatment option in these patients who experience a very high unmet medical need.

1.3.2 Risk

Treatment with crovalimab was safe and well-tolerated in both healthy subjects (Part 1 of Study BP39144) and treatment-naive patients with PNH (Part 2 and Part 4/Arm A of Study BP39144).

As a class effect of complement inhibitors, there is a risk of meningococcal infection; the same mitigation strategies used for other C5 inhibitor therapies (vaccination, high clinical suspicion for infection with monitoring) have been applied to patients treated with crovalimab, with no observed cases of meningococcal infection to date.

In Study BP39144, development of DTDCs (that comprise eculizumab-C5-crovalimab) occurred transiently in all patients who switch from eculizumab to crovalimab (Part 3 and Part 4/Arm A). Optimized dosing strategy and risk minimization strategy including patient selection, monitoring, and management of clinical manifestation of DTDC (Section 1.2.2.1) were implemented after the occurrence of two DTDC-related adverse events in Study BP39144. No further clinical manifestations of DTDC were observed. In this study, the risk of DTDC is relevant only to patients who might switch to crovalimab after completing 24 weeks of eculizumab treatment and to patients who discontinue crovalimab and switch to a SOC inhibitor that binds to a different C5 epitope. The dosing and risk-minimization strategies identified based on Study BP39144 will be implemented for these patients.

1.3.3 Benefit and Risk

In the context of lifelong therapy with complement inhibition, the benefit of reduced treatment burden with optimal disease control could be substantial in many patients with PNH who require lifelong complement inhibition. Crovalimab has shown promising clinical efficacy with effective reduction in intravascular hemolysis and effective terminal complement inhibition across treatment-naive and treatment-switch patients in Study BP39144. Moreover, crovalimab has shown promising efficacy in patients with C5 *R885* polymorphisms who do not benefit from treatment with eculizumab. Current clinical experience in patients treated with crovalimab indicate that the drug is well-tolerated in treatment-naive patients, with no significant adverse events observed. The potential class effect of meningococcal infections can be effectively managed with established risk mitigation strategies. Similarly, the clinical symptomatology of DTDC manifestation, which in this study is only relevant to patients who might switch to crovalimab after completing 24 weeks of eculizumab treatment and to patients who discontinue crovalimab and switch to a SOC inhibitor, has been transient, predictable, and medically manageable without long-term sequelae. In conclusion, the overall benefit–risk may be considered positive in naive patients with PNH.

1.3.3.1 Benefit and Risk with COVID-19

Crovalimab is not expected to increase the likelihood of patients becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Risitano et al. 2020). Thus, the benefit and risk profile of crovalimab remains the same, and no changes to study conduct specifically related to coronavirus disease 2019 (COVID-19) are considered necessary.

2. OBJECTIVES AND ENDPOINTS

This is a Phase III, randomized, open-label, active-controlled, multicenter study designed to evaluate the efficacy and safety of crovalimab compared to eculizumab in patients with PNH who have not been previously treated with a complement-inhibitor therapy.

This study is divided into two parts as follows:

- Randomized arms (Arms A and B), consisting of adult patients ($\geq$18 years old)
- A descriptive arm (Arm C), consisting of pediatric patients ($<$18 years old)

Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective (Randomized Arms)

The primary efficacy objective for this study is to evaluate the efficacy of crovalimab compared to eculizumab, based on the non-inferiority assessment of the following co-primary endpoints:

- Proportion of patients who achieve TA from baseline through Week 25 (after 24 weeks on treatment)

  TA is defined as patients who are packed RBC (pRBC) transfusion-free and do not require transfusion per protocol-specified guidelines.

- Proportion of patients with hemolysis control, measured by LDH $\leq 1.5 \times$ ULN from Week 5 through Week 25 (as measured at the central laboratory)

The superiority of crovalimab vs. eculizumab will be evaluated provided that non-inferiority has first been demonstrated.

2.1.2 Secondary Efficacy Objective (Randomized Arms)

The secondary efficacy objective for this study is to evaluate efficacy of crovalimab compared with eculizumab, based on the non-inferiority assessment of the following endpoints:

- Proportion of patients with BTH from baseline through Week 25

  BTH is defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin $<$10 g/dL], a major adverse vascular event [MAVE; as defined in Appendix 4, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH $\geq 2 \times$ ULN after prior reduction of LDH to $\leq 1.5 \times$ ULN on treatment.

- Proportion of patients with stabilization of hemoglobin from baseline through Week 25

  Stabilized hemoglobin is defined as avoidance of a $\geq$2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion.

- Mean change from baseline to Week 25 in fatigue, as assessed by the FACIT−Fatigue

The superiority of crovalimab vs. eculizumab will be evaluated provided that non-inferiority has first been demonstrated.

2.1.3 Exploratory Efficacy Objective (All Arms)

The exploratory efficacy objective for this study is to evaluate the treatment effect of crovalimab compared to eculizumab on the basis of the following endpoints:

- Total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25
- Proportion of patients with central LDH $\leq$1 ULN from Week 5 through Week 25

- Time from baseline to the first time central LDH ≤1 ×ULN
- Time from baseline to the first time central LDH ≤1.5 ×ULN
- Percent change from baseline to Week 25 in central LDH levels
- Proportion of patients who reach a hemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in the absence of a transfusion
- Proportion of patients experiencing MAVE from baseline through Week 25
- Mean change from baseline to Week 25 in Physical Functioning, Role Functioning, and Global Health Status/Quality of Life (QoL) scales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life–Core 30 (QLQ-C30), and select disease-related symptoms (abdominal pain, headaches, dyspnea, dysphagia, chest pain, and erectile dysfunction) of the EORTC Item Library (for patients aged ≥ 18 years)
- Mean change from baseline to Week 25 in Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale (MFS), and the Physical Functioning scale of the PedsQL Core (for patients aged 8–17 years)
- Proportion of patients with a ≥5-point improvement from baseline in the FACIT-Fatigue at Week 25 (for adults aged ≥18 years)
- Mean treatment satisfaction with crovalimab or eculizumab, as assessed by the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) at Week 25 (for patients aged ≥18 years)
- Proportion of patients with preference for crovalimab or eculizumab at Week 41, for patients randomized to eculizumab who switch to crovalimab after 24 weeks of eculizumab treatment, as assessed through use of the Patient Preference Questionnaire developed by the Sponsor (Section 4.5.10) (for patients aged ≥18 years)
- Mean change over time in quality of life, as assessed by Quality of Life Questionnaire – Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria (QLQ-AA/PNH), and in overall health status, as assessed by Patient Global Impression of Severity Survey (PGIS) (for patients aged ≥18 years)

Additional exploratory efficacy analyses may be conducted in patients randomized to eculizumab who switch to crovalimab after completing the primary treatment period (after 24 weeks of eculizumab treatment).

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the overall safety of crovalimab compared to eculizumab, on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5 (CTCAE v5)
- Change from baseline in targeted vital signs

- Change from baseline in targeted clinical laboratory test results
- Incidence and severity of injection-site *reactions,* infusion-related reactions, hypersensitivity, and infections (including meningococcal meningitis)
- Incidence of adverse events leading to study drug discontinuation
- Incidence and severity of clinical manifestations of DTDC formation in patients who switched to crovalimab treatment from eculizumab treatment

The exploratory safety objective for this study is as follows:

- *To descriptively compare the safety and tolerability of crovalimab between the different injection sites*

2.3 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to evaluate the pharmacokinetics of crovalimab and eculizumab on the basis of the following endpoints:

- Serum concentrations of crovalimab and eculizumab over time

The exploratory PK objectives for this study are as follows:

- To evaluate potential relationships between drug exposure and the efficacy and safety of crovalimab (patients randomized to crovalimab)
- To evaluate potential relationships between drug exposure and the efficacy and safety of eculizumab (patients randomized to eculizumab)
- To evaluate relationship between DTDC size and kinetics and PK parameters of crovalimab (for patients randomized to eculizumab who switch to crovalimab after completion of eculizumab treatment)
- *To compare serum concentrations of crovalimab at trough across the different injection sites*

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to crovalimab on the basis of the following endpoints:

- Prevalence of ADAs at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate the potential effects of ADA on PK, PD, efficacy and safety endpoints.

2.5 BIOMARKER OBJECTIVE

The biomarker objective for this study is to identify and/or evaluate biomarkers that can potentially provide evidence of crovalimab and eculizumab activity (i.e., PD biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), or can increase the

knowledge and understanding of disease biology and drug safety on the basis of the following endpoints:

- Change over time in PD biomarkers, including complement activity (CH50) measured by a LIA and total C5 concentration.
- Change over time in free C5 concentration in crovalimab-treated patients.
- Observed value and absolute change from baseline to Week 25 in parameters reflecting hemolysis (e.g., reticulocyte count, free hemoglobin, haptoglobin).
- Change over time in additional exploratory biomarkers, including but not limited to PNH clone size, markers from the complement system, and markers for intra- and extra-vascular hemolysis (e.g., C3, C4, C3d on RBCs, and sC5b9 complex), as well as markers of endothelial cell activation and markers from the coagulation system (e.g., *von Willebrand factor* [vWF], P-selectin, D-dimer, thrombin-anti-thrombin complexes, thrombin generation) may also be evaluated.
- To investigate potential treatment resistance mechanisms, Arg885 and additional polymorphisms in C5 and in other complement-related genes may be analyzed. Human leukocyte antigen typing to investigate potential mechanisms of immunogenicity may also be performed.

Additionally, the relationship between blood biomarkers and efficacy, safety, pharmacokinetics, and immunogenicity will be investigated.

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of pediatric (aged ≥ 12 years and < 18 years) and adult (aged ≥ 18 years) patients treated with crovalimab compared to eculizumab, on the basis of the following endpoint:

- Health status of patients according to EuroQoL 5-Dimension Questionnaire, 5-level version (EQ5D-5L) index based and visual analog scale (VAS) scores at specified timepoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This randomized, multicenter, open-label, active-controlled Phase III clinical study will enroll patients who have a body weight ≥ 40 kg, have been diagnosed with PNH, and have not been previously treated with a complement-inhibitor therapy.

The screening period of the study will last up to 28 days.

This study is divided into two parts: randomized arms (Arms A and B), consisting of adult patients (≥ 18 years old), that will contribute to the primary analysis; and a descriptive analysis arm (Arm C), consisting of pediatric patients (< 18 years old), that will contribute to the exploratory analysis. Figure 2 presents an overview of the study

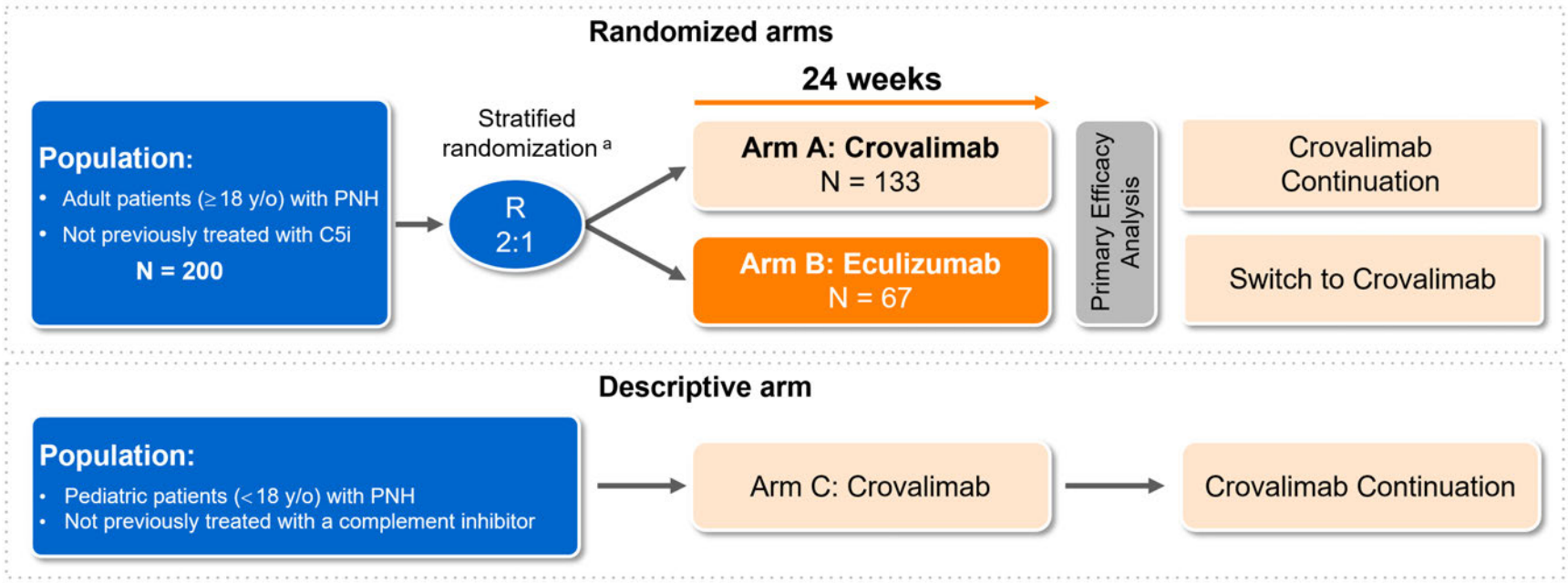
design, and Figure 3 presents the study periods. The schedules of activities are provided in Appendix 1.

3.1.1 Randomized Arms (Arms A and B)

Approximately 200 adult patients (≥ 18 years old) will be randomized in a 2:1 ratio to the following regimens:

- Crovalimab
- Eculizumab

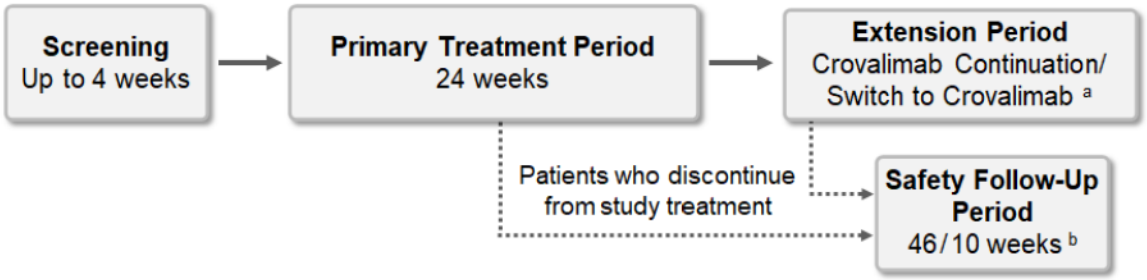
Figure 2 Study Design



PNH = paroxysmal nocturnal hemoglobinuria; R = randomization; ULN = upper limit of normal; y/o = years old.

[a] Randomization is stratified based on the most recent LDH value (≥2 to ≤4 × ULN, and >4 × ULN) and packed RBC transfusion history (0, >0 to ≤6, and >6 units) within 6 months. Patients will be randomized 2:1 to crovalimab or eculizumab, respectively.

Figure 3 Study Periods



[a] After 24 weeks in the primary treatment period, patients may continue/switch to crovalimab for a maximum of 5 years and then according to Roche Global Policy on Continued Access to Investigational Medicinal Products. See Sections 3.1.1 and 3.1.2 for more details.

[b] Safety follow-up period is 46 weeks for patients who discontinue crovalimab (including a safety follow-up site visit 24 weeks after treatment discontinuation and a safety telephone call 46 weeks [approximately 10.5 months] after treatment discontinuation) and 10 weeks for patients who discontinue eculizumab.

Enrollment of patients without a history of transfusion in the past year will be capped at 20%. If necessary, patients may be transfused prior to randomization to reach a hemoglobin level above the specified transfusion threshold (per Sections 4.1.2 and 4.5.7). The patient's post-transfusion hemoglobin value should be confirmed before randomization by local laboratory to be above the protocol-specified transfusion threshold for eligibility.

Randomization will be stratified according to the following factors:

- LDH level (most recent value prior to randomization, locally performed): ≥ 2 to $\leq 4 \times$ ULN or $> 4 \times$ ULN
- Number of pRBC units administered within 6 months prior to randomization: 0 units, $> 0 - \leq 6$ units or > 6 units

The study will aim to demonstrate the efficacy of crovalimab compared with eculizumab, based on the non-inferiority assessment of both TA and hemolysis control; superiority will be evaluated for both endpoints provided that non-inferiority has first been demonstrated. The primary efficacy analysis will be performed when all randomized patients have either completed the primary treatment period (24 weeks of treatment in the study) or discontinued from treatment, whichever occurs first. Patients must have received at least one dose of treatment with crovalimab/eculizumab and have at least one central LDH level assessment after the first study drug infusion to be included in the primary efficacy analysis.

For patients who are randomized to crovalimab, an initial IV loading dose will be administered on Week 1 Day 1, followed by four weekly crovalimab SC doses on Week 1 Day 2, then on Weeks 2, 3, and 4. Maintenance dosing will begin at Week 5 and will continue Q4W thereafter, for a total of at least 24 weeks of primary treatment period, followed by the treatment extension period of no more than 5 years. All patients who receive crovalimab as part of this study will do so according to a weight-based tiered dosing approach schedule (Table 1).

For patients who are randomized to eculizumab, dosing will follow local prescribing information or, if enrolled in a country without access to commercial eculizumab, the pharmacy manual. Initial weekly doses for 4 weeks will be followed by Q2W administrations starting on Week 5 (see Section 4.3.2). To obtain additional efficacy and safety data, patients who are randomized to eculizumab will have the opportunity to switch to crovalimab as part of the extension period of the study, once they have completed 24 weeks of treatment with eculizumab, if the treating physician determines that this is in their best interest. More details are provided in Section 4.3.2.2.

All patients who receive crovalimab (those randomized to crovalimab and those who opt to switch to crovalimab after completing the 24 weeks of the primary treatment period) will continue to do so during the extension period for a maximum of 5 years and then

according to the Roche Global Policy on Continued Access to Investigational Medicinal Products (see Section 4.3.5).

Treatment discontinuation date is defined as the last day the patient receives a dose of medication on the study. All patients who discontinue from crovalimab treatment while on the study will return for a safety follow-up site visit 24 weeks after treatment discontinuation and a safety telephone call 46 weeks (approximately 10.5 months) after treatment discontinuation, unless they continue crovalimab outside the study. If patients discontinue and switch to a different C5 inhibitor, they should remain in safety follow-up and be monitored as detailed in Section 5.1.1.2. Patients who discontinue from study eculizumab treatment will return for a safety follow-up visit 10 weeks after treatment discontinuation date. For all patients who discontinue study treatment, the day of the safety follow-up visit represents the end of study. More details are provided in Section 4.6.

3.1.2 Descriptive Analysis Arm (Arm C)

The descriptive analysis arm will consist of pediatric patients (<18 years old) and body weight ≥40 kg who meet all the other inclusion and exclusion criteria for the study.

If necessary, patients may receive a blood transfusion prior to enrollment to reach a hemoglobin level above the protocol-specified transfusion threshold (see Sections 4.1.2 and 4.5.7 for details). The patient's post-transfusion hemoglobin value should be confirmed before enrollment by local laboratory to be above the protocol-specified transfusion threshold for eligibility.

Patients in Arm C will receive a loading series of crovalimab doses comprised of an IV dose on Day 1 of Week 1, followed by weekly crovalimab SC doses for 4 weeks at Week 1 (Day 2) and then at Weeks 2, 3, and 4. Maintenance doses will begin at Week 5 and will be administered Q4W thereafter.

After 24 weeks of crovalimab treatment, patients who derive benefit from treatment may continue to receive crovalimab for a maximum of 5 years in the extension period and then according to Roche Global Policy on Continued Access to Investigational Medicinal Products (see Section 4.3.5).

3.1.3 Independent Data Monitoring Committee

An iDMC composed of external members (including PNH/bone marrow failure expert[s], clinician[s] with experience in drug development, statistician, and clinical pharmacology expert) will be in place for this study. iDMC members will not be investigators on this study and will have no contact with the clinical sites.

All analyses for review by the iDMC that will take place before the primary analysis will be prepared by an independent data coordinating center (iDCC) that is independent of

the Sponsor. The iDCC will perform unblinded analyses and provide tables and listings to support the iDMC data review.

Analyses of safety events will be conducted at prespecified intervals, the timing of which will be defined in the iDMC Charter. Following each meeting, the iDMC will recommend whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of data review.

The meeting schedule and all other iDMC-related activities will be specified in the iDMC charter. The final decision of acting upon the iDMC's recommendations will rest with the Sponsor. The policies and procedures will be detailed in a separate iDMC Charter document.

3.1.4 Exploratory Substudies

At selected sites, the Sponsor may propose and conduct exploratory substudies associated with the BO42162 study protocol. Each substudy will be introduced in a separate substudy protocol and will have a separate associated Informed Consent Form.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient's last visit (LPLV) occurs, or the date at which the last data point required for the final statistical analysis is collected, whichever occurs later. The end of the study is expected to occur 6 years after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 7 years.

3.3 *DURATION OF PARTICIPATION*

The total duration of study participation for each individual who continues in the extension period is expected to be approximately 6 years. The total duration of study participation for each individual who does not continue in the extension period is expected to be approximately 6 months.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Crovalimab Dose and Schedule

The goal of treatment with C5 inhibitor therapy is to achieve a rapid and complete suppression of C5 activity and to maintain this suppression throughout the dosing interval.

Data from Phase I/II Study BP39144 indicate that above crovalimab concentration of 100 μg/mL, complete complement inhibition was achieved.

This study will include two weight-based doses for crovalimab (see Table 1).

3.4.1.1 Rationale for Crovalimab Dose and Schedule in Patients Switching from Eculizumab

In patients switching from eculizumab to crovalimab, DTDCs form as eculizumab and crovalimab bind different C5 epitopes. Formation of DTDCs could result in a transient lower crovalimab exposure that could lead to transient suboptimal complement inhibition.

The goal of the dosing regimen is to maintain crovalimab above 100 μg/mL to ensure a complete complement inhibition despite the transient formation of DTDCs.

Two complementary modeling approaches were used to determine the crovalimab dose and dosing regimen:

- An empirical popPK model was used to recommend a dose and regimen, achieving and maintaining crovalimab concentrations above a concentration of approximately 100 μg/mL associated with complete complement inhibition throughout the dosing interval in the majority of the patients. In the population PK model, body weight was tested as a covariate for crovalimab clearance and volume of distribution and was found to statistically influence these parameters when incorporated using allometric scaling with a coefficient fixed to 0.75 for the clearances and 1.0 for the volumes. As a consequence, for a given dose, larger patients tend to be under-exposed as compared with smaller patients. To compensate for the effect of body weight, a weight-based tiered dosing approach is proposed to ensure that all patients receive a comparable crovalimab exposure.
- A mechanistic model describing, simultaneously, the kinetics of total and free C5, the pharmacokinetics of crovalimab and eculizumab, and the kinetics of DTDCs was also used to recommend a dose and regimen minimizing the formation of large DTDCs in patients switching to crovalimab while maximizing the level of free crovalimab binding sites in all the patients.

The proposed dose and dosing regimen in this study has been investigated in Study BP39144 Part 4. The preliminary PK data collected in naive and switch patients in Part 4 indicate that the exposure of crovalimab was maintained over 100 μg/mL and induced complete complement inhibition across all patients.

In addition, the preliminary DTDC data showed that the proposed dose and dosing regimen reduced the proportion of large DTDCs in most of the patients from Part 4 as predicted by the model. The median percentage of the largest DTDCs (the sum of Fraction 1 to 4) was reduced by 67% in patients switching from eculizumab in Part 4 who received the optimized crovalimab dose and dosing regimen as compared to data from Part 3 patients.

Based on PK modeling and the preliminary data from Study BP39144 Part 4, the proposed dose and dosing regimen for patients switching from eculizumab to

crovalimab will maintain crovalimab concentrations above approximately 100 μg/mL while minimizing the formation of large DTDCs.

3.4.2 Rationale for Patient Population

3.4.2.1 Primary Population

Adult patients (from treatment arms A and B) with PNH who were never treated with a complement inhibition therapy prior to study entry will comprise the randomized population for this Phase III study aiming to demonstrate non-inferior efficacy and safety of crovalimab compared to eculizumab. Patients will be included if their LDH at screening is at least 2 × ULN. This requirement was specifically chosen to ensure inclusion of patients who have significant hemolysis and therefore have the highest therapeutic need and chance to benefit from C5 inhibition treatment.

3.4.2.2 Inclusion of Pediatric Patients

The descriptive analysis arm (Arm C) will include pediatric patients weighting ≥40 kg with PNH who were never treated with complement inhibition therapy. PNH onset among pediatric patients is rare. However, when occurring, PNH in children is indistinguishable from adults. Regardless of age of onset, PNH is defined by the occurrence of *PIGA* mutations in the hematopoietic stem cell resulting in loss of GPI-anchored proteins. Pediatric patients and adult patients have similar disease process and similar response to intervention (Urbano-Ispizua et al. 2011). Based on PK simulation, pediatric and adult patients are expected to have similar exposure–response relationships; therefore, similar crovalimab PK and PD responses in pediatric and in adult patients are expected. Furthermore, the clinical manifestations and the response to treatment with C5 inhibitors are similar in patients with PNH across the age continuum, justifying inclusion of pediatric patients in this trial. Importantly, for these young individuals the potential for reduced treatment burden offered by crovalimab may be particularly meaningful.

The Sponsor anticipates that, because of the rarity of disease among pediatric patients, too few of them will be enrolled to allow for dedicated comparisons. Inclusion of these patients in a descriptive arm, where all patients receive crovalimab, maximizes the number of pediatric patients treated with crovalimab in the study and provides important age-specific safety and PK/PD data. Thus, Arm C will provide a clinically valuable description of the outcome of these patients receiving crovalimab treatment, and will contribute to the overall safety database.

3.4.3 Rationale for Control Group

Eculizumab, which was approved by FDA and EMA in 2007 for the treatment of PNH, was selected as the comparator regimen because it represents the SOC in most of the countries where patients will be enrolled. No C5 inhibitor has been shown to be superior to eculizumab on clinically meaningful endpoints, therefore eculizumab is deemed an appropriate benchmark for comparison (Kulasekararaj et al. 2018; Lee et al. 2019).

In a double-blind, randomized, placebo-controlled clinical trial (Hillmen et al. 2006), eculizumab was shown to significantly reduce intravascular hemolysis as demonstrated by decrease in mean LDH from 2199.7 U/l at baseline to 327.3 U/l after 26 weeks of treatment (compared to an increase from 2258.0 U/l to 2418.9U/l in the placebo group). It stabilized hemoglobin (49% of the patients treated with eculizumab, compared to 0% of patients on placebo), reduced the need for RBC transfusions (51% of the patients were transfusion-independent after 26 weeks of treatment, compared with 0% of the patients in the placebo group) and improved fatigue (as measured by FACIT-Fatigue scale]) and health-related quality of life (HRQoL) (as measured by QLQ-C30 instrument).

This study will evaluate efficacy of crovalimab, compared to eculizumab, based on non-inferiority assessments. The key aspects of the study population and design are similar to those used in a more recent Phase III randomized, active-controlled, open-label clinical trial that demonstrated the non-inferiority of ravulizumab versus eculizumab (NCT02946463; Lee et al. 2019) and led to ravulizumab approval in the PNH population in the U.S. and E.U.

3.4.4 Rationale for Stratification Factors

Randomization will be stratified by most recent LDH level prior to randomization and number of pRBC units administered within the 6 months prior to randomization. These have been selected to balance the treatment group assignment, since pretreatment LDH and recent transfusion experience are expected to be of strong prognostic value for the co-primary endpoints of hemolysis (measured by LDH) and TA.

3.4.5 Rationale for Co-Primary Endpoints

The goal of the study is to demonstrate that in previously untreated PNH patients crovalimab can establish control of hemolysis. This will be done through complementary co-primary endpoints. Serum LDH is the primary biochemical marker of intravascular hemolysis and therefore linked to the clinical manifestations of disease. As such, it is commonly used as a clinical measure for intravascular hemolysis. TA is a disease-related event for patients with PNH and is a clinically significant measure of disease control. TA has high clinical interpretability and can be used by physicians and patients to make treatment decisions. Using LDH and TA as co-primary endpoints provides a complete and meaningful picture of drug's efficacy, integrating the assessment of the effect on hemolysis with that on clinical outcomes.

LDH normalization (defined as patients achieving LDH $\leq$ULN) was used in NCT02946463 to demonstrate response to treatment (Lee et al. 2019). However, the exact definition of LDH cutoff point that carries clinical significance is not clear. Lee et al. (2019) found that LDH normalization was achieved only in 49%–54% of the patients, while 66%–74% of the patients achieved TA and only 4%–11% had a BTH event. These results underscore that LDH normalization has suboptimal sensitivity as a marker to define clinical response. Conversely, data from Jang et al. (2016) demonstrate that LDH

≤ 1.5xULN was the most sensitive and specific predictor of mortality (standard mortality ratio of 4.81 for patients with PNH compared with age- and sex-matched general population at or above this LDH threshold, and SMR of 1.17 below this threshold), making this a clinically meaningful threshold of disease control. Lee et al. (2011, 2013) also demonstrated that LDH values ≤1.5 × ULN are associated with significantly increased risks of thromboembolic events and mortality, and the same threshold was used by Schrezenmeier et al. (2014) to further investigate the relationship between LDH increase and disease-related characteristics and morbidity. Recognizing the inherent subjectivity of choosing an LDH cutoff that defines adequate hemolysis control, LDH ≤1.5 × ULN was selected given the available literature supporting its clinical relevance, and exploratory analyses using LDH ≤ ULN will investigate the sensitivity of results to the choice of cut point. Importantly, the clinical value will be further supported by the co-primary endpoint of TA.

3.4.6 Rationale for Biomarker Assessments

Inadequate C5 inhibition and detectable hemolytic activity have been reported in patients with PNH during SOC treatment (de Latour et al. 2015). Thus, PD biomarkers will be assessed to monitor the biologic activity of crovalimab treatment. To monitor complement inhibition, the capacity of patients' serum to lyse marker enzyme-containing liposomes ex vivo will be determined. The activity of the liberated marker enzyme is proportional to the complement activity in the sample (Jaskowski et al. 1999) and thus, a surrogate for the complement inhibitory activity of crovalimab. Total and free C5 concentrations will also be measured in patients' serum to assess the interaction with the target.

Additional exploratory biomarkers, including but not limited to PNH clone size, markers from the complement system, and markers for intra- and extra-vascular hemolysis (e.g., complement components C3, C4, C3d on RBCs, and sC5b-9 complex), may be measured in blood samples. Interplay between the complement and coagulation systems may contribute to thrombosis in PNH (Keragala et al. 2018). Thus, markers from the coagulation system, including but not limited to endothelial activation (e.g., vWF, P-selectin), D-dimer, thrombin-anti-thrombin complexes, and thrombin generation, may also be measured. The relationship between exploratory biomarkers and serum concentrations of crovalimab may be evaluated. Residual blood from these collected samples may be used for additional crovalimab-related research, including exploratory biomarker profiling or assay development and validation. Any analyses not specifically listed in the protocol may be performed only if permitted by local regulations.

Poor response to C5 inhibition by eculizumab has been described in patients with PNH with C5 Arg885 polymorphisms (Nishimura et al. 2014). To investigate potential treatment resistance mechanisms, a blood sample for targeted clinical genotyping will be collected, and may be used to analyze polymorphisms in C5 and in other complement-

related genes in countries where local regulations permit. Human leukocyte antigen typing to investigate potential mechanisms of immunogenicity may also be performed.

3.4.7 Rationale for Patient-Reported Outcomes

Patients with PNH experience persistent intravascular hemolysis that causes anemia, hemoglobinuria, and a variety of disease-related symptoms that can negatively impact their day-to-day functioning and QoL. Patients report significant fatigue that is disproportionate to their degree of anemia (Hillmen et al. 2006), as well as dyspnea, headaches, abdominal pain, dysphagia, chest pain, and erectile dysfunction in men (Weitz et al. 2013; Schrezenmeier et al. 2014; Yenerel et al. 2017). Experience of these symptoms, particularly fatigue, is in turn associated with decreased functioning and HRQoL (Schrezenmeier et al. 2014).

To characterize the HRQoL of adult patients in this study, fatigue will be assessed using the FACIT-Fatigue while physical functioning, role functioning, and general health status/QoL will be assessed using selected scales of the EORTC QLQ-C30. These are validated patient-reported outcome (PRO) measures that have been shown to be relevant to patients with PNH (Weitz et al. 2013). Additional disease-related symptoms will be assessed through the use of selected relevant items from the EORTC Item Library. Age appropriate, self-report pediatric measures, the PedsQL MFS and Physical Functioning Scale of the PedsQL Core, will be used to assess fatigue and physical functioning, respectively, in pediatric patients. In addition, treatment satisfaction using the TSQM-9 (adult patients) and patient preference (adult patients) will be assessed. The EQ-5D-5L (patients aged ≥12 years) will be administered for the purpose of producing health utility scores for economic modeling.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 200 adult patients with PNH will be included in the randomized arms of this study. Pediatric patients will be included in the descriptive analysis arm.

4.1.1 Inclusion Criteria

4.1.1.1 Inclusion Criteria for All Arms

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards
- Body weight ≥40 kg at screening
- Willingness and ability to comply with all study visits and procedures
- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of WBCs with granulocyte or monocyte clone size of ≥10%, within 6 months prior to randomization

- LDH level $\geq 2 \times$ ULN at screening (as per local assessment)
- Presence of one or more of the following PNH-related signs or symptoms within 3 months prior to screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin $<$10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion because of PNH
- Vaccination against *Neisseria meningitidis* serotypes A, C, W, and Y $<$ 3 years prior to initiation of study treatment. Vaccination against serotype B should be administered in accordance with the most current local guidelines or SOC, as applicable in patients with complement deficiency. If not previously administered or no longer current, vaccination must be completed no later than 1 week after the first study drug administration. Vaccination currency with vaccination against serotypes A, C, W, Y and B should be maintained throughout the study, according to local guidelines or SOC as applicable in patients with complement deficiency. In the absence of clear local guidelines for Neisseria meningitidis, the Advisory Committee on Immunization Practices 2020 Guidelines are recommended.

  If vaccination is completed $<$ 2 weeks prior to initiation or after the start of study treatment, appropriate antibiotic prophylaxis must be maintained from first study drug administration, continuing for at least 2 weeks after completion of vaccination or according to local SOC as applicable in patients with complement deficiency, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to the first dose of study drug. Patients who refuse vaccination against Neisseria meningitidis are not eligible for the study.
- Vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* according to national vaccination recommendations (e.g., Advisory Committee on Immunization Practices guidelines). If not previously administered or no longer current, vaccination should be completed no later than 1 week after the first study drug administration. If vaccination is completed $<$ 2 weeks prior to initiation or after the start of study treatment, appropriate antibiotic prophylaxis must be maintained from first study drug administration, continuing for at least 2 weeks after completion of vaccination or according to local SOC, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to enrollment. Patients who refuse vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* when recommended are not eligible for the study.
- Patients who have been vaccinated (partially or in full) against SARS-CoV-2 with a locally approved vaccine are eligible to be randomized/enrolled in the study, 3 days or longer after inoculation. Patients who have not been vaccinated against SARS-CoV-2 are also eligible to be in the study.
- Platelet count $\geq$ 30,000/mm^3 at screening without transfusion support within 7 days of lab testing.

- ANC $>500/\mu l$ at screening
  - Short-acting granulocyte colony-stimulating factors (G-CSFs) must not have been administered within 14 days of lab testing.
  - Long-acting G-CSFs must not have been administered within 28 days of lab testing.
- For patients receiving other therapies (e.g., immunosuppressants, corticosteroids, iron supplements, anticoagulants, erythrocyte-stimulating agents): stable dose for $\geq$28 days prior to the first study drug administration
- Adequate hepatic function, with ALT $\leq 3 \times$ ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine $\leq 2.5 \times$ULN and creatinine clearance by Cockcroft-Gault formula $\geq$30 mL/min
- For female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Female patients of childbearing potential must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for 46 weeks (approximately 10.5 months) after the final dose of crovalimab and 3 months after the final dose of eculizumab (or longer if required by the local product label, e.g., 5 months after the final dose of eculizumab in the United Kingdom and the European Union according to the Summary of Product Characteristics [SmPC]).

  A female patient is considered to be of childbearing potential if the patient is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
  If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.1.2 Additional Inclusion Criteria for Patients in the Randomized Arms

Patients must meet the following additional criterion to qualify for the Randomized Arms:

- Age ≥18 years at time of signing Informed Consent Form

4.1.1.3 Additional Inclusion Criteria for Patients in the Descriptive Arm

Patients must meet the following additional criterion to qualify for the Descriptive Arm:

- Age <18 years at time of signing of Informed Consent Form

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pre-enrollment hemoglobin value ≤7 g/dL, or pre-enrollment hemoglobin value >7 g/dL and≤9 g/dL with concurrent signs and symptoms of anemia, including: angina, syncope, lightheadedness, confusion, severe or worsening shortness of breath, severe or worsening fatigue, stroke, transient ischemic attack, or new or worsening heart failure.

  Hemoglobin must be measured prior to randomization/enrollment, within 5 days before Week 1 Day 1 of study drug administration (i.e., Day −4 to Day 1). At that time, if the patient does not meet the eligibility criteria, the patient may be transfused with pRBCs to meet the hemoglobin eligibility threshold. The patient must be reassessed with a post-transfusion hemoglobin measurement to confirm eligibility before randomization/enrollment. If more convenient and if in accordance with local regulations, screening hemoglobin measurements may be performed at a hospital or laboratory that is not the study site.
- Current or previous treatment with a complement inhibitor
- History of allogeneic bone marrow transplantation
- History of *Neisseria meningitidis* infection within 6 months prior to screening and up to first study drug administration
- Known or suspected immune deficiency (e.g., history of frequent recurrent infections)
- Known or suspected hereditary complement deficiency
- Know HIV infection and with a $CD4^+$ cell count <200 cells/μL within 24 weeks prior to screening

  Patients with HIV infection who have a $CD4^+$ cell count >200 cells/μL and meet all other criteria are eligible.
- Infection requiring hospitalization or treatment with IV antibiotics within 28 days prior to screening and up to the first drug administration, or oral antibiotics within 14 days prior to screening and up to the first drug administration
- Active systemic bacterial, viral, or fungal infection within 14 days before first drug administration
- Presence of fever (≥38°C) within 7 days before the first drug administration

- Immunized with a live attenuated vaccine within 1 month before first drug administration
- History of malignancy within 5 years prior to screening and up to the first drug administration, with the following exceptions:

  Patients with any malignancy treated with curative intent and the malignancy has been in remission without treatment for >5 years prior to the first drug administration are eligible.

  Patients with curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix at any time prior to the first drug administration, with no evidence of recurrence, are eligible.

  Patients with low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to the first drug administration are eligible.
- History of myelodysplastic syndrome with Revised International Prognostic Scoring System (IPSS-R) prognostic risk categories of intermediate, high and very high
- History of hypersensitivity, allergic, or anaphylactic reactions to any ingredient contained in crovalimab or eculizumab, including hypersensitivity to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product
- Pregnant or breastfeeding, or intending to become pregnant during the study, within 46 weeks (approximately 10.5 months) after the final dose of crovalimab, or 3 months after final dose of eculizumab (or longer if required by the local product label, e.g., 5 months after the final dose of eculizumab in the United Kingdom and the European Union according to the SmPC)

  Female patients of childbearing potential must have a negative serum pregnancy test result within 28 days prior to initiation of study drug.
- Participation in another interventional treatment study with an investigational agent or use of any experimental therapy within 28 days of screening or within 5 half-lives of that investigational product, whichever is greater
- Substance abuse within 12 months prior to screening, in the investigator's judgment
- Concurrent disease, treatment, procedure or surgery, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose any additional risk for the patient, or would, in the opinion of the investigator, preclude the patient's safe participation in and completion of the study
- Splenectomy ≤6 months prior to screening
- Positive for hepatitis B surface antigen (HBsAg) at screening
- Positive for hepatitis C virus (HCV) antibody at screening

  Patients who are seropositive for HCV but without detectable HCV RNA are eligible.
- History of or ongoing cryoglobulinemia at screening

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

PNH patients ≥ 18 years old who have never received complement inhibitor treatment prior to study entry will be randomized in a 2:1 ratio to receive either crovalimab or eculizumab. A central randomization procedure will be used for all patients that fulfill the entry criteria at screening. A block-based randomization method will be used, stratified by the most recent LDH value (≥ 2 to≤ 4 × ULN, and > 4 × ULN) and by the transfusion history (0, > 0 to ≤ 6, and > 6 pRBC units administered within 6 months prior to randomization). The proposed randomization method is designed to balance treatment group assignment within the prognostic stratification factors.

All patients in the descriptive analysis arm will receive crovalimab.

After written informed consent has been obtained and eligibility has been established, the study site will enter demographic and baseline characteristics in the interactive voice or web-based response system (IxRS). For those patients who are eligible for enrollment, the study site will obtain the patient's identification number and treatment assignment from the IxRS.

Patients should be screened within 28 days prior to the first drug administration; otherwise, patients must be re-screened to determine if they continue to meet the inclusion and exclusion criteria. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. If a patient has previously been randomized or assigned to a treatment in this study, they cannot be re-screened.

4.2.2 Blinding

The study will not be blinded to patients and investigators. In order to maximize the integrity of the study, the Sponsor will not have access to aggregated data by treatment until the time of the primary analysis.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are crovalimab and eculizumab. Appendix 6 identifies all IMPs and non-IMPs for this study.

Patients should receive their first dose of study drug on Week 1 Day 1, which should be no longer than 1 calendar day after randomization/enrollment.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Crovalimab for IV Infusion and SC Administration

Crovalimab will be supplied by the Sponsor as a single-use vial formulation that is suitable for IV or SC administration. For information on the formulation and handling of crovalimab, see the pharmacy manual and the Crovalimab Investigator's Brochure.

Each crovalimab vial will contain an extractable volume of 1 mL (170 mg [nominal]) crovalimab or an extractable volume of 2 mL (340 mg [nominal]) crovalimab.

For IV infusion, crovalimab solution for infusion is diluted in 0.9% (w/v) sodium chloride solution prior to administration.

For SC administration, crovalimab solution for injection is used undiluted. In order to minimize the number of SC injections for patients, the administration per single injection of up to 2 mL drug product solution is permitted. Considerations for vial pooling are as follows:

- The 1 mL (170 mg) configuration will require combining of crovalimab drug product solution (vial pooling) from two 1-mL vials into a single syringe, as described in the Instruction for use.
- The 2 mL (340 mg) configuration will not require the vial-pooling step. The Instruction for Use will be adapted accordingly.

4.3.1.2 Eculizumab

Eculizumab will be provided by the Sponsor to investigator sites as an IMP for IV infusion. For information on the formulation, packaging, and handling of eculizumab, see the local prescribing information for eculizumab or, if treated in a country without access to commercial eculizumab, information in the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The study treatments are summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing and any dose modification) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12. Crovalimab may be administered within ±2 days of the scheduled dose, except the Week 1 Day 1 and Week 1 Day 2 doses (Section 4.3.2.1), which should be administered on the scheduled day. Eculizumab may be administered within ± 2 days of the scheduled dose, except for the doses administered in the first 4 weeks, which should be administered on the scheduled day.

Guidelines for discontinuation for patients who experience adverse events are provided in Section 5.1.3.

4.3.2.1 Crovalimab

Crovalimab will be administered as described in Table 1.

Table 1 Weight-Based Tiered Crovalimab Dosing Schedule

Body Weight	Crovalimab Loading Doses (Weeks 1–4)	Crovalimab Maintenance Doses (Week 5 and Q4W thereafter)
≥40 kg to <100 kg	Week 1 Day 1: 1000 mg IV Day 2: 340 mg SC Weeks 2, 3 and 4 340 mg SC QW	680 mg SC
≥100 kg	Week 1 Day 1: 1500 mg IV Day 2: 340 mg SC Weeks 2, 3 and 4 340 mg SC QW	1020 mg SC

QW = every week; Q4W = every 4 weeks.

For the IV infusion on Week 1 Day 1, crovalimab solution should be diluted in 0.9% (w/v) sodium chloride solution prior to administration. A 0.2 μm in-line filter must be used with the infusion set during administration. For those patients receiving an initial IV loading dose of 1000 mg, the infusion will be delivered over 60 (±10) minutes. For those patients receiving an initial IV loading dose of 1500 mg, the infusion will be delivered over 90±10 minutes. Patients should be observed by a health care professional during the IV infusion and for 60 minutes following the completion of IV infusion.

The first five SC doses (Day 2 of Week 1, and Weeks 2, 3, 4, and 5) must be administered in a monitored setting, such as an infusion center, clinic, or hospital. For the first three SC doses (Day 2 of Week 1, and Week 2 and Week 3), patients should be observed by a health care professional for 60 minutes following the drug administration.

For all patients, weight will be assessed at screening, at Weeks 13, 25, 33, 41, and 49, and every 12 weeks thereafter. Dose modification is only required if the patient's body weight changes by 10% or more (compared with screening or the visit when the latest dose modification occurred, whichever is later), to exceed or become equal to 100 kg or to fall below 100 kg during the course of therapy.

Patients with two or more qualifying intravascular hemolysis events that occur in 24 weeks without an identifiable trigger (such as an infectious trigger) and patients with sustained intravascular hemolysis also occurring without an identifiable trigger may be considered for an increased maintenance dose in consultation with the Medical Monitor (Section 5.1.3.1).

If a dose of crovalimab is missed, administer as soon as possible and then resume usual doing schedule. Do not administer two doses on the same day to make up for missing

doses. Resuming treatment after longer than 28 days of interruption should be done in consultation with the Medical Monitor.

SC injection of crovalimab must be performed only in the abdomen for the first 24 weeks of treatment with crovalimab. Alternative sites of injections (thigh or arm) are permitted after the first 24 weeks of treatment with crovalimab after adequate training and supervision as described in Patient Selection of Alternative Injection Sites.

Training for Self-Administration

The first five SC doses (Day 2 of Week 1, and Weeks 2, 3, 4, and 5) must be administered in a monitored setting, such as an infusion center, clinic, or hospital. Over the course of the first five SC doses, patients and/or caregiver(s) will be trained in SC administration of crovalimab by a health care provider (HCP). The HCP will explain the process used for SC injection, facilitated by Instructions for Use written specifically for crovalimab. Through this process under supervision, the patient and/or caregiver(s) will gain proficiency in the correct and safe self-administration of SC crovalimab. The HCP is to inform the patient/caregiver of the dose to be administered and dosing frequency. Note that during the course of the study, should the patient's body weight change to affect the dose, the new dose to be administered must be communicated to the patient/caregiver(s).

Crovalimab is intended to be self-administered (for patients ≥12 years old) as an SC injection Q4W, after in-clinic training and supervised self-administration. Initial SC administrations should be performed by the patient and/or caregiver(s) in a monitored setting while being observed by an HCP prior to starting self-administration. At that time, the HCP will provide training and evaluate the self-injection capability of each patient and/or caregiver(s). Self-injection by the patient (for patents ≥12 years old) or injection by the caregiver(s) will be allowed only once the HCP certifies that adequate proficiency was achieved. Starting at Week 9, SC injections may be self-administered by the patient (for patients ≥12 years old) or caregiver(s) if the HCP has confirmed proficiency. Additional training and guidance by HCP will be available to each patient and/or caregiver(s), at the discretion of the patient or the investigator. For patients <12 years *of age*, SC administrations should be performed by a caregiver(s). Patients have the option to come to the clinic for treatment administration, if *they* prefer.

Patient and/or caregiver(s) compliance with self-administration will be assessed in two ways during the study: 1) patients and/or caregiver will record self-administered doses in a patient diary and will bring this diary to each clinic visit as a record of self-administration and 2) patients and/or caregivers will bring used drug vials in their boxes (including the labels) to each clinic visit for verification of use.

Patient Selection of Alternative Injection Sites

Following completion of at least 24 weeks of crovalimab SC treatment in the abdomen as described in the Instructions for Use, patients may choose to administer crovalimab SC in either the posterolateral aspect of the upper arm or the anterior thigh. As per the Training for Self-Administration section, patients and/or caregivers will gain proficiency in the correct and safe administration of crovalimab to the selected alternative injection site(s).

If a patient chooses an alternative injection site in the arm or thigh (following at least 24 weeks of administration in the abdomen), the patient and/or caregiver should perform at least six consecutive injections (i.e., 24 weeks) in this new chosen alternative injection site. This is to ensure that steady state concentrations are achieved (three half-lives) for the new injection site.

> *For the first administration in the new chosen alternative injection site, the patient and/or caregiver must receive in-clinic training and HCP supervision.*
>
> *For subsequent administrations in the chosen alternative injection site, patients and/or caregivers may choose to perform the injections without supervision. Unsupervised self-injection or injection by the patient and/or caregiver should only occur after proficiency has been achieved per investigator's assessment.*
>
> *If there is a need to change to an alternative injection site or return to abdominal injection before six injections, this should be discussed with the Medical Monitor.*

After six consecutive injections in the chosen alternative site of injection, the patient (and/or caregiver, as applicable) can:

a) Continue to inject in the alternative site of injection, or

b) Choose to inject in the abdomen (i.e., the original site of injection), or

c) Choose to use another alternative injection site

> *For any new chosen alternative injection site, at least six consecutive injections should be performed by the patient and/or caregiver. In-clinic training and HCP supervision must be provided for the first injection.*

For example, if a patient chooses to switch from administration of crovalimab SC in the abdomen to administration in the thigh at week 25, they will continue administration in the thigh for six consecutive injections (24 weeks). After six administrations of crovalimab SC in the thigh, they may continue with administration in the thigh, return to administration in the abdomen, or choose to switch to administration in the arm. If they choose to switch to SC injection in the arm, they should perform at least six consecutive injections in the arm.

Patients and/or caregivers may come to the clinic for HCP administration or HCP-supervised administration of the injection at any time. Additional training, guidance, and supervision may be provided by the HCP and will be made available to patients during the initial six injections using the alternative injection site as well as on an ongoing basis. Regular review of injection technique should be done at the on-site visit where the patient attends in-person assessments (see Appendix 1 as per the Schedule of Assessments.

Under certain circumstances, crovalimab, which is required by the patient for continued study participation, could be shipped directly to the patient. Circumstances that may necessitate shipments to the patient include, but are not limited to: home visits due to the COVID-19 pandemic, reduction of patient burden *and/or* obligation in attending study site(s) for the sole purpose of drug administration, or to enable mobile nursing (MN) visits to the patient's home or other designated convenient location.

The schedule of activities is provided in Appendix 1.

4.3.2.2 Eculizumab

Eculizumab dosing will follow the description in the local prescribing information or, if the patient is enrolled in a country without access to commercial eculizumab, in the pharmacy manual. Patients randomized to eculizumab will receive induction doses of 600 mg on Days 1, 8, 15, and 22, followed by maintenance doses of 900 mg on Day 29 and Q2W thereafter.

No eculizumab dose modifications are permitted during the study.

Switching from Eculizumab to Crovalimab after 24 Weeks of Treatment

To obtain additional efficacy and safety data on crovalimab, patients who are randomized to eculizumab will have the opportunity to switch to crovalimab once they have completed 24 weeks of treatment with eculizumab (i.e., the last dose of eculizumab will have been received at the Week 23 visit). The first crovalimab dose will be administered at the visit when the next scheduled administration of eculizumab would have occurred (i.e., Week 25 visit). In case a patient is unable to switch at the planned Week 25 visit, the patient should continue on the same eculizumab dosing schedule and switch later. Continuation of eculizumab beyond Week 29 should be discussed with the Medical Monitor. Patients who switch from eculizumab will follow the same crovalimab dosing and schedule as patients randomized or assigned to crovalimab, starting with an initial IV loading dose, followed by four weekly SC doses on Weeks 1-4 and maintenance doses Q4W starting on Week 5 (see Section 4.3.2.1 and Appendix 1 for details).

4.3.3 Rescue Dosing

4.3.3.1 Crovalimab IV

If a patient who receives crovalimab experiences signs and symptoms of his or her underlying PNH, such as BTH, which may be due to an acute event such as acute illness, trauma, or surgery, one or more additional IV doses of crovalimab may be administered based on investigator assessment. Prior to this IV dose, unscheduled laboratory assessments (e.g., LDH, PK, ADA, biomarker [refer to Section 4.5.8 and Appendix 1] and other appropriate clinical investigations) should be done to further characterize the BTH and evaluate the underlying cause, unless samples were already collected within 24 hours of the IV rescue dose. The recommended dose to be administered is crovalimab IV 340 mg (regardless of body weight) to be infused over 30 minutes.

The investigator should inform the Sponsor within 24 hours of the time of the decision to administer a rescue IV dose and record this additional dose on the eCRF. For situations in which a patient requires more than one additional dose in less than 1 month, the investigator needs to justify the need with the Sponsor before initiation of another dose.

Crovalimab rescue doses may only be used for patients currently receiving crovalimab treatment.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice (see Section 4.4.1).

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Continued Access to Crovalimab

The Sponsor will offer continued access to Roche IMP (crovalimab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (crovalimab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP (crovalimab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for PNH
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for PNH
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from the first screening visit prior to initiation of study drug until 46 weeks (approximately 10.5 months) after the final dose of crovalimab. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1)
- Immunosuppressant therapy
- Corticosteroids
- Iron supplements
- Folic acid

Patients may receive other concomitant medication which must be recorded on the Concomitant Medication eCRF.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to CYP Enzymes

To date, no PD drug–drug interaction studies have been conducted.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies (such as traditional Chinese medicine) is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days (or 5 half-lives) prior to initiation of study treatment and during study treatment.
- Other complement inhibitors (except for eculizumab, as discussed below)

The use of eculizumab is prohibited for patients randomized or enrolled to crovalimab; conversely, the use of crovalimab is prohibited for patients randomized to eculizumab.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 . All activities should be performed and documented for each patient.

At applicable sites, certain study assessments and study drug administration may be performed by a MN professional at the patient's home or another suitable location, to improve access and convenience for patients participating in the study. The Sponsor will select a health care company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a

patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional.

At the Week 46 safety follow-up telephone call, female patients of childbearing potential will independently conduct a home pregnancy study assessment within two days of the scheduled call, the results of which will be reported during the call (see Appendix 1).

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Patients under 18 years of age will sign an Assent Form, and their parent or legally authorized representative(s) will sign an Informed Consent Form.

All screening evaluations must be completed within 28 days prior to the first dose and reviewed to confirm that patients meet all eligibility criteria before enrollment and randomization. If re-screening is required, then viral testing from the initial screening may be acceptable for screening assessment if performed ≤60 days prior to the first drug administration. The investigator will maintain a detailed record of all patients screened and document eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, immunization history, and use of alcohol and drugs of abuse, will be recorded at screening. PNH history, including date of diagnosis and clone size should be recorded, as well as details of pRBC transfusions performed within the past 12 months prior to screening.

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from the first screening visit prior to initiation of study drug until 46 weeks (approximately 10.5 months) after the final dose of crovalimab will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and medical conditions should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. For all patients, weight will be measured at screening, at Weeks 13, 25, 33, 41, and 49, and every 12 weeks thereafter. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Special focus should be on signs and symptoms of infections and signs of Type III hypersensitivity reactions as detailed in the Crovalimab Investigator's Brochure or eculizumab local prescribing information.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Immunizations

Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH, may experience increased signs and symptoms of their underlying disease, such as hemolysis. Patients should be closely monitored for disease symptoms after receiving vaccination.

4.5.5.1 *Neisseria meningitidis*, *Haemophilus influenzae* Type B, and *Streptococcus pneumoniae* Vaccinations

Vaccination against *Neisseria meningitidis* serotypes A, C, W, and Y must be administered <3 years prior to initiation of study treatment; **or**, if not previously done, vaccination must be administered no later than one week after the first drug administration. Vaccination against serotype B should be administered in accordance with the most current local guidelines or SOC, as applicable in patients with complement deficiency. Vaccination currency with vaccination against serotypes A, C, W, Y and B should be maintained throughout the study in accordance with most current local guidelines or SOC as applicable in patients with complement deficiency. In the absence of clear local guidelines for *Neisseria meningitidis*, the Advisory Committee on Immunization Practices 2020 Guidelines are recommended (Mbaeyi et al. 2020).
If vaccination is completed <2 weeks prior to initiation or after the start of study treatment, appropriate antibiotic prophylaxis must be maintained from first study drug administration, continuing for at least 2 weeks after completion of vaccination or

according to local SOC as applicable in patients with complement deficiency, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to the first dose of study drug.

Haemophilus influenzae type B and *Streptococcus pneumoniae* vaccinations should be done according to national vaccination recommendations (e.g., Advisory Committee on Immunization Practices guidelines). If not previously administered or no longer current, vaccination should be completed no later than 1 week after the first study drug administration. If vaccination is completed < 2 weeks prior to initiation or after the start of study treatment, appropriate antibiotic prophylaxis must be maintained from first study drug administration, continuing for at least 2 weeks after completion of vaccination or according to local SOC, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to enrollment.

4.5.5.2 Other Vaccinations

Any other vaccines (with the exception of vaccines discussed in Section 4.5.5.1) should not be administered on the same day as a crovalimab administration but, ideally, at a time point between Day +3 after a maintenance dose and Day –3 before the next maintenance dose administration. Live vaccinations should be discussed with the Medical Monitor.

Vaccinations against SARS-CoV-2 (including locally approved vaccines) are permissible during the course of the study. The administration of the vaccine against SARS-CoV-2 should ideally follow the schedule recommended above for other vaccines.

4.5.6 Breakthrough Hemolysis

Monitoring of BTH will occur on an ongoing basis during the study. Investigators will document symptoms of BTH and provide the local LDH, potassium, hemoglobin, total and direct bilirubin results, once available, on the eCRF.

In addition, as soon as possible, blood samples will have to be drawn for central testing: LDH, potassium, free hemoglobin, haptoglobin, pharmacokinetics, ADA, and biomarkers. If blood transfusions are required, the number of units of pRBCs will be also documented in the eCRF.

4.5.7 Transfusions

A pRBC transfusion can be administered when a patient meets either of the following criteria:

- Hemoglobin value ≤9 g/dL, with signs and symptoms of sufficient severity to warrant a transfusion per the clinical judgment of the investigator
- Hemoglobin value ≤7 g/dL, regardless of presence of clinical signs or symptoms

The clinical signs and symptoms of anemia that may warrant a transfusion include angina, syncope, lightheadedness, confusion, severe or worsening shortness of breath, severe or worsening fatigue, stroke, transient ischemic attack, or new or worsening heart failure.

If a patient meets either of the transfusion criteria above, the investigator will determine the appropriate number of units of pRBCs to be administered. It is recommended that the transfusion be administered within 48 hours of the hemoglobin determination precipitating the transfusion.

If there is a compelling need to deviate from these transfusion guidelines, the Medical Monitor should be consulted before the transfusion is administered.

For transfusions during the screening period and during the study, the signs and symptoms of anemia associated with a patient's need for transfusion, the hemoglobin results, the administration of the transfusion, and the number of units transfused should all be documented on the eCRF.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Laboratory assessments for LDH, hematology, chemistry (including potassium), coagulation, urinalysis, biomarker, and PK assessments will be taken as specified in the schedule of activities (Appendix 1). Refer to the laboratory manual for additional details on laboratory assessments and sample handling. On days of study drug administration, laboratory samples should be drawn before the administration of the study drug.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, reticulocytes absolute count (percentage count may be reported if the absolute count is not available), and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered SOC for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, and LDH
- Screening PNH clone size
- Coagulation: aPTT and PT/INR

- LDH levels

  LDH sample should also be taken for unplanned events, such as BTH, or for other unforeseen events as clinically appropriate.

  If unscheduled LDH measurements are taken for determination of sustained intravascular hemolysis (see Section 5.1.3.1), they must be recorded on the eCRF.
- Hepatitis B virus (HBV) serology: HBsAg at screening
- HCV serology: HCV antibody and, if HCV antibody test is positive, then HCV RNA (at screening)
- Pregnancy test (urine and/or serum)

  All female patients of childbearing potential will have a serum pregnancy test at screening. Either urine or serum pregnancy tests will be performed at specified subsequent visits. Additionally, at the end of the study, a urine pregnancy test will be performed by the patient no more than 2 days before the 46-week (approximately 10.5 months) safety telephone call. The patient should report the result of the pregnancy test during the telephone call. If a urine pregnancy test is positive, including the home urine pregnancy test at week 46 of the safety follow-up, it must be confirmed by a serum pregnancy test.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood)

  If there is a clinically significant positive result (i.e., confirmed by a positive repeat sample), urine will be sent to the laboratory for microscopic examination and culture (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) unless there is a known explanation for the positive dipstick result (e.g., menses), which should be recorded.

  For patients randomized to eculizumab who switch to crovalimab after completing 24 weeks of treatment, during the first 10 weeks on crovalimab, a urine sample should be sent to the laboratory for microscopy, urine protein, urine creatinine, and urine micro-albumin. No prior dipstick test is needed.

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum samples for measurement of LDH levels and potassium levels
- Blood samples for measurement of free hemoglobin and haptoglobin levels
- Blood samples for PNH clone size for all post-screening measurements
- Serum ADA samples for crovalimab immunogenicity analysis
- Serum samples for crovalimab PK analysis
- Serum samples for eculizumab PK analysis
- Serum samples for DTDC (only for patients randomized to eculizumab after they switch to crovalimab)

- Plasma, serum, and blood samples for exploratory research on biomarkers (including PD biomarkers)

For the pediatric population, assessments that require blood draws should be monitored closely to ensure that institutional mandates regarding total sample blood volumes are followed. In situations where no institutional guidance is available, the following limits should be used and have been included in the design of the sampling program: No more than 1% of the total blood volume should be taken at one time and no more than 3% of the total blood volume should be taken over a 30-day period. Refer to the laboratory manual for detailed blood sampling guidelines.

Exploratory biomarker research may include, but will not be limited to, PNH clone size, markers from the complement system, and markers for intra- and extra-vascular hemolysis (e.g., complement components C3, C4, C3d on RBCs, and sC5b 9 complex), as well as markers of endothelial cell activation and markers from the coagulation system (e.g., vWF, P-selectin, D-dimer, thrombin-anti-thrombin complexes, thrombin generation). These assessments will be done if the local regulations permit it. A mandatory blood sample for clinical genotyping will be collected at predose on Week 1 Day 1 (see Appendix 1). From the DNA obtained from blood, genes involved or linked to the innate and adaptive immune response (e.g., complement factors) will be analyzed by a targeted next generation sequencing approach. The aim is to understand whether polymorphisms in C5 and other genes that are part of the immune pathways could influence or alter treatment response. Human leukocyte antigen genotype may also be determined.

If the sample is missed on Week 1 Day 1, it can be collected at any other scheduled visit. Only one clinical genotyping sample is required per patient. If the patient gives consent, the remainder of the clinical genotyping sample (blood) and any derivatives thereof (e.g., DNA) will be stored under the Research Biosample Repository (RBR) policy (see Section 4.5.11, otherwise the remainder will be destroyed.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed no later than 5 years after the completion of the final Clinical Study Report.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.9 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) with the exception of PRO assessments, and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected through use of Fridericia's formula (QTcF) based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular timepoint the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. SOC treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.6.1. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.10 Patient-Reported Outcomes

PRO instruments will be completed to assess the treatment benefit of crovalimab in comparison with eculizumab. In addition, PRO instruments (described in Section 4.5.10.2) will enable the capture of each patient's direct experience with crovalimab.

PRO data will be collected through use of the following instruments:

- For adult patients (aged ≥18 years): FACIT-Fatigue Scale, EORTC QLQ-C30 (selected scales), EORTC Item Library (selected symptom items), TSQM-9, Patient Preference Questionnaire, QLQ-AA/PNH, and PGIS
- For pediatric patients (aged 8–17 years): PedsQL MFS and the PedsQL Core (Physical Functioning scale)
- For patients aged ≥ 12 years: EQ-5D-5L

4.5.10.1 Data Collection Methods for Patient-Reported Outcomes

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). At the clinic visits, instruments will be administered before the patient receives any information on disease status and prior to the administration of study treatment. Instruments should be administered prior to the performance of non-PRO assessments whenever possible.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in pre-printed paper booklets to enable the instrument to be administered at each specified timepoint. The booklets will be labeled with the timepoint of administration. Following completion, data will be entered into the study database by site personnel.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be about 10 minutes at each specified visit to complete them all.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

4.5.10.2 Description of Patient-Reported Outcome Instruments

FACIT-Fatigue

The FACIT-Fatigue (Version 4) is a validated, reliable self-report measure for use in a variety of conditions, including anemia (Yellen et al. 1997; Lai et al. 2011; Cella et al. 2005; Acaster et al. 2015). Recent content validation research supports its use in patients with PNH finding it is well understood and comprehensively covers PNH-related fatigue (Weitz et al. 2013). The FACIT-Fatigue consists of 13 items that assess fatigue using a 7-day recall period. Items are scored on a response scale that ranges from 0 ("not at all) to 4 ("very much so"). Relevant items are reverse scored, and all items are summed to create a total score, with a higher score indicative of better functioning (i.e., less fatigue). This instrument will be administered to adult patients only.

EORTC QLQ-C30

The EORTC QLQ-C30 (Version 3) is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999). Although the measure was originally developed for use in patients undergoing cancer treatment, recent content validation research supports its use in patients with PNH (Weitz et al. 2013). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), Global Health Status and QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptom items are scored on a 4-point scale that ranges from "not at all" to "very much," and the Global Health Status/QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." Higher scores indicate higher response levels (i.e., higher health-related QoL, higher symptom severity). This measure will be administered to adult patients only. Patients will complete a truncated version of the measure (EORTC IL17) that includes only the Physical Functioning, Role Functioning, and Global Health Status/QoL scales.

EORTC Item Library: PNH Symptoms

The EORTC Item Library is a database of items used in fully and partially validated EORTC QoL questionnaires. Eight items from the library will be used to assess disease-related symptoms that are relevant to patients with PNH that are not sufficiently covered in the other PRO measures (EORTC IL40). Selected symptoms include headache, dyspnea at rest and upon exertion, dysphagia, abdominal pain, chest pain, and erectile dysfunction (Weitz et al. 2013; Schrezenmeier et al. 2014; Yenerel et al. 2017). All items are scored on a 4-point scale that ranges from "not at all" to "very

much," with higher scores indicative of higher symptom severity. All symptom items will be scored individually unless they comprise a scale (i.e., dyspnea). This measure will be administered to adult patients only.

TSQM-9

The TSQM-9 is an abbreviated, validated version of the TSQM (v1.4) that includes 9-items to assess perceived effectiveness (3 items), convenience of medication (3 items), and global satisfaction with medication (3 items) (Atkinson et al. 2004; Bharmal et al. 2009). The items are scored into three respective domains that range from 0 to 100, with higher scores representing higher satisfaction. This instrument will be administered to adult patients only.

PedsQL Core

The PedsQL Core (Version 4) is a valid, reliable measure for assessing HRQoL in healthy children and adolescents, and those with acute or chronic health conditions (Varni et al. 2001, 2007). Self-report versions are available for children and adolescents that contain developmentally appropriate language for defined age groups (i.e., 5–7, 8–12, 13–17 years). This version contains 23 items that are scored into four respective domains: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). Physical and psychosocial health summary scores, as well as an overall total score, can be created by further combining domains. Domain and total scores are converted to a 0–100 scale, with higher scores indicative of better functioning. For this study, only the Physical Functioning scale of the self-report version with a 1-week recall period (i.e., acute version) will be used for patients aged 8–17 years.

PedsQL MFS

The PedsQL MFS is a valid, reliable measure for assessing fatigue in healthy children and adolescents, and those with a range of acute and chronic health conditions (Varni et al. 2002, 2004, 2009, 2013; Panepinto et al. 2014). Self-report versions are available for children and adolescents that contain developmentally appropriate language for defined age groups (i.e., 5–7, 8–12, 13–17 years). This version contains 18 items that are scored into three respective domains: General Fatigue (6 items), Sleep/Rest Fatigue (6 items), and Cognitive Fatigue (6 items). Domains can be further combined into an overall total fatigue score. Domain and total scores are converted to a 0–100 scale, with higher scores indicative of lower fatigue. For this study, the self-report version with a 1-week recall period (i.e., acute version) will be used for patients aged 8–17 years.

Patient Preference Questionnaire

The patient preference questionnaire is a two-item measure of treatment preference developed by the Sponsor. Patients are asked to indicate their preference for IV eculizumab or SC crovalimab and indicate the reasons for their preference (refer to the

patient questionnaire booklet for a copy of the Patient Preference Questionnaire). This instrument will be administered to patients aged ≥18 years randomized to eculizumab who switch to crovalimab (Arm B).

EQ-5D-5L

The EQ-5D-5L, is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.
This instrument will be administered to patients aged ≥12 years.

Quality of Life Questionnaire – Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria

The QLQ-AA/PNH is a disease-specific measure for PNH patients that is under development (Groth et al. 2017). The measure has been content validated in PNH patients (Niedeggen et al. 2019) but to date lacks psychometric validation evidence. It consists of 54 questions that assess ten aspects of HRQoL (fatigue, other symptoms, infections, physical functioning, role functioning, emotional functioning, body image, stigmatization, social support, and fear of progression/illness intrusiveness). The first 52 items use a 14-day recall period, whereas the last two items use a 6-month recall period. All items are scored on a 4-point scale that ranges from “not at all” to “very much.” This measure will be administered to adult patients if available in the local language, only for the purpose of exploring its measurement characteristics in an investigational setting.

Patient Global Impression of Severity

The PGIS is a one-item global rating measure of perceived symptom severity. Patients will be asked “Overall, how would you rate your Paroxysmal Nocturnal Hemoglobinuria symptoms during the past 14 days?” on a 0-10 scale from “no symptoms” to “as bad as you can imagine.” This measure will be administered to adult patients if available in the local language, only to support the evaluation of the measurement characteristics of the QLQ-AA/PNH.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR

samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

As permitted by the local regulations, samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to crovalimab, diseases, or drug safety:

- Leftover blood from the clinical genotyping sample, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)
- Leftover blood, serum, and plasma samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)
- Leftover tissue samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides) from medically indicated procedures (e.g., skin or kidney biopsies) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new

therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples 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.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be

required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR patient's death or loss of competence, the patient's samples and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Symptomatic deterioration attributed to disease progression, if judged by the investigator that continuation with treatment is not in the patient's best interest

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Discontinuation from crovalimab: All patients who discontinue from crovalimab treatment while on the study will return for a safety follow-up visit 24 weeks, and a safety telephone call 46 weeks (approximately 10.5 months), after treatment discontinuation. Patients who discontinue crovalimab and switch to treatment with another C5 inhibitor should remain in safety follow-up. See detailed monitoring guidance in Section 5.1.1 and Appendix 2.

Discontinuation from eculizumab: Patients who discontinue from study eculizumab treatment will return for a safety follow-up visit 10 weeks after treatment discontinuation date.

Patients who discontinue crovalimab or eculizumab without switching to another complement inhibitor should be monitored for signs and symptoms of serious intravascular hemolysis for at least 20 weeks (if discontinuing crovalimab) or for at least 8 weeks (if discontinuing eculizumab) (see details in Sections 5.1.1.6 and 5.1.2.5).

Signs and symptoms of serious hemolysis occurring after treatment discontinuation and until completion of the safety follow-up visit should be reported as adverse events in the eCRF.

Pregnancy and study treatment continuation: If a female patient becomes pregnant, study treatment will continue only if it is in the best interest of the patient after an assessment of the risks and benefits conducted by the investigator. For this decision, the investigator must consider the potential risks related to the study treatment, the risks related to discontinuing treatment, and the risks related to switching to another C5-inhibitor (e.g., DTDC-mediated Type III hypersensitivity reactions) in a pregnant patient with PNH. The investigator should counsel the patient regarding the risks to the

pregnancy and the possible effects on the fetus. If the investigator decides to continue treatment, he or she must consult with the Medical Monitor before proceeding.

For all patients, the day of the safety follow-up visit represents study discontinuation date.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Crovalimab is not approved by any health authority, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with crovalimab in the ongoing Study BP39144 as well as on the known class effects of available marketed C5 inhibitors. The anticipated important safety risks for crovalimab, as well as measures intended to avoid or minimize such toxicities, are outlined below. Please refer to the Crovalimab Investigator's Brochure for a complete summary of safety information.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria (see Section 4.1.1 and Section 4.1.2, respectively) and close monitoring (as indicated below and in Section 5.1). Details regarding safety reporting for this study are provided in Section 5.4. An iDMC has also been incorporated into the study design to periodically review aggregate safety data (see Section 3.1).

All adverse events and serious adverse events will be recorded during the study and for up to 46 weeks (approximately 10.5 months) after the last dose of crovalimab and 10 weeks after the last dose of eculizumab. After this period, investigators should report serious adverse events and adverse events of special interest that are believed to be related to prior treatment with crovalimab.

5.1.1 Risks Associated with Crovalimab

5.1.1.1 Meningococcal Infection

Crovalimab blocks terminal complement activation; therefore, based on the class effect, patients will likely have increased susceptibility to infections, especially with encapsulated bacteria.

Life-threatening and fatal meningococcal infections have occurred in patients treated with eculizumab, (Soliris SmPC; Soliris U.S. Prescribing Information [USPI]). Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

Patients in clinical studies of crovalimab will receive meningococcal vaccinations as described in Section 4.5.5. Vaccination may not be sufficient to prevent meningococcal infection.

Closely monitor patients for early signs and symptoms of meningococcal infection, and evaluate patients immediately if an infection is suspected and treat with antibiotics if necessary. Monitoring of patients for meningococcal infections should be continued for at least 46 weeks (approximately 10.5 months) after the last dose of crovalimab. Discuss continuation of crovalimab with Medical Monitor for patients who are undergoing treatment for serious meningococcal infections.

All patients should be counseled about the risks and common signs and symptoms of meningococcal infections as well as antibiotics therapy.

Guidelines for the management of meningococcal infections are provided in Table 2.

5.1.1.2 Type III Hypersensitivity Reactions Associated with Drug-Target–Drug Complex Formation

Due to the transient formation of DTDCs made of eculizumab, C5, and crovalimab, Type III hypersensitivity may occur in patients randomized to eculizumab who opt to switch to crovalimab after completing 24 weeks of treatment. Such DTDCs could also form if patients transition from crovalimab to a SOC C5 inhibitor that binds to a different epitope than crovalimab, upon discontinuation from or completion of a clinical study of crovalimab (see Section 1.2.2.1 for details). Characteristics of Type III hypersensitivity reactions associated with DTDC formation may include:

- Typical onset is delayed by a week or more after dose administration, and the reaction may persist for days to over a week
- Reactions may involve the skin, joints, and/or kidneys
- Typical signs and symptoms may include: purpura; petechial or urticarial rashes affecting the lower extremities bilaterally; arthralgia; enlarged and/or tender lymph nodes/spleen
- Histopathological finding of small vessel vasculitis and laboratory evidence of glomerulonephritis
- Type III hypersensitivity reactions are not expected to occur after the clearance period of DTDCs (see Section 1.2.2.1)

To minimize the risk for patients, monitoring guidelines are provided for patients who discontinue crovalimab and switch to other C5 inhibitors. Additionally, enhanced monitoring during study was implemented for patients who switch from eculizumab to crovalimab after completing 24 weeks of eculizumab treatment. Guidelines for the proper management of Type III hypersensitivity reactions are provided in Table 2.

Monitoring for Patients who Discontinue Crovalimab and Switch to Other C5 Inhibitors

Patients might discontinue study treatment with crovalimab and switch to treatment with a different C5 inhibitor that binds to a different epitope to crovalimab, at the discretion of

the treating physician. Such patients should remain in safety follow-up because of the potential risk of developing a DTDC-mediated Type III hypersensitivity reaction, especially within the first few weeks of switching from one C5 inhibitor to another. Blood samples for monitoring will be collected after the first administration of the C5-inhibitor, then once weekly for the first 5 weeks (Weeks 1–5), and then at Week 7 and Week 9 after switching from crovalimab to SOC C5 inhibitor (as detailed in Appendix 2).

Guidelines for the management of Type III hypersensitivity reactions are provided in Table 2.

Due to the potential risk of DTDC-mediated Type III hypersensitivity reactions, it is recommended that patients who discontinue from study and choose not to remain in safety follow-up while switching to another C5-inhibitor also be monitored by the treating physician in the same manner.

Enhanced Monitoring during the Study for Patients who Switch from Eculizumab to Crovalimab after Completing 24 Weeks of Eculizumab Treatment

Patients who are randomized to eculizumab will have the opportunity to switch to crovalimab once they have completed 24 weeks of treatment with eculizumab, if their treating physician determines it is in their best interest to do so. All such patients should be closely monitored, especially within the first few weeks of switching to crovalimab, because of the potential risk of developing a DTDC-mediated Type III hypersensitivity reaction.

- As part of the monitoring, site investigators will call patients on Week 1 Day 4 and Week 2 Day 12 (in between visits) of crovalimab treatment to assess whether any adverse events have occurred.
- Patients should be closely monitored for signs or symptoms of Type III hypersensitivity, especially skin abnormalities, including physical examinations to focus on signs and symptoms of Type III hypersensitivity. If observed, prompt treatment should be initiated per the guidelines in Table 2.
- Hypersensitivity reactions are defined as adverse events of special interest (Section 5.2.3) and have to be reported to the Sponsor in an expedited manner by the investigators (within 1 day of their occurrence).
- In case of an adverse event of Type III hypersensitivity reaction, unscheduled biomarker, PD, ADA, exploratory safety (DTDC), and PK samples are to be taken (see Appendix 1, Table 3).
- Biopsies of skin manifestations can be done, if considered clinically indicated.

Blood samples for monitoring will be collected after the first administration of crovalimab, then once weekly for the first 5 weeks (Weeks 1–5 of crovalimab administration), then Q2W through Week 9 (Weeks 7 and 9 of crovalimab administration), and then every

4 weeks through Week 25 of crovalimab administration. The following laboratory assessments will be collected and assessed locally, as detailed in Appendix 1, Table 3:

- Safety laboratory assessments (chemistry and hematology), urinalysis, vital signs/limited physical exams, adverse event reporting, monitoring for BTH and transfusions, and LDH

Guidelines for the management of Type III hypersensitivity reactions are provided in Table 2.

5.1.1.3 Other Hypersensitivity Reactions and Infusion-Related Reactions

As with any biologic, there is a risk of hypersensitivity reactions and infusion-related reactions, which can range from a mild rash to life-threatening anaphylaxis. For the IV infusion and the first five SC injections, crovalimab should be administered in a clinical environment where resuscitation equipment is available for immediate use.

Guidelines for the management of hypersensitivity and infusion-related reactions are provided in Table 2.

5.1.1.4 Injection-Site Reactions

As with any SC injections, there is a possible risk of injection-site reactions, which can range from slight irritation to possible necrosis.

Patients and caregivers should be instructed to recognize the signs and symptoms of hypersensitivity reactions and to seek immediate medical attention if the patient develops symptoms of serious allergic reactions.

Guidelines for the management of injection-site reactions are provided in Table 2.

5.1.1.5 Other Infections

Crovalimab blocks terminal complement activation. Therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria.

Guidelines for the management of infections are provided in Table 2.

5.1.1.6 Immunogenicity

Neutralizing *or clearing* antibodies may develop in crovalimab-treated patients, leading to decrease or loss of crovalimab exposure with potential impact on clinical response.

5.1.1.7 Treatment Discontinuation from Crovalimab without Switching to Another Complement Inhibitor

If patients discontinue treatment with crovalimab, without switching to another complement inhibitor, they should be monitored for at least 20 weeks for signs and symptoms of serious intravascular hemolysis (e.g., elevated LDH, sudden decrease in hemoglobin, or re-appearance of hemolysis symptoms).

Signs and symptoms of serious hemolysis occurring after treatment discontinuation and until completion of the safety follow-up visit should be recorded as adverse events in the eCRF.

5.1.2 Risks Associated with Eculizumab

5.1.2.1 Meningococcal Infection

Due to its mechanism of action, the use of eculizumab increases the patient's susceptibility to meningococcal infection (*Neisseria meningitidis*). To reduce the risk of infection, all patients must be vaccinated as per Section 4.5.5.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH, may experience increased signs and symptoms of their underlying disease, such as hemolysis. Therefore, patients should be closely monitored for disease symptoms after recommended vaccination. Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to the appropriate use of antibacterial agents.

Cases of serious or fatal meningococcal infections have been reported in eculizumab-treated patients. Sepsis is a common presentation of meningococcal infections in patients treated with eculizumab. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. Patients should be informed of these signs and symptoms and steps taken to seek medical care immediately.

5.1.2.2 Other Systemic Infections

Due to its mechanism of action, eculizumab therapy should be administered with caution to patients with active systemic infections. Patients may have increased susceptibility to infections, especially with *Neisseria* and encapsulated bacteria. Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.

Patients should be counseled to increase their awareness of potential serious infections and the signs and symptoms of them. Patients should also be counseled about gonorrhea prevention.

5.1.2.3 Infusion Reactions

Administration of eculizumab may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis), though immune system disorders within 48 hours of eculizumab administration did not differ from placebo treatment in PNH studies conducted with eculizumab. In clinical trials, no PNH patients experienced an infusion reaction that required discontinuation of eculizumab. Eculizumab administration should be interrupted in all patients experiencing severe infusion reactions and appropriate medical therapy administered.

5.1.2.4 Immunogenicity

Infrequent antibody responses have been detected in eculizumab-treated patients across all clinical studies. In PNH placebo-controlled studies, low antibody responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%). There has been no observed correlation of antibody development to clinical response or adverse events.

5.1.2.5 Treatment Discontinuation from Eculizumab without Switching to Another Complement Inhibitor

If patients discontinue treatment with eculizumab, they should be closely monitored for signs and symptoms of serious intravascular hemolysis. Serious hemolysis is identified by serum 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 or less; a hemoglobin level of $<$5g/dL or a decrease of $>$4 g/dL in 1 week or less; angina; change in mental status; a 50% increase in serum creatinine level; or thrombosis.

Monitor any patient who discontinues eculizumab for at least 8 weeks to detect serious hemolysis and other reactions. If serious hemolysis occurs after eculizumab discontinuation, consider the following procedures/treatments: blood transfusion (pRBCs), or exchange transfusion if the PNH RBCs are $>$50% of the total RBCs by flow cytometry; anticoagulation; corticosteroids; or reinstitution of eculizumab. In PNH clinical studies, 16 patients discontinued the eculizumab treatment regimen. Serious hemolysis was not observed.

5.1.3 Management of Patients Who Experience Adverse Events

For patients treated with eculizumab, guidelines from the eculizumab local prescribing information or (in countries without access to commercial eculizumab) from the pharmacy manual will be followed for management of specific adverse events related to eculizumab.

Guidelines for the management of adverse events related to crovalimab are outlined in Table 2.

5.1.3.1 Dose Modifications

Dose modification is only required if the patient's body weight changes by 10% or above to exceed or become equal to 100 kg or to fall below 100 kg during the course of therapy.

In consultation with the Medical Monitor, dosing modification may also be considered for:

- Patients with two or more qualifying intravascular hemolysis events in 24 weeks that occur without an identifiable trigger (such as an infectious episode).

  Qualifying intravascular hemolysis events are those consistent with the definition of BTH (described in Section 2.1.2) that occur within 1 week before the next maintenance dose.

- Patients with sustained intravascular hemolysis that occur without an identifiable trigger.

  Sustained intravascular hemolysis is defined as LDH ≥2 ULN measured at 3 consecutive assessments and persisting for at least 4 weeks, where each LDH ≥2 ULN measurement is accompanied by at least one sign or symptom of intravascular hemolysis (listed as part of the BTH definition in Section 2.1.2), during the maintenance phase of crovalimab treatment (Week 5 or thereafter). Local LDH measurement at unscheduled assessments may be used to determine the presence of sustained intravascular hemolysis, and must be recorded on the eCRF.

Patients for whom a dose modification is appropriate based on the criteria described above will increase their maintenance dosing regimen indefinitely, for the duration of the crovalimab treatment, as follows:

- Patients with body weight ≥40 kg to <100 kg would increase their maintenance dose from 680 mg Q4W to 1020 mg Q4W.
- Patients with body weight ≥100 kg would increase their maintenance dose from 1020 mg Q4W to 1360 mg Q4W.

Patients whose maintenance dose is increased due to experiencing two or more qualifying intravascular hemolysis events or sustained intravascular hemolysis should have additional laboratory assessments performed as follows (also see Appendix 1, Tables 1, 2 and 3):

- The patient's LDH, PK, PD, and ADA should be assessed centrally before the first administration of the increased maintenance dose and four weeks after the first administration of the increased maintenance dose.
- CBC and LDH should be assessed locally before the first administration of the increased dose, at four weeks after the first administration of the increased maintenance dose, and as clinically indicated thereafter to monitor clinical response. Locally assessed CBC and LDH should be recorded on the eCRF.

For patients with persistent sustained intravascular hemolysis after 4 weeks of treatment with the increased dose, the risks and benefits of continuing crovalimab treatment should be evaluated, in consultation with the Medical Monitor.

5.1.3.2 Treatment Interruption

There are no planned treatment interruptions of crovalimab in this study. If a dose of crovalimab is missed, administer as soon as possible and then resume the usual

dosing schedule. Do not administer two doses on the same day to make up for a missed dose. Resuming treatment after longer than 28 days of interruption should be done in consultation with the Medical Monitor.

5.1.3.3 Management Guidelines

Crovalimab (for the initial IV infusion and the first five SC administrations) should be administered in a clinical environment where resuscitation equipment is available for immediate use.

Guidelines for management of specific adverse events related to crovalimab are outlined in Table 2. Additional guidelines are provided in the subsections below.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events

Event	Action to Be Taken
Anaphylaxis	• If an anaphylactic reaction occurs, stop administration and permanently discontinue crovalimab. • Follow anaphylaxis treatment guidelines in Appendix 3.
Infusion-related reaction (IRR)	
IRR: Grade 1, 2, or 3	• The crovalimab infusion should be temporarily held until resolution of symptoms to Grade 1 or better. • Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Crovalimab may be continued at the investigator's discretion.
IRR: Grade 4	• The crovalimab infusion should be stopped and not re-initiated. Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Discontinue crovalimab.
Injection-Site Reactions	
Injection-site reaction Grade 1 or 2	• Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Crovalimab may be continued at the investigator's discretion.
Injection-site reaction Grade 3 [a] or 4	• Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Crovalimab may be continued at the investigator's discretion and in discussion with Medical Monitor for Grade 3 ISR. • Discontinue crovalimab if Grade 4 ISR occurs.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Type III Hypersensitivity Reactions (Serum Sickness [b])	
General Guideline	• Upon clinical presentation of a suspected Type III hypersensitivity reaction (initial manifestation of vasculitis, purpura, pruritus, arthralgia, etc.), treat according to severity [a].
Grade 1 or 2 signs and symptoms	• For arthralgia, administer analgesics and nonsteroidal anti-inflammatory agents. • For pruritis and rash, administer antihistamines and topical corticosteroids. • Monitor kidney function and perform urinalysis (Section 4.5.8). • Continue crovalimab.
Grade 3 signs and symptoms	• For high fever (e.g., temperature > 38.5°C [> 101.3°F]), more severe arthritis and arthralgias, or more extensive rashes, including extensive vasculitic eruptions, administer oral or IV methylprednisolone 1−2 mg/kg (or equivalent dose of other glucocorticoid). • Glucocorticoids can frequently be rapidly tapered, with a total duration of therapy of less than 1 week. However, withdrawal will occasionally result in recurrence of the symptoms, in which case glucocorticoids should be restarted and tapered more slowly. • Monitor kidney function and perform urinalysis (Section 4.5.8) • Continue crovalimab.
Grade 4 signs and symptoms	• Treat as Grade 3 reaction above • May be continued at the investigator's discretion and in discussion with the Medical Monitor.
Infections	
Meningococcal meningitis	• Treat according to standard of care. • Discuss continuation of crovalimab with Medical Monitor.
Any other infection	• Treat according to standard-of-care on a case-by-case basis, depending on signs and symptoms. • Discuss continuation of crovalimab with Medical Monitor for Grade 3 infections that persist for > 7 days. • Discuss continuation of crovalimab with Medical Monitor for any Grade 4 infection.

Other Treatment-related Toxicities Not Described Above	
Grade 1, 2, or 3	• Treat according to local practice. • Crovalimab may be continued at the investigator's discretion.
Grade 4	• Treat according to local practice. • Discontinue crovalimab.
Hy's Law	• Treat according to local practice. • Discontinue crovalimab.

[a] Grade 3 injection-site reactions defined as ulceration or necrosis; severe tissue damage; operative intervention indicated. Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.

[b] Serum sickness and serum sickness-like reactions; Wener 2018.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.2.3.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- 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 considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 5.3.5.10 for more information)
- 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., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

BTH, transfusion, anemia, or MAVE due to PNH should not be considered adverse events unless serious (see Section 5.2.2) and should be reported in the appropriate dedicated eCRF pages.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life-threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions). Adverse events of special interest for this study are as follows:

- Type III hypersensitivity reactions are described in Section 5.1.1.2.

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definitions) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of crovalimab, all adverse events will be reported until 46 weeks (approximately 10.5 months) after the final dose of crovalimab.

For patients randomized to eculizumab who decided not to switch to crovalimab after 24 weeks on study treatment eculizumab, all adverse events will be reported until 10 weeks after the final dose of eculizumab.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related and Injection-Site Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion or injection should be captured as a diagnosis (e.g., "infusion-related reaction" or "injection-site reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction or Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction or Injection Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related or injection-site reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported

adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.5,) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4). This includes death attributed to progression of PNH.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of PNH, "paroxysmal nocturnal hemoglobinuria progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Paroxysmal Nocturnal Hemoglobinuria

Medical occurrences or symptoms of deterioration that are anticipated as part of PNH should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of PNH on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of paroxysmal nocturnal hemoglobinuria").

An exception to this is events of BTH or MAVE (i.e., anemia, smooth muscle dystonia, hemoglobinuria, and thrombosis), which should not be recorded as an adverse event unless serious. These data will be captured as efficacy assessment data only on the Breakthrough Hemolysis Monitoring eCRF. If there is any uncertainty as to whether the event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2, except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4). For crovalimab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with crovalimab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements).
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements).
- Pregnancies (see Section 5.4.3 for details on reporting requirements).

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 46 weeks (approximately 10.5 months) after the final dose of crovalimab and 10 weeks after the final dose of eculizumab. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 46 weeks (approximately 10.5 months) after the final dose of crovalimab and 10 weeks after the final dose of eculizumab are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or following study drug discontinuation, within 46 weeks (approximately 10.5 months) after the final dose of crovalimab or for 3 months after the final dose of eculizumab (or longer

if required by the local product label, e.g., 5 months after the final dose of eculizumab in the United Kingdom and the European Union according to the SmPC). A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF.

Continuation on study treatment may be permitted based on investigator's clinical judgment in consultation with the Medical Monitor. The investigator should counsel the patient and discuss the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 46 weeks [approximately 10.5 months] after the final dose of crovalimab and 10 weeks after the final dose of eculizumab), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the Crovalimab Investigator's Brochure (for crovalimab) and the E.U. Summary of Product Characteristics (for eculizumab)

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is to assess non-inferiority of crovalimab compared to eculizumab, with respect to the co-primary endpoints of TA and hemolysis control (as assessed by centrally measured LDH $\leq 1.5 \times$ ULN), within the first 24 weeks of treatment period (Section 3.2).

The sample size estimation for the randomized portion of the study (Arms A and B) is based on the non-inferiority assessment of the co-primary endpoints of hemolysis control, as assessed by centrally measured LDH, and the proportion of patients who achieve TA during the efficacy period. The final target sample size corresponds to the endpoint that requires the larger number of patients, i.e., TA from baseline to Week 25. Approximately 200 adult patients will be randomly assigned in a 2:1 ratio to receive either crovalimab (n = 133) or eculizumab (n = 67), to ensure approximately 180 evaluable patients, assuming a 10% drop-out rate. This sample size will provide 80% power to demonstrate the non-inferiority of crovalimab to eculizumab with respect to TA, using a non-inferiority margin (NIM) of −20%, and one-sided Type 1 error rate of 2.5% (Table 4).

The NIM for TA was determined based on the data reported in protocol ALXN1210-PNH-301, comparing eculizumab-treated patients with untreated patients from the global PNH Registry for eculizumab-treated patients, i.e., patients treated with

eculizumab showed a benefit over untreated patients, with a difference of approximately 40% (TA proportion of 57.1% and 18.6%, respectively), after adjustment for history of transfusions 12 months prior to enrollment. Hence, a difference in proportions of −20%, the NIM, would preserve at least 50% of the control treatment effect. This NIM was also defined based on operational considerations, given the rarity of PNH. A more conservative NIM would have resulted in the estimated sample size being too large and infeasible. Lee et al. (2019) reported a proportion of patients with TA of 66.1% (95%CI: 65.9% to 74.6%) in treatment-naive patients in eculizumab.

With regard to hemolysis control, 116 patients are required in a 2:1 ratio to test the non-inferiority of crovalimab vs. eculizumab, with a non-inferiority margin of 0.2 in the OR scale, 80% power, and 1-sided test at 0.025 Type I error rate. Incidentally, a similar sample size was required to test for non-inferiority in the probability scale when the NIM is −0.2. Lee et al. (2019) also reported a proportion of LDH normalization below 1 × ULN of 49.4%. Under the assumption of LDH being log-normally distributed, the expected proportion below 1.5x ULN is 86%. The same proportion was assumed for crovalimab. The NIM in the OR scale was obtained as $1/OR^{0.5}$, where OR = 24.6 assuming 86% of patients receiving eculizumab will reach LDH ≤1.5 × ULN compared to an upper bound of the 95% CI of the proportion among placebo-treated patients of 20%. Note that both proportions are approximately twice the ones used in protocol ALXN1210-PNH-301 for LDH ≤1 × ULN), and a fraction of 0.5 of that effect is retained (Ng 2008). Assuming a 10% drop-out, the total needed sample size would be 128 patients (85 randomized to crovalimab and 43 to eculizumab). With 180 evaluable patients expected in the study, the power for this endpoint will be 94%. Hence, the joint power for both TA and LDH would be 75% if they were uncorrelated. It is likely that co-primary endpoints are correlated and hence joint power would be higher. If there were no drop-outs and all 200 patients contributed at least one LDH sample then the power for TA would be 84% and for LDH 96%.

The calculation of sample size used the functions TwoSampleProportion.NIS and RelaiveRisk.NIS from the package TrialSize v1.3 (Chow et al. 2008), R v3.5.3 (Team, 2019).

Table 4 Sample-Size Estimation for the Co-Primary Endpoints of Transfusion Avoidance and Hemolysis Control (LDH ≤1.5 × ULN)

	Crovalimab	Eculizumab	Total
Transfusion Avoidance	67%	66%	
Required N	120	60	180
N with 10% drop-out	133	67	200
Hemolysis Control	86%	86%	
Required N	77	39	116
N with 10% drop-out	85	43	128

ULN = upper limit of normal.

Note: Operating characteristics: one-sided non-inferiority testing, margin = –20%, power = 80%, Type I error rate = 0.025, drop-out = 10%, 2:1 randomization ratio.

Pediatric patients will be enrolled in the descriptive arm (Arm C) throughout the duration of the study. No target sample size is specified.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized and displayed in a CONSORT diagram. In addition, reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race, ethnicity, weight, temperature, history of pRBC transfusions (0, 1 to 6, and >6), total number of pRBC transfused, and baseline LDH category (≥2 to ≤4 × ULN and >4 × ULN) will be summarized by treatment using number of records per variable, means, standard deviations, medians, and ranges (continuous variables) or proportions (categorical variables), as appropriate.

6.4 EFFICACY ANALYSES

The analysis population for the primary and key secondary efficacy analyses to evaluate the non-inferiority of crovalimab compared with eculizumab will include all randomized patients who received at least one dose of treatment with crovalimab or eculizumab and have at least one centrally processed LDH level assessment after the first IV infusion.

For patients enrolled in the descriptive analysis arm, the analysis population for the descriptive efficacy analyses will include all patients who received at least one dose of treatment with crovalimab and have at least one central LDH level assessment after the first IV infusion.

6.4.1 Primary Estimand

The primary efficacy estimand in this study has been defined as follows:

- Population: All randomized patients in Arms A and B who have met the inclusion and exclusion criteria (Section 4.1), have received at least one dose of study drug and have at least one centrally processed LDH level assessment after the first IV infusion.
- Variables: central LDH measured at prespecified hospital visits from Week 5 to Week 25, and any transfusion event from baseline to Week 25.
- Inter-current events (ICEs):
  - TA: early withdrawal from study treatment
  - Hemolysis control:
    - Early withdrawal from study treatment
    - Dose modification due to experiencing two or more qualifying intravascular hemolysis events or sustained intravascular hemolysis
- Handling of ICEs:
  - TA: composite strategy

    Patients with data missing due to an ICE will be hypothetically assumed to have experienced an unfavorable outcome, i.e., have required transfusion in the unobserved period, assuming transfusion had not been observed prior to ICE.
  - Hemolysis control:
    - Early withdrawal from treatment: hypothetical strategy

      Any data missing due to an ICE will not be imputed for the primary analysis; rather, the generalised estimating equation (GEE) model uses all observed data in order to provide estimates for the full 24-week period.
    - Dose modification due to experiencing two or more qualifying intravascular hemolysis events or sustained intravascular hemolysis: treatment policy strategy

      Per treatment policy strategy, data collected after dose modification due to sustained or qualifying intravascular hemolysis (see Section 5.1.3.1 on dose modifications) will be included in the primary analysis.
- Population-level summary (estimate):
  - TA: the difference in proportion of TA, from baseline through Week 25, between the crovalimab and eculizumab arms
  - Hemolysis control: the odds ratio for hemolysis control between crovalimab and eculizumab arms, as assessed from Week 5 through Week 25

Additional analyses may be conducted to assess the impact of missing data. This will be described in more detail in the statistical analysis plan (SAP).

Prior to any analysis of the efficacy data, the assignment of all reasons for treatment discontinuation to the study drug related (SDR) and non-study drug related (NSDR) categories will be documented in the SAP. The Sponsor will encourage investigators to minimize withdrawals from treatment as well as withdrawal from the study. Also, the importance of providing detailed reasons for study treatment discontinuation as well as discontinuation from the study will be emphasized to the investigators to allow appropriate assignment of any intercurrent events to the SDR or NSDR category.

The Sponsor will put mechanisms in place to ensure that, as much as possible, all patients are followed and their data are collected, up to and including the Week 25 visit, regardless of adherence to treatment ("retrieved dropout" strategy).

6.4.2 Primary Efficacy Analyses

Both of the co-primary endpoints that need to be met in order to conclude non-inferiority of crovalimab to eculizumab are: proportion of patients achieving TA and hemolysis control, measured by estimated proportion of patients with LDH $\leq 1.5 \times$ ULN from baseline through Week 25.

For the primary analysis, no imputation will be made for missing values. Tracking of causes for dropping out of the study before Week 25 will allow performing sensitivity analyses such as assuming transfusion status if drop out was for treatment-related reasons and no transfusion for other dropouts. These sensitivity analyses will be described in more detail in the SAP.

6.4.2.1 Transfusion Avoidance

TA is defined as the patients who are pRBC transfusion-free and do not require transfusion per protocol-specified guidelines from baseline through Week 25.

The difference in proportion of patients with TA between crovalimab and eculizumab arms, together with its 95% CI will be calculated as a weighted combination across stratification factors of transfusion history and baseline LDH using Mantel-Haenszel weights (Agresti 2013) and the Newcombe Confidence Interval method (Yan and Su 2010). The non-inferiority hypothesis for the difference in proportions between crovalimab and eculizumab will be tested by comparing the lower limit (LL) of the 95% CI for the difference in proportions to the non-inferiority margin of −20%:

H_0:LL 95% CI Difference $\leq -20\%$

vs.

H_1:LL 95% CI Difference $> -20\%$

The null hypothesis of inferiority will be rejected if the LL of the 95% CI of the difference in proportion of TA between arms is above −20%.

6.4.2.2 Hemolysis Control

LDH will be evaluated as scheduled in Appendix 1. Measures taken from Week 5 through Week 25 correspond to period of stability in treatment-naive patients and will be used in the statistical analysis, as treatment-naive patients are expected to reach a stable LDH plateau by the end of the first month of treatment. For each patient at each visit, a binary variable will be created with the value of one, if LDH $\leq 1.5 \times$ ULN, and 0, otherwise. A GEE model will be used to estimate the adjusted log-odds ratio of LDH $\leq 1.5 \times$ ULN due to treatment. The non-inferiority hypothesis between crovalimab relative to eculizumab will be tested by comparing the LL of the 95% CI for the OR to the non-inferiority margin of 0.2 (see Section 6.1):

H_0: LL 95% CI (OR) ≤ 0.2

vs.

H_1: LL 95% CI (OR) > 0.2

The null hypothesis will be rejected if the LL of the CI is above 0.2.

6.4.3 Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- Proportion of patients with BTH from baseline through Week 25
- Proportion of patients with stabilization of hemoglobin from baseline through Week 25
- Change from baseline to Week 25 in FACIT-Fatigue

Primary and secondary analyses will be performed in a hierarchical order as defined in the SAP.

Superiority will also be tested following non-inferiority analyses, using a closed testing procedure. More details regarding the order of the hierarchy will be specified in the SAP. Due to the hierarchical testing order specified, no adjustment of the Type I error is required.

6.4.3.1 Breakthrough Hemolysis

The definition of BTH is provided in Section 1.2.2.4. BTH will be analyzed using the same methodology as TA. The non-inferiority hypothesis will be tested comparing the UL of the 95% CI for the difference with a non-inferiority margin of 20%. Non-inferiority of crovalimab compared to eculizumab will be declared if the null hypothesis of inferiority is rejected.

6.4.3.2 Hemoglobin Stabilization

The definition of hemoglobin stabilization is provided in Section 1.2.2.4. Hemoglobin stabilization will be analyzed using the same methodology as TA.

The non-inferiority hypothesis will be tested comparing the LL of the 95% CI for the difference with a non-inferiority margin of –20%. Non-inferiority of crovalimab compared to eculizumab will be declared if the null hypothesis of inferiority is rejected.

6.4.3.3 Fatigue

The change from baseline to Week 25 in FACIT-Fatigue total scores (range of 0–52) will be compared in terms of non-inferiority between crovalimab and eculizumab arms in adult patients. A linear model assuming normally distributed scores will be fitted with stratification factors (baseline LDH level and transfusion history) as factors to adjust for initial disease severity. The non-inferiority margin will be a 5-point score, where higher scores indicate less fatigue.

6.4.4 Exploratory Efficacy Analyses

All exploratory efficacy endpoints have been defined in Section 2.1.3. None of the exploratory endpoints will be formally tested. Instead, they will be described with summary statistics. Hence, no adjustments for multiplicity will be required. In addition, figures may be used to highlight treatment differences, and temporal trends. Differences between treatment arms will be reported as differences or ratios between crovalimab and eculizumab, along with 95% CIs. Details will be provided in the SAP.

For patients in the descriptive analysis arm, with the exception of FACIT-Fatigue endpoint which is intended for adults only, the exploratory efficacy endpoints (see Section 2.1.3) will also include the primary and secondary endpoints as defined in Sections 2.1.1 and 2.1.2 for the Randomized arms.

Additional exploratory efficacy analyses, including intra-patient analyses, may be conducted in patients randomized to eculizumab who switch to crovalimab after completing the primary treatment period (after 24 weeks of eculizumab treatment).

6.4.5 Handling Missing Data

Missing data will not be imputed. For the assessment of LDH, missing data will be assumed to be missing at random/completely at random. Since missing data that are missing not at random might still occur, sensitivity analyses involving multiple imputation such as pattern mixture model will be used to assess the robustness of the primary endpoint results with regards to the missing at random assumption.

The criterion of similarity between analyses using non-imputed and imputed data sets (sensitivity analyses) and details of the missing imputation procedure will be further discussed in the SAP.

It is expected that all transfusions will be recorded.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety evaluable population, defined as all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received. Data from patients switching from eculizumab to crovalimab will be summarized separately for the time period under eculizumab treatment and under crovalimab treatment. The safety evaluable population for the descriptive arm (Arm C) is defined as all pediatric patients who received at least one dose of study drug, and will be reported separately.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to scale in NCI CTCAE v5. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital signs (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

The PK analyses will be performed on the PK-evaluable population, defined as all patients who received at least one dose of study treatment.

For all patients, serum concentrations of crovalimab and eculizumab will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Non-linear mixed effects modeling will be used to analyze the dose−concentration−time data of crovalimab. Population PK parameters, such as total exposure (AUC), C_{max}, clearance, and volume of distribution will be estimated. A similar analysis may be performed to analyze the dose-concentration-time data of eculizumab. The influence of various covariates, such as age, sex, and body weight, on these parameters will be investigated graphically. Inter-patient variability and drug accumulation will be

evaluated. Additional PK analyses may be conducted as appropriate, *e.g., to investigate the effect of different injection sites*. The relationship between PK and PD, efficacy or safety endpoints may also be explored. Details and results of the mixed effects modeling and exploratory PK analyses will be reported in a document separate from the Clinical Study Report.

Data may be pooled for analysis with data from other studies investigating crovalimab. These PK analyses will be reported in a dedicated report.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment. When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 4-fold greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and PD endpoints may be analyzed and reported via descriptive statistics. These analyses will be described in more details in the SAP.

6.8 BIOMARKER ANALYSES

Change over time in PD parameters (e.g., complement inhibition by LIA, C5 levels) and other exploratory biomarkers will be presented using summary statistics (e.g., arithmetic and geometric means, median, range, standard deviations, and coefficients of variation). Association of C5 polymorphisms and other complement-related gene polymorphisms with safety, efficacy, PK, and PD endpoints may be explored and reported descriptively.

Descriptive statistics for Arm C will be reported separately. Data may be analyzed in aggregate with data from other studies.

6.9 HEALTH STATUS UTILITY ANALYSES

Summary statistics will be calculated for the EQ-5D-5L health utility index−based and VAS scores, and changes in scores over the course of the study will be summarized

descriptively. Additional economic modeling analyses will be conducted post-hoc to support the integrated evidence plan and detailed in relevant analysis plans outside of the study SAP. Descriptive statistics for Arm C will be reported separately.

6.10 INTERIM ANALYSES

No interim efficacy analysis is planned.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered on the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for

the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014), and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative(s), per local laws and regulations, before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or the legally authorized representative(s), per local laws and regulations must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative(s). 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 study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor 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.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator 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, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be co-sponsored and managed by F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd. The Sponsors will provide clinical operations management (involving clinical research organization), data management, and medical monitoring.

Approximately 80–100 sites globally will participate to enroll approximately 200 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will participate in monitoring and evaluating patients' safety, according to the iDMC Charter.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to health care professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only.

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Appendix 1 Schedule of Activities

Table 1: Schedule of Activities for All Patients for Treatment Weeks ≤24

Study Week	Screen	Randomized Treatment Period (All Patients)																Safety Follow-Up Site Visit (Crovalimab and Eculizumab Patients) [b]	Safety Follow-Up Telephone Call (Crovalimab Patients only) [b]
	–4 to –1	1 (Day 1)	1 (Day 2 [a])	2	3	4	5	7	9	11	13	15	17	19	21	23	25		
Informed consent [c]	x																		
Neisseria *meningitidis*, *Haemophilus influenzae* type B and *Streptococcus pneumoniae* vaccinations [d]	x																		
Medical history and baseline conditions [e]	x																		
Demographic data [f]	x																		
Viral serology (HBV, HCV) [g]	x																		
Blood sample for PNH clone size [h]	x	x									x						x	x	
Blood sample for clinical genotyping [i]		x																	
Complete PE [j]	x																		
Limited PE [j]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Vital signs [k, l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1: Schedule of Activities (cont.)

Study Week	Screen	Randomized Treatment Period (All Patients)																Safety Follow-Up Site Visit (Crovalimab and Eculizumab Patients) [b]	Safety Follow-Up Telephone Call (Crovalimab Patients only) [b]
	–4 to –1	1 (Day 1)	1 (Day 2 [a])	2	3	4	5	7	9	11	13	15	17	19	21	23	25		
Pregnancy test [l, m]	x	x					x		x		x		x		x		x	x	x
12-Lead ECG [n]	x	x					x										x		
Concomitant medications [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
pRBC transfusions [p]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Hematology [l, q, dd]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Hemoglobin test pre-study enrollment [ee]	x	x																	
Free hemoglobin, haptoglobin [l, r, s]		x		x	x	x	x		x		x		x		x		x	x	
Coagulation [l, t]	x	x					x				x						x	x	
Chemistry [l, u, dd]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Urinalysis [l, v]	x	x							x				x				x	x	
Adverse events [w]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assessment and documentation of BTH [l, x]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1: Schedule of Activities (cont.)

	Screen	Randomized Treatment Period (All Patients)																Safety Follow-Up Site Visit (Crovalimab and Eculizumab Patients) [b]	Safety Follow-Up Telephone Call (Crovalimab Patients only)[b]
Study Week	–4 to –1	1 (Day 1)	1 (Day 2 [a])	2	3	4	5	7	9	11	13	15	17	19	21	23	25		
Serum sample for central LDH and central potassium [l, y, dd]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Plasma and serum sample set for PD biomarkers [z, aa, dd, ff]		x		x	x	x	x		x		x		x		x		x	x	
Serum ADA sample for crovalimab (Arms A and C) [l, z, dd]		x		x	x	x	x		x		x		x		x		x	x	
Serum PK sample for crovalimab (Arms A and C) [l, z, bb, dd]		x	x	x	x	x	x		x		x		x		x		x	x	
Serum PK sample for eculizumab (Arm B) [l, z, bb]		x		x	x	x	x		x		x		x		x		x	x	
FACIT-Fatigue, EORTC QLQ-C30 scales, and EORTC Item Library symptoms (patients aged ≥ 18 years) [cc]		x		x			x		x				x				x	x	

Appendix 1: Schedule of Activities (cont.)

Study Week	Screen	Randomized Treatment Period (All Patients)															Safety Follow-Up Site Visit (Crovalimab and Eculizumab Patients) [b]	Safety Follow-Up Telephone Call (Crovalimab Patients only) [b]
	–4 to –1	1 (Day 1)	1 (Day 2 [a])	2	3	4	5	7	9	11	13	15	17	19	21	23	25		
PedsQL Core and PedsQL MFS (patients aged 8–17 years) [cc]		x		x			x		x				x				x	x	
EQ-5D-5L (patients aged ≥ 12 years) [cc]		x		x			x		x				x				x	x	
TSQM-9 (patients aged ≥ 18 years) [cc]											x						x		
QLQ-AA/PNH and PGIS (patients aged ≥ 18 years) [cc]	x																		
Crovalimab administration (Arms A and C)		x	x	x	x	x	x		x		x		x		x				
Eculizumab administration (Arm B)		x		x	x	x	x	x	x	x	x	x	x	x	x	x			

ADA = anti-drug antibody; BTH = breakthrough hemolysis; eCRF = electronic Case Report Form; EoI = end of injection; FACIT = Functional Assessment of Cancer Therapy; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; EORTC = European Organisation for Research and Treatment of Cancer; HBV = hepatitis B virus; HCV = hepatitis C virus; MFS = Multidimensional Fatigue Scale; PD = pharmacodynamic; PE = physical examination; PedsQL = pediatric quality of life; PGIS = Patient Global Impression of Severity Survey; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed RBC; QLQ = Quality of Life Questionnaire; QLQ-AA/PNH = Quality of Life Questionnaire – Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria; QW = every week; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SOC = standard of care; Screen = screening; TSQM-9 = Treatment Satisfaction Questionnaire for Medication.

Note: All assessments should be performed within ±2 days of the scheduled visit. All assessments should be performed prior to dosing unless otherwise specified. Crovalimab may be administered within ±2 days of the scheduled dose, except the Week 1 Day 1 and Week 1 Day 2 doses, which should be administered on the scheduled day. Eculizumab may be administered with ±2 days of the scheduled dose, except for the doses administered in the first 4 weeks, which should be administered on the scheduled day.

Note: After 24 weeks in the primary treatment period, patients may continue/switch to crovalimab for a maximum of 5 years on the study (extension period) and then according to the Roche Global Policy on Continued Access to Investigational Medicinal Products.

Note: Mobile Nursing is available for all patients from Week 7 (inclusive) onwards except for the visits at Weeks 13 and 25 and the study discontinuation visit.

[a] Only for patients randomized/assigned to crovalimab.

[b] Only for patients who discontinue at or before Week 25. All other patients should follow schedules in Appendix 1 Table 2 or Table 3 for assessments after Week 25. For patients who discontinue from crovalimab, follow-up assessments should be taken 24 weeks (site visit) and 46 weeks (safety telephone call) after the final dose of crovalimab. Note that patients who continue crovalimab after discontinuation from the study treatment do not need to return for the safety follow-up visit. For patients who discontinue from eculizumab treatment, follow-up assessments should be taken 10 weeks after the final dose of eculizumab.

[c] Obtain written informed consent (or patient's assent and legal representative's written informed consent for patients < 18 years old) before collection of any data. Patients will be enrolled and randomized after giving informed consent or assent (when appropriate).

[d] Vaccination against *Neisseria meningitidis* serotypes A, C, W, and Y must be administered < 3 years prior to initiation of study treatment. Vaccination against serotype B must be administered in accordance with most current local guidelines or SOC as applicable for patients with complement deficiency. Vaccination currency with vaccination against serotypes A, C, W, Y and B should be maintained throughout the study according to local guidelines or SOC as applicable in patients with complement deficiency. Vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* should be administered according to national vaccination recommendations. If not previously administered or no longer current, vaccination must be completed no later than one week after the first study drug administration. See Section 4.5.5.1 for further details. Patients who receive the vaccine within 2 weeks prior to initiating study treatment or after start of study treatment must receive appropriate prophylactic antibiotics from initiation of study treatment, continuing for at least 2 weeks after the vaccination or according to local

SOC as applicable in patients with complement deficiency, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to the first dose of study drug.

[e] Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, immunization history, and use of alcohol and drugs of abuse, will be recorded at screening. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and medical condition should be recorded on the eCRF.

[f] Demographics include age, sex, and self-reported race/ethnicity.

[g] Viral serology includes HBsAg and HCV antibody. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[h] Blood sample to determine PNH clone size. At screening only, historical data collected no more than 6 months prior to randomization may be reported; if no historical data are available, a sample will be collected at screening and tested locally. At all the other timepoints, including Day 1, a sample will be collected, and PNH clone size (WBC and RBC) and C3d on RBCs will be measured centrally.

[i] Blood sample for clinical genotyping to be collected at screening or at any other time during the treatment period. It may be analyzed for C5 polymorphisms and other complement-related gene polymorphisms, as well as human leukocyte antigen genotype.

[j] A complete physical examination, including evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems, is required at screening; thereafter, only a limited physical examination will be required. Weight will be recorded at screening and at Weeks 13 and 25.

[k] Vital signs include measurements of blood pressure (systolic and diastolic) while the patient is in a seated position, pulse rate, respiratory rate, and body temperature. *Assessment is to be performed before study drug dose administration.*

[l] To be collected prior to study drug dose administration. Whenever possible, crovalimab PK and ADA samples should be collected at the same time.

[m] Pregnancy tests will be conducted for female patients of childbearing potential prior to dosing. A serum pregnancy test should be performed at the screening visit. Subsequent pregnancy tests will be urine or serum tests performed locally. A urine pregnancy test will also be performed by the patient within 2 days prior to the final telephone call follow-up (i.e., 46 weeks [approximately 10.5 months] after the final dose of crovalimab). The patient should report the result of the pregnancy test during the telephone call. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[n] If screening and Week 1 ECG assessments occur on the same day, do not repeat.

[o] Report any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from first screening visit prior to initiation of the study drug until 46 weeks (approximately 10.5 months) after the final dose of crovalimab.

[p] Report previous and concurrent pRBC transfusions.

[q] Hematology will be assessed locally. It includes RBC count, hemoglobin, hematocrit, platelet count, WBC count, reticulocyte count (or percentage count if absolute count is not available) and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[r] Sample will be sent to a central laboratory for analysis.

[s] Samples will not be collected at some timepoints from pediatric patients to ensure the drawn blood volumes will not exceed the limits described in Section 4.5.8.

[t] Coagulation includes locally assessed aPTT and PT/INR.

[u] Chemistry panel (serum or plasma) will be assessed locally. It includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered SOC for the region), glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST and LDH. Serum bicarbonate may be omitted for screening or on-study serum measurements in countries where serum bicarbonate is not considered a standard chemistry measurement. If unscheduled LDH measurements are taken for determination of sustained intravascular hemolysis, they must be recorded on the eCRF.

[v] Urinalysis will be performed through dipstick (pH, specific gravity, glucose, protein, ketones, and blood). If there is a clinically significant positive result (i.e., confirmed by a positive repeat sample), urine will be sent to the laboratory for microscopy and culture (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). If there is a known explanation for the positive dipstick result (e.g., menses), it should be recorded, and there is no need to perform laboratory for microscopy and culture.

[w] After informed consent has been obtained but prior to initiation of the study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. Subsequently, all adverse events will be reported until 46 weeks (approximately 10.5 months) after the final dose of the study drug, unless the patient continues crovalimab treatment as part of an open-label extension study, or as per the Roche Global Policy on Continued Access to Investigational Medicinal Products or as commercial product. For patients randomized to eculizumab who do not switch to crovalimab after 24 weeks of treatment, all adverse events will be reported until 10 weeks after the final dose of the study drug. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to crovalimab at any timepoint. See Section 5 for additional details and reporting requirements.

[x] Symptoms of BTH and confirmation of blood sampling for local LDH, potassium, hemoglobin and bilirubin measurements, as well as the local results of these tests, once available, should be documented in the eCRF. Blood samples will be drawn for central testing for LDH, potassium, free hemoglobin, haptoglobin, pharmacokinetics, ADA, and biomarkers. If blood transfusions are required, the number of units of pRBCs will be also documented in the eCRF.

[y] Additional LDH and potassium samples will be obtained and sent to a central laboratory for analysis.

[z] In case of an adverse event of BTH or a hypersensitivity reaction on a patient randomized to crovalimab, an additional sample for pharmacokinetics (for crovalimab), ADAs (for crovalimab), and biomarkers should be drawn as close as possible to the onset of the event,

unless they have already been collected as a part of the scheduled assessment. In the event of BTH accompanied by an IV rescue dose of crovalimab, the sampling should occur prior to the drug administration. Eculizumab PK sample does not need to be collected for BTH events.

[aa] Exploratory biomarker sample for central coagulation tests will not be collected from pediatric patients in all visits to ensure the drawn blood volumes will not exceed the limits described in Section 4.5.8.

[bb] At Day 1 visit, the PK samples for crovalimab or eculizumab should be collected before the start of infusion and within 30 minutes after the end of infusion.

[cc] Completion of PRO questionnaires should occur prior to the performance of non-PRO assessments whenever possible. PRO questionnaires will be self-administered before a patient receives any information on disease status and prior to the administration of crovalimab or eculizumab. QLQ-AA/PNH and PGIS instruments will be administered if available in the local language.

[dd] For patients whose maintenance dose is increased due to experiencing two or more qualifying intravascular hemolysis events or sustained intravascular hemolysis, additional samples for central LDH, potassium, PK (for crovalimab), ADA (for crovalimab), and PD biomarkers should be drawn prior to the first administration of the increased maintenance dose and 4 weeks after the first administration, unless these have already been collected as part of a scheduled assessment. CBC and LDH should be assessed locally prior to the first administration of the increased maintenance dose, at four weeks after the first administration, and as clinically indicated thereafter to monitor clinical response. Locally assessed CBC and LDH should be recorded on the eCRF.

[ee] A local hemoglobin assessment must be performed within 5 days prior to Week 1 Day 1 (Days –4 to Day 1). The measurement can also be taken on Day 1 prior to randomization/enrollment, if randomization/enrollment takes place on Day 1), as an eligibility criterion. If the hemoglobin assessment taken at the screening visit is within this time interval, and patient meets the hemoglobin eligibility requirement, it does not need to be repeated. Patient may be transfused with pRBCs to meet hemoglobin eligibility requirement. They must have their hemoglobin re-assessed for eligibility with a post-transfusion hemoglobin assessment prior to randomization/enrollment (see Section 4.1.2).

[ff] PD biomarkers will include CH50 measured by a liposome immunoassay, total and free C5 concentration, sC5-b9 concentration and coagulation studies.

Table 2: Schedule of Activities for Patients Randomized to Crovalimab Continuing Treatment at Weeks ≥ 25

Study Week	Week 25	Week 33 and Q8W Thereafter	Week 49 and Q12W Thereafter	Safety Follow-Up Site Visit (24 Weeks After Last Dose) [a]	Safety Follow-Up Telephone Call (46 Weeks After Last Dose) [a]
Blood sample for PNH clone size [b]	Follow Table 1 Week 25 Schedule for each corresponding row			x	
Limited PE [c]		X	x	x	
Vital signs [d]		X	x	x	
Pregnancy test [e, f]		X	x	x	x
12-Lead ECG					
Concomitant medications [g]		x	x	x	x
pRBC transfusions [h]		x	x	x	
Hematology [e, i, u]		x	x	x	
Free hemoglobin, haptoglobin [e, j]		x	x	x	
Coagulation [e, k]		x	x	x	
Chemistry [e, l, u]		x	x	x	
Urinalysis [e, m]		x	x	x	
Adverse events [n]		x	x	x	x
Assessment and documentation of BTH [e, o]		x	x	x	
Serum sample for central LDH and central potassium [e, p, u]		x	x	x	
Plasma and serum sample set for PD biomarkers [e, q, u, v]		X	x	x	

Appendix 1: Schedule of Activities (cont.)

Study Week	Week 25	Week 33 and Q8W Thereafter	Week 49 and Q12W Thereafter	Safety Follow-Up Site Visit (24 Weeks After Last Dose) [a]	Safety Follow-Up Telephone Call (46 Weeks After Last Dose) [a]
Serum ADA sample for crovalimab [e, q, u]		X	x	x	
Serum PK sample for crovalimab [e, q, u]		X	x	x	
FACIT-Fatigue, EORTC QLQ-C30 scales, and EORTC Item Library symptoms (patients aged ≥ 18 years) [r]	Follow Table 1 Week 25 Schedule for each corresponding row	X	x	x	
PedsQL Core and PedsQL MFS (patients aged 8-17 years) [r]		X	x	x	
EQ-5D-5L (patients aged ≥ 12 years) [r]		X	x	x	
TSQM-9 (patients aged ≥ 18 years) [r]			x [s]		
QLQ-AA/PNH and PGIS (patients aged ≥ 18 years) [r]		x [t]			
Crovalimab administration	Q4W				

ADA = anti-drug antibody; BTH = breakthrough hemolysis; eCRF = electronic Case Report Form; EoI = end of injection; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; EORTC = European Organisation for Research and Treatment of Cancer; FACIT = Functional Assessment of Cancer Therapy; MFS = Multidimensional Fatigue Scale; PD = pharmacodynamic; PE = physical examination; PGIS = Patient Global Impression of Severity Survey; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed RBC; PK = pharmacokinetic; QLQ = Quality of Life Questionnaire; QLQ-AA/PNH = Quality of Life Questionnaire – Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria; Q4W = every 4 weeks; Q8W = every 8 weeks; SOC = standard of care; TSQM-9 = Treatment Satisfaction Questionnaire for Medication.

Notes: All assessments should be performed within ±7 days of the scheduled visit. All assessments should be performed prior to dosing unless otherwise specified. Crovalimab may be administered within ±2 days of the scheduled dose.

After 24 weeks in the primary treatment period, patients may continue/switch to crovalimab for a maximum of 5 years on the study (extension period) and then continue crovalimab, according to the Roche Global Policy on Continued Access to Investigational Medicinal Products.

Mobile Nursing is available for patients in Arm A and C from Week 29 (inclusive) onwards except for the study discontinuation visit.

Study Week	Week 25	Week 33 and Q8W Thereafter	Week 49 and Q12W Thereafter	Safety Follow-Up Site Visit (24 Weeks After Last Dose) [a]	Safety Follow-Up Telephone Call (46 Weeks After Last Dose) [a]

[a] Follow-up safety assessments *should* be taken 24 weeks (site visit) and 46 weeks (safety telephone call) after the final dose of crovalimab. Note that patients who continue crovalimab after discontinuation from the study treatment do not need to return for the safety follow-up visit.

[b] Blood sample to determine PNH clone size. A sample will be collected, and PNH clone size (WBC and RBC) and C3d on RBCs will be measured centrally.

[c] Weight will be recorded at Weeks 33, 41, 49, and every 12 weeks thereafter.

[d] Vital signs include measurements of blood pressure (systolic and diastolic) while the patient is in a seated position, pulse rate, respiratory rate, and body temperature. *Assessment is to be performed before study drug dose administration.*

[e] To be collected prior to study drug dose administration. Whenever possible, crovalimab PK and ADA samples should be collected at the same time.

[f] Urine or serum pregnancy tests will be conducted locally for female patients of childbearing potential prior to dosing and Q4W thereafter. A urine pregnancy test will also be performed by the patient within 2 days prior to the final telephone call follow-up (i.e., 46 weeks [approximately 10.5 months] after the final dose of crovalimab). The patient should report the result of the pregnancy test during the telephone call. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[g] Report any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment until 46 weeks (approximately 10.5 months) after the final dose of crovalimab.

[h] Report previous and concurrent pRBC transfusions.

[i] Hematology will be assessed locally. It includes RBC count, hemoglobin, hematocrit, platelet count, WBC count, reticulocyte count (or percentage count if absolute count is not available), and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[j] Sample will be sent to a central laboratory for analysis.

[k] Coagulation includes locally assessed aPTT and PT/INR.

[l] Chemistry panel (serum or plasma) will be assessed locally. It includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered SOC for the region), glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST and LDH. Serum bicarbonate may be omitted for screening or on-study serum measurements in countries where serum bicarbonate is not considered a standard chemistry measurement. If unscheduled LDH measurements are taken for determination of sustained intravascular hemolysis, they must be recorded in the eCRF.

[m] Urinalysis will be performed through dipstick (pH, specific gravity, glucose, protein, ketones, and blood). If there is a clinically significant positive result (i.e., confirmed by a positive repeat sample), urine will be sent to the laboratory for microscopy and culture (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). If there is a known explanation for the positive dipstick result (e.g., menses), it should be recorded, and there is no need to perform laboratory for microscopy and culture.

[n] All adverse events will be reported until 46 weeks (approximately 10.5 months) after the final dose of the study drug, unless the patient continues crovalimab treatment as part of an open-label extension study, or as per the Roche Global Policy on Continued Access to Investigational Medicinal Products or as commercial product. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to crovalimab at any timepoint. See Section 5 for additional details and reporting requirements.

[o] Symptoms of BTH and confirmation of blood sampling for local LDH, potassium, hemoglobin and bilirubin measurements, as well as the local results of these tests, once available, should be documented in the eCRF. Blood samples will be drawn for central testing for LDH, potassium, free hemoglobin, haptoglobin, pharmacokinetics, ADA, and biomarkers. If blood transfusions are required, the number of units of pRBCs will be also documented in the eCRF.

[p] Additional LDH and potassium samples will be obtained and sent to a central laboratory for analysis.

[q] In case of an adverse event of BTH or a hypersensitivity reaction on a patient randomized to crovalimab, an additional sample of PK (for crovalimab), ADA (for crovalimab), and biomarkers should be drawn as close as possible to the onset of the event, unless they have already been collected as a part of the scheduled assessment. In the event of BTH accompanied by an IV rescue dose of crovalimab, the sampling should occur prior to the drug administration.

[r] Completion of PRO questionnaires should occur prior to the performance of non-PRO assessments whenever possible. PRO questionnaires will be self-administered before a patient receives any information on disease status and prior to the administration of crovalimab. QLQ-AA/PNH and PGIS instruments will be administered if available in the local language.

[s] TSQM-9 will be administered to patients (aged ≥ 18 years) at Week 49 only.

[t] QLQ-AA/PNH and PGIS will be administered to patients (aged ≥ 18 years) at Week 33 only.

[u] For patients whose maintenance dose is increased due to experiencing two or more qualifying intravascular hemolysis events or sustained intravascular hemolysis, additional samples for central LDH, potassium, PK (for crovalimab), ADA (for crovalimab), and PD biomarkers should be drawn prior to the first administration of the increased maintenance dose and 4 weeks after the first administration, unless these have already been collected as part of a scheduled assessment. CBC and LDH should be assessed locally prior to the first administration of the increased maintenance dose, at four weeks after the first administration, and as clinically indicated thereafter to monitor clinical response. Locally assessed CBC and LDH should be recorded on the eCRF.

[v] PD biomarkers will include CH50 measured by a liposome immunoassay, total and free C5 concentration, sC5-b9 concentration and coagulation studies.

Table 3: Schedule of Activities for Patients Randomized to Eculizumab Switching to Crovalimab at Week 25

Overall Study Week (Day)	Crovalimab Treatment										Week 49 and Q12W Thereafter	Safety Follow-Up Site Visit (24 Weeks After Last Dose)[a]	Safety Follow-Up Telephone Call (46 Weeks After Last Dose) [a]
	25 (Day 1)	25 (Day 2)	26	27	28	29	31	33	37	41	45			
Limited physical examination [b]	Follow Table 1 Week 25 Schedule for each corresponding row	x	x	x	x	x	x	x	x	x	x	x	x	
Vital signs [c]		x	x	x	x	x	x	x	x	x	x	x	x	
Pregnancy test [d, e]						x		x	x	x	x	x	x	x
12-Lead ECG						x								
Concomitant medications [f]		x	x	x	x	x	x	x	x	x	x	x	X	x
pRBC transfusions [g]		x	x	x	x	x	x	x	x	x	x	x	X	
Blood sample for PNH clone size [h]									x				X	
Hematology [d, i]			x	x	x	x	x	x	x	x	x	x	X	
Free hemoglobin, haptoglobin [d, j]			x	x	x	x	x	x	x	x	x	x	X	
Coagulation [d, k]						x			x			x	X	
Chemistry [d, l]			x	x	x	x	x	x	x	x	x	x	X	
Urinalysis [d, m]		x	x	x	x	x	x	x		x		x	X	
Adverse events [n]		x	x	x	x	x	x	x	x	x	x	x	X	x

Appendix 1: Schedule of Activities (cont.)

Overall Study Week (Day)	Crovalimab Treatment											Week 49 and Q12W Thereafter	Safety Follow-Up Site Visit (24 Weeks After Last Dose)[a]	Safety Follow-Up Telephone Call (46 Weeks After Last Dose) [a]
	25 (Day 1)	25 (Day 2)	26	27	28	29	31	33	37	41	45			
Assessment and documentation of BTH [d, o]	Follow Table 1 Week 25 Schedule for each corresponding row	x	x	x	x	x	x	x	x	x	x	x	X	
Serum sample for central LDH and central potassium [d, p, v]		x	x	x	x	x	x	x	x	x	x	x	X	
Plasma and serum for PD biomarkers [d, s, v, w]			x	x	x	x	x	x	x	x	x	x	X	
FACIT-Fatigue, EORTC QLQ-C30 scales, and EORTC Item Library symptoms [q]			x			x		x		x		x	x	
EQ-5D-5L [q]			x			x		x		x		x	x	
TSQM-9 [q]												x[r]		
Serum ADA sample for crovalimab [d, s, v]	x		x	x	x	x		x	x	x	x	x	x	
Serum PK sample for crovalimab [d, s, t, v]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum DTDC sample [d, u]	x	x	x	x	x	x	x	x	x	x	x		x	
QLQ-AA/PNH and PGIS [q]							x							

Appendix 1: Schedule of Activities (cont.)

Overall Study Week (Day)	Crovalimab Treatment											Week 49 and Q12W Thereafter	Safety Follow-Up Site Visit (24 Weeks After Last Dose)[a]	Safety Follow-Up Telephone Call (46 Weeks After Last Dose) [a]
	25 (Day 1)	25 (Day 2)	26	27	28	29	31	33	37	41	45			
Patient Preference Questionnaire [q]										x				
Crovalimab administration	x	x	x	x	x	Q4W								

ADA = anti-drug antibody; BTH = breakthrough hemolysis; DTDC = drug-target-drug complex; eCRF = electronic Case Report Form; EoI = end of injection; FACIT = Functional Assessment of Cancer Therapy; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; EORTC = European Organisation for Research and Treatment of Cancer; MFS = Multidimensional Fatigue Scale; PD = pharmacodynamic; PGIS = Patient Global Impression of Severity Survey; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed RBC; PK = pharmacokinetic; QLQ = Quality of Life Questionnaire; QLQ-AA/PNH = Quality of Life Questionnaire – Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria; Q4W = every 4 weeks; Q8W = every 8 weeks; Q16W = every 16 weeks; SOC = standard of care; TSQM-9 = Treatment Satisfaction Questionnaire for Medication.

Note: All assessments should be performed within ±2 days of the scheduled visit until Study Week 49 and then ±7 days thereafter. All assessments should be performed prior to dosing, unless otherwise specified. Crovalimab may be administered within ±2 days of the scheduled dose, except for the Week 25 Day 1 and Week 25 Day 2 doses, which should be administered on the scheduled day.

Note: After 24 weeks in the primary treatment period, patients may continue/switch to crovalimab for a maximum of 5 years on the study (extension period) and then continue crovalimab according to the Roche Global Policy on Continued Access to Investigational Medicinal Products.

Note: Mobile Nursing is available for patients in Arm B from Week 31 (inclusive) onwards except for the visits on Weeks 37 and 49 and the study discontinuation visit.

[a] Follow-up safety assessments to be taken 24 weeks (site visit) and 46 weeks (safety telephone call) after the final dose of crovalimab. Note that patients who continue crovalimab after discontinuation from the study treatment do not need to return for the safety follow-up visit.

[b] Weight will be recorded at Weeks 33, 41, and 49, and every 12 weeks thereafter.

[c] Vital signs include measurements of blood pressure (systolic and diastolic) while the patient is in a seated position, pulse rate, respiratory rate, and body temperature. *Assessment is to be performed before study drug dose administration.*

[d] To be collected prior to study drug dose administration. Whenever, possible crovalimab PK and ADA samples should be collected at the same time.

[e] Serum or urine pregnancy tests will be locally performed for patients of childbearing potential prior to dosing and Q4W thereafter. A urine pregnancy test will also be performed by the patient within 2 days prior to the final telephone call follow-up (i.e., 46 weeks [approximately 10.5

months] after the final dose of crovalimab). The patient should report the result of the pregnancy test during the telephone call. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[f] Report any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment until 46 weeks (approximately 10.5 months) after the final dose of crovalimab.

[g] Report previous and concurrent pRBC transfusions.

[h] Blood sample to determine PNH clone size. A sample will be collected, and PNH clone size (WBC and RBC) as well as C3d on RBCs will be measured centrally.

[i] Hematology will be assessed locally. It includes RBC count, hemoglobin, hematocrit, platelet count, WBC count, reticulocyte count (or percentage count if absolute count is not available), and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[j] Samples will be sent to a central laboratory for analysis.

[k] Coagulation includes locally assessed aPTT and PT/INR.

[l] Chemistry panel (serum or plasma) will be assessed locally. It includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered SOC for the region), glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST and LDH. Serum bicarbonate may be omitted for screening or on-study serum measurements in countries where serum bicarbonate is not considered a standard chemistry measurement. If unscheduled LDH measurements are taken for determination of sustained intravascular hemolysis, they must be recorded in the eCRF.

[m] Urinalysis will be performed through dipstick (pH, specific gravity, glucose, protein, ketones, and blood). If there is a clinically significant positive result (i.e., confirmed by a positive repeat sample), urine will be sent to the laboratory for microscopy and culture (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). If there is a known explanation for the positive dipstick result (e.g., menses), it should be recorded, and there is no need to perform laboratory for microscopy and culture. During the first 10 weeks on crovalimab, instead of dipstick, a urine sample should be sent to the laboratory for microscopy.

[n] All adverse events will be reported until 46 weeks (approximately 10.5 months) after the final dose of crovalimab, unless the patient continues crovalimab treatment as part of an open-label extension study, or as per the Roche Global Policy on Continued Access to Investigational Medicinal Products or as commercial product. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to the study drug. See Section 5 for additional details and reporting requirements.

[o] Symptoms of BTH and confirmation of blood sampling for local LDH, potassium, hemoglobin and bilirubin measurements, as well as the local results of these tests, once available, should be documented in the eCRF. Blood samples will be drawn for central testing LDH, potassium, free hemoglobin, haptoglobin, pharmacokinetics, ADA, and biomarkers. If blood transfusions are required, the number of units of pRBCs will be also documented in the eCRF.

[p] Additional LDH and potassium samples will be obtained and sent to a central laboratory for analysis.

[q] Completion of PRO questionnaires should occur prior to the performance of non-PRO assessments whenever possible. PRO questionnaires will be self-administered before a patient receives any information on disease status and prior to the administration of crovalimab or eculizumab. QLQ-AA/PNH and PGIS instruments will be administered if available in the local language.

[r] TSQM-9 will be administered to patients at Week 49 only.

[s] In case of an adverse event of BTH or a hypersensitivity reaction on a patient randomized to crovalimab, an additional sample for pharmacokinetics (for crovalimab), ADAs (for crovalimab), and biomarkers should be drawn as close as possible to the onset of the event, unless they have already been collected as a part of the scheduled assessment. In the event of BTH accompanied by an IV rescue dose of crovalimab, the sampling should occur prior to the drug administration.

[t] At Week 25 Day 1 visit, the PK samples for crovalimab should be collected before the start of infusion and within 30 minutes after the end of infusion.

[u] On Day 1 of Week 25, DTDC sample is to be collected before and after the end of infusion of the first dose of crovalimab. Subsequent DTDC samples are to be collected before the crovalimab dose. *If this occurs after Week 25 post crovalimab treatment initiation, DTDC samples should not be collected.*

[v] For patients whose maintenance dose is increased due to experiencing two or more qualifying intravascular hemolysis events or sustained intravascular hemolysis, additional samples for central LDH, potassium, PK (for crovalimab), ADA (for crovalimab), and PD biomarkers should be drawn prior to the first administration of the increased maintenance dose and 4 weeks after the first administration, unless these have already been collected as part of a scheduled assessment. CBC and LDH should be assessed locally prior to the first administration of the increased maintenance dose, at four weeks after the first administration, and as clinically indicated thereafter to monitor clinical response. Locally assessed CBC and LDH should be recorded on the eCRF.

[w] PD biomarkers will include CH50 measured by a liposome immunoassay, total and free C5 concentration, sC5-b9 concentration and coagulation studies.

Appendix 2 Schedule of Activities for Patients Who Discontinue Crovalimab and Switch to Other C5 Inhibitors

	Treatment with Other C5 Inhibitor						
Week	1	2	3	4	5	7	9
Physical examination [a, b]	x	x	x	x	x	x	x
Vital signs [b, c]	x	x	x	x	x	x	x
Safety laboratory assessments [b, d]	x	x	x	x	x	x	x
Urinalysis [b, e]	x	x	x	x	x	x	x
Adverse events [f]	x	x	x	x	x	x	x

BTH = breakthrough hemolysis; C5 = component 5.

[a] Only a limited physical examination is required.

[b] Assessment/sampling should be performed before the C5 inhibitor dose.

[c] Vital signs include measurements of blood pressure (systolic and diastolic) while the patient is in a seated position, pulse rate, respiratory rate, and body temperature.

[d] Safety laboratory assessments include hematology and chemistry panels as per investigator's judgement in order to monitor the safety of a patient.

[e] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood). If there is a clinically significant positive result (i.e., confirmed by a positive repeat sample), urine will be sent to the laboratory for microscopy and culture (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). If there is a known explanation for the positive dipstick result (e.g., menses), it should be recorded, and there is no need to perform laboratory for microscopy and culture.

[f] All adverse events will be reported until 46 weeks (approximately 10.5 months) after the final dose of the study drug. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to crovalimab at any timepoint. See Section 5 for additional details and reporting requirements.

Appendix 3 Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 4 Major Adverse Vascular Events (MAVEs)

The description of the Major adverse vascular events (MAVEs) including the method of diagnosis (e.g., MRI, ultrasound, angiogram), date of diagnosis, and the date resolved (or ongoing) will be collected on the eCRF as part of the patient's medical history (prior to baseline). A MAVE is defined as any of the following events:

- Thrombophlebitis/deep vein thrombosis
- Pulmonary embolus
- Myocardial infarction
- Transient ischemic attack
- Unstable angina
- Renal vein thrombosis
- Acute peripheral vascular occlusion
- Mesenteric/visceral vein thrombosis or infarction
- Mesenteric/visceral arterial thrombosis or infarction
- Hepatic/portal vein thrombosis (budd-Chiari syndrome)
- Cerebral arterial occlusion/cerebrovascular accident
- Cerebral venous occlusion
- Renal arterial thrombosis
- Gangrene (non-traumatic, non-diabetic)
- Amputation (non-traumatic, non-diabetic)
- Dermal thrombosis
- Other, specify

Appendix 5 Suspected Unexpected Serious Adverse Reactions (SUSARs): Reporting Obligations

The Sponsor has a legal obligation to immediately, within 15 days of detection, report all suspected unexpected serious adverse reactions (SUSARs) to the European Medicines Agency's (EMA) database of suspected adverse drug reactions. SUSARs are defined as suspected adverse reactions which are not listed in the reference safety information contained in the Investigator's Brochure. The content of the database is confidential and only accessible by authorized medicines agencies within the European Union, the EMA, and the European Commission. Fatal and life-threatening adverse reactions have to be reported within seven days of the Sponsor becoming aware of them. For other serious adverse reactions, the deadline is 15 days.

Appendix 6 Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 1 Investigational and Non-Investigational Medicinal Product Designations for European Economic Area and United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in EEA and UK	Used within Marketing Authorization
Crovalimab	IMP (test product)	Unauthorized	Not applicable
Eculizumab	IMP (comparator)	Authorized	Yes

EEA = European Economic Area; IMP = investigational medicinal product; NIMP = non-investigational medicinal product

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