Official Title: A Phase III, Multicenter, Single Arm Study Evaluating the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Crovalimab in Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) Not Previously Treated With Complement Inhibition

NCT Number: NCT04654468

Document Date: Protocol Amendment Version 5: 23-November-2022

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, SINGLE ARM STUDY EVALUATING THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CROVALIMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITION**
PROTOCOL NUMBER:	YO42311
VERSION NUMBER:	5
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	Not Applicable
NCT NUMBER:	NCT04654468
TEST PRODUCT:	Crovalimab (RO7112689)
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic *signature and* date stamp *on the final page of this document*.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	*See electronic date stamp on the final page of this document.*
4	*14 February 2022*
3	13 August 2021
2	5 November 2020
1	1 June 2020

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol YO42311 has been primarily amended to reflect changes associated with the re-estimated half-life of crovalimab.

Based on the emergent pharmacokinetic (PK) data, the terminal half-life of crovalimab was re-estimated from approximately 30 days to approximately 59 days. The population PK model was updated due to the availability of the primary analysis data from the Phase III Study YO42311 (this study) in patients with paroxysmal nocturnal hemoglobinuria (PNH). Model parameters were re-estimated using pooled PK data from treatment-naive patients with PNH from the Phase I/II Study BP39144, and Study YO42311. The update in the half-life estimate was driven by a more informative PK sampling that was implemented in Study YO42311 and a larger dataset that was available for the model update (Sections 1.2.2.2).

Changes to the protocol based on the above rationale for the re-estimated half-life are summarized below.

- The safety follow-up period has been extended from 24 to 46 weeks (approximately 10.5 months) to maintain 5.5 half-lives of follow-up. As a result, a safety telephone call has been added to collect safety information 46 weeks (approximately 10.5 months) after the final dose of crovalimab. The safety telephone call 46 weeks after the final dose of crovalimab will assess adverse events and changes to concomitant medications. A urine pregnancy test will be performed by the patient no more than two days before the safety telephone call (female patients of childbearing potential only), and the patient should report the result during the safety telephone call (Sections 3.1, 4.4, 4.5, 4.5.2, 4.5.8, 4.6.1, 5.1, 5.1.1.1, 5.3.1, 5.4.2.2, and 5.6; Appendices 1 and 2).
- Section 3.2 has been simplified to remove subsections and provide clear definition of the end of this study and length of the study. The expected end of the study and total length of the study have been extended to 6 years and 7 years, respectively, as a consequence of the amended safety follow-up period (Section 3.2).
- The time frame in which female patients of childbearing potential must remain abstinent or use contraception has been extended from 6 months to 46 weeks (approximately 10.5 months) after the final dose of crovalimab (Section 4.1.1).
- The time frame for the exclusion of patients who are intending to become pregnant has been extended from 6 months to 46 weeks (approximately 10.5 months) after the final dose of crovalimab (Section 4.1.2).
- The reporting period for pregnancies has been updated from 6 months to 46 weeks (approximately 10.5 months) after the final dose of crovalimab (Section 5.4.3.1).

Additional changes to the protocol, along with a rationale for each change, are summarized below:

- The efficacy objectives were clarified to state that lactate dehydrogenase values from the central laboratory will be utilized (Sections 2.1.3 and 6.4.1).

- The exploratory immunogenicity objective has been clarified to include pharmacodynamic endpoints (Sections 2.4 and 6.7).
- Text has been added so that the Sponsor may propose and conduct exploratory substudies associated with the YO42311 study protocol; each substudy will be introduced in a separate substudy protocol (Section 3.1).
- Requirements regarding vaccination currency against *Neisseria meningitidis* have been clarified (Sections 4.1.1 and 4.5.5.1; Appendix 1).
- It has been clarified that crovalimab, which is required by the patient for continued study participation, could be shipped directly to the patient under certain circumstances (Section 4.3.2.1).
- Text has been added to specify that, for transfusions that occur during the study period, the signs and symptoms of anemia associated with the patient's need for a transfusion, the hemoglobin results, the administration of the transfusion, and the number of units transfused should be documented in the electronic Case Report Form (Section 4.5.7).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol. Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites (Section 5.4.1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with current guidelines (Section 8.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Sections 9.6).

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

TITLE:	**A PHASE III, MULTICENTER, SINGLE ARM STUDY EVALUATING THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CROVALIMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITION**
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SPONSOR:	F. Hoffmann-La Roche 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

TITLE:	**A PHASE III, MULTICENTER, SINGLE ARM STUDY EVALUATING THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CROVALIMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITION**
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TEST PRODUCT:	Crovalimab (RO7112689)
PHASE:	III
INDICATION:	Paroxysmal nocturnal hemoglobinuria (PNH)
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This is a Phase III, multicenter, single-arm study designed to evaluate the efficacy, safety, pharmacokinetics, pharmacodynamics, and health status of crovalimab in patients with paroxysmal nocturnal hemoglobinuria (PNH) aged ≥12 years and ≥40 kg who have not been previously treated with a complement-inhibitor therapy.

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

EFFICACY OBJECTIVES

PRIMARY EFFICACY OBJECTIVE

The primary efficacy objective for this study is to evaluate the effect of crovalimab based on crossing the threshold of the co-primary endpoint hemolysis control and the superiority intra–patient assessment of the co-primary endpoint of transfusion avoidance (TA) on the basis of following endpoints:

- Mean proportion of patients with hemolysis control, measured by lactate dehydrogenase (LDH) ≤1.5×upper limit of normal (ULN) from Week 5 through Week 25 (as measured at the central laboratory)
- The difference in the proportion of patients who achieve TA from baseline through Week 25 (after 24 weeks on treatment) and proportion of patient who were TA within 24 weeks prior to screening.

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

  TA within 24 weeks prior to screening is based on the pRBC transfusion history in the medical records.

SECONDARY EFFICACY OBJECTIVE

The secondary efficacy objectives for this study are to evaluate the efficacy of crovalimab on the basis of the following 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×ULN after prior reduction of LDH to ≤1.5×ULN on treatment.
- Proportion of patients with stabilized hemoglobin from baseline through Week 25

  Stabilized hemoglobin is defined as avoidance of a ≥ 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 through the use of the Functional Assessment of Chronic Illness Therapy–Fatigue (adults aged ≥18 years)

OTHER EFFICACY OBJECTIVES

The other efficacy objective for this study is to evaluate the efficacy of crovalimab on the basis of the following endpoints:

- Total number of units of pRBCs transfused per patient from baseline to Week 25
- Mean proportion of patients with $central$ LDH ≤1×ULN from Week 5 through Week 25 (as measured at the central laboratory)
- Mean LDH levels from baseline to Week 25 by visit
- Percent change from baseline to Week 25 in $central$ LDH levels by visit
- Time from baseline to first reach of $central$ LDH ≤1×ULN
- Time from baseline to first reach of $central$ LDH ≤1.5×ULN
- 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 from baseline to Week 25
- Proportion of patients with MAVE from baseline to Week 25
- Mean change from baseline to Week 25 in Physical Function, Role Function, and Global Health Status/Quality of Life scales of the European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire (for adults aged ≥18 years)
- Mean change from baseline to Week 25 in Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale, and the Physical Functioning scale of the PedsQL Core (for adolescents aged 12–17 years)
- Proportion of patients with a ≥5 point improvement from baseline in the FACIT-Fatigue at Week 25 (for adults aged ≥ 18 years)

SUPPORTIVE HISTORICAL OBJECTIVES

The supportive historical objectives are to characterize the efficacy of best supportive care and intra-patient comparison based on the following endpoints:

- Mean LDH, and hemoglobin within 24 weeks prior to screening
- Mean number of blood transfusion and number of units of pRBC transfused within 24 weeks prior to screening
- Proportion of patients who had MAVE as documented in the medical records within 24 weeks prior to screening

SAFETY OBJECTIVE

The safety objective for this study is to evaluate the overall safety of crovalimab 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 (CTCAE), 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

PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to evaluate the pharmacokinetics of crovalimab on the basis of the following endpoints:

- Trough serum concentrations of crovalimab over time
- Serum concentrations of crovalimab at specified timepoints

The other PK objective for this study is as follows:

- To evaluate potential relationships between drug exposure and the efficacy and safety of crovalimab

IMMUNOGENICITY OBJECTIVES

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

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

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

BIOMARKER OBJECTIVE

The biomarker objective for this study is to identify and/or evaluate biomarkers that can provide evidence of crovalimab activity (i.e., pharmacodynamic [PD] biomarkers) on the basis of the following endpoints:

- Change over time in PD biomarkers, including complement activity measured by a liposome immunoassay (LIA)
- Change over time in total and free C5 concentration
- Observed value and absolute change from baseline to Week 25 in parameters reflecting hemolysis (reticulocyte count, free hemoglobin, haptoglobin)

The other biomarker objectives for this study are as follows:

- To evaluate the change over time in red cell clone size by flow cytometry and markers from the coagulation system (D-dimer)
- To evaluate the change over time in additional biomarkers of the complement system and markers for intra–andextra–vascular hemolysis (e.g., C3d on RBCs).

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

HEALTH STATUS UTILITY OBJECTIVE

The health status utility objective for this study is to evaluate health status utility scores of adolescent and adult patients treated with crovalimab on the basis of the following endpoint:

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

STUDY DESIGN

DESCRIPTION OF STUDY

This single-arm, multicenter, China Phase III study is designed to evaluate the efficacy, safety, PK/PD of crovalimab in patients with PNH, aged 12 years or older, with a body weight ≥40 kg, who have not been previously treated with complement-inhibitor therapy.

This study will enroll approximately 50 patients with PNH who will be treated with crovalimab for at least 24 weeks. The primary efficacy analysis will take place when all patients have either completed 24 weeks of treatment with crovalimab or discontinued from the treatment, whichever occurs first. Patients must have received at least one dose of treatment with crovalimab and have at least one central LDH level assessment after the first intravenous (IV) infusion to be included in the primary efficacy analysis.

At screening, all the medical records should be provided to the investigators in the site for eligibility check and medical history data collection. The screening period of the study will be up to 28 days in length for each screening. A maximum of two re-screenings, for a total of three screenings, will be allowed. At screening, LDH testing will be performed for two times with at least 2 weeks interval between the measurements by central laboratory.

An initial IV loading dose will be administered on Week 1 Day 1, followed by four weekly crovalimab subcutaneous (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 (Q4W) thereafter, for a total of at least 24 weeks of study treatment. All patients who receive crovalimab as part of this study will do so according to a weight-based tiered dosing approach schedule.

After completing 24 weeks of treatment with crovalimab (i.e., Week 25 visit), patients will be allowed to continue crovalimab Q4W until they can switch to an open-label extension study (if available), to commercial product, or receive crovalimab as per 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*. If these patients switch to a different C5 inhibitor, they should remain in safety follow-up and be monitored.

Efficacy assessments will include TA, centrally analyzed LDH levels, occurrence of BTH, number of blood transfusions, hemoglobin levels, and health-related quality of life outcome measures. Safety assessments will include vital signs, physical examination, blood sample analysis for hematological and biochemical abnormalities, urine analysis, and monitoring for adverse events, including those of special interest graded per NCI CTCAE v5.

As a supportive measure, all the medical records including data of PNH history should be provided to the investigators in the site for eligibility check and medical history data collection.

NUMBER OF PATIENTS

Approximately 50 patients with PNH will be enrolled in this study.

TARGET POPULATION

Inclusion Criteria

All patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards
- Age ≥12 years at time of signing ICF or Assent Form
- Body weight ≥40 kg at screening
- Willingness and ability to comply with all the 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 screening
- LDH level ≥2×ULN at screening (as per central assessment)
- Patients who have at least four transfusions during 12 months prior to screening (documented in the medical record)
- Presence of one or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), history of a MAVE (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 (Day 1). *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 pneumonia* according to national vaccination recommendations
- Patients who have been vaccinated (partially or in full) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with a locally approved vaccine are eligible to be 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 ≥30,000/mm^3 at screening without transfusion support within 7 days of lab testing.
- ANC >500/μl 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 ≥28 days prior to screening and up to the first drug administration
- Adequate hepatic function, with ALT ≤3×ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine ≤2.5×ULN and creatinine clearance by Cockcroft-Gault formula ≥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 6 months after the final dose of crovalimab.

  A female patient is considered to be of childbearing potential if the patient is postmenarcheal, has not reached a postmenopausal state (≥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.

Exclusion Criteria

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

- Current or previous treatment with a complement inhibitor
- History of allogeneic bone marrow transplantation
- History of *N. meningitidis* infection within 6 months prior to screening and up to first drug administration
- Known or suspected immune deficiency (e.g., history of frequent recurrent infections)
- Known or suspected hereditary complement deficiency
- Known HIV infection with CD4 count $<$ 200 cells/μL within 24 weeks prior to screening

  Patients with HIV infection who have CD4 $>$ 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 ($\geq$38°C) within 7 days before the first drug administration
- Splenectomy $<$6 months before screening
- 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, including hypersensitivity to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product
- Pregnant, breastfeeding, or intention of becoming pregnant during the study or within *46 weeks (or approximately 10.5* months*)* after the final dose of the study treatment

  Women 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

END OF STUDY *AND LENGTH OF STUDY*

The end of this study is defined as the date *when the last patient's last visit 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.

Investigational Medicinal Product

The investigational medicinal product for this study is crovalimab.

TEST PRODUCT (CROVALIMAB)

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

Crovalimab for IV infusion and SC Administration

Crovalimab vials will be supplied by the Sponsor as a solution for infusion (IV)/solution for injection (SC) from a single-use vial, which contains 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 pharmacy manual.
- The 2 mL (340 mg) configuration will not require the vial-pooling step. The pharmacy manual will be adapted accordingly.

STATISTICAL METHODS

PRIMARY EFFICACY ANALYSIS

The primary efficacy analysis will take place when all patients have either completed 24 weeks of treatment with crovalimab or have discontinued the study drug, whichever occurs first.

Hemolysis Control

The co-primary endpoint of the mean proportion of patients with hemolysis control is defined as LDH$\leq$1.5$\times$ULN from Week 5 through Week 25 (as measured at the central laboratory).

For each patient at each visit, a binary variable will be created with the value of 1, if LDH $\leq$1.5$\times$ULN, and 0, otherwise. A Generalized Estimating Equation (GEE) will be used to estimate the mean proportion of hemolysis control (i.e., LDH $\leq$1.5$\times$ULN from Week 5 through Week 25 and 95% confidence interval).

The primary analysis will use the standard GEE based on the available LDH assessments, assuming the missing data are missing completely at random.

Transfusion Avoidance

The co-primary endpoint of proportion of patients who achieve TA consists of proportion of patients who achieve TA from baseline through Week 25 (after 24 weeks on treatment) and proportion of patients who were TA within 24 weeks prior to screening. TA is defined as patients who are pRBC transfusion-free and do not require transfusion per protocol-specified guidelines.

The intra-patient comparison between proportion of patients with TA from baseline through Week 25 and proportion of patients who were TA within 24 weeks prior to screening will be

made using a paired McNemar test at two-sided Type 1 error level of 0.05. The proportion of TA and corresponding 95% CIs based on Wilson's method (1927) will be provided.

For the primary analysis, patients who withdrew early before Week 25 independent of the reason for withdrawal will be included in the analysis as non–responders (i.e., requiring transfusion).

DETERMINATION OF SAMPLE SIZE

Approximately 50 patients with PNH will be enrolled in the study.

Assuming 86% of patients receiving eculizumab and 20% of untreated patients will reach LDH $\leq 1.5 \times$ULN, the minimum proportion of patients with LDH $\leq 1.5 \times$ULN being crossing the efficacy threshold of 60% will preserve about 60% of the effect of eculizumab with sample size of 50. The study will be regarded as reaching the co-primary endpoint of hemolysis control (based on LDH $\leq 1.5 \times$ULN) if the 95%CI lower bound is at least 60%.

Proportion of patients who achieve TA from baseline through Week 25 will be compared with proportion of patients who were TA within 24 weeks prior to screening. The study will be regarded as reaching the co-primary endpoint of TA if the intra-patient difference of proportions of patients with TA is significant at the two-sided Type 1 error level of 0.05 using a paired McNemar test.

INTERIM ANALYSES

There are no planned interim analyses for this study.

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
$C_{max, SS}$	maximum concentration observed at steady state
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DTDC	drug-target-drug complex
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire
EQ-5D-5L	EuroQoL 5-Dimension Questionnaire, 5–level
FACIT	Functional Assessment of Chronic Illness Therapy
FcRn	neonatal fragment crystallizable receptor
G-CSF	granulocyte colony-stimulating factor
GEE	Generalized Estimating Equation
GPI	glycosylphosphatidylinositol
HCP	health care provider
HRQoL	health-related quality of life
HV	healthy volunteer
ICE	inter-current event
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IFUIRB	Institutional Review Board
IV	intravenous
IxRS	Interactive Voice/Web Response System
LDH	lactate dehydrogenase
LIA	liposome immunoassay
MAC	membrane attack complex
MAVE	major adverse vascular event
MCAR	missing completely at random
MFS	Multidimensional Fatigue Scale
NCI	National Cancer Institute

Abbreviation	Definition
OLE	open-label extension
PD	pharmacodynamics
PedsQL	Pediatric Quality of Life
PK	pharmacokinetic
PNH	paroxysmal nocturnal hemoglobinuria
popPK	*population pharmacokinetic*
pRBC	packed red blood cell
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	Quality of Life
QLQ-C30	Quality of Life-Core 30
QTcF	QT interval corrected through use of Fridericia's formula
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SmPC	Summary of Product Characteristics
SMR	standard mortality ratio
SNP	single nucleotide polymorphism
SOC	*standard of care*
TA	transfusion avoidance
ULN	upper limit of normal
VAS	visual analog scale

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. There is no reported incidence or prevalence in China in the past two decades. Incidence in China is expected to be similar to global estimate (approximate 1.3/1,000,000; data from

Great Britain/France). 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. However, eculizumab is not yet available in China. In China, glucocorticoids are still the first-line drug for the treatment of PNH to control hemolysis attacks though there is significant inferiority to C5 inhibitors. 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 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%–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 one or more of the following: infections, inadequate C5 inhibition by eculizumab, surgery, pregnancy, underlying bone marrow failure, and 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 (RecyclingAntibody®; 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 weeks (Q4W) subcutaneous (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.

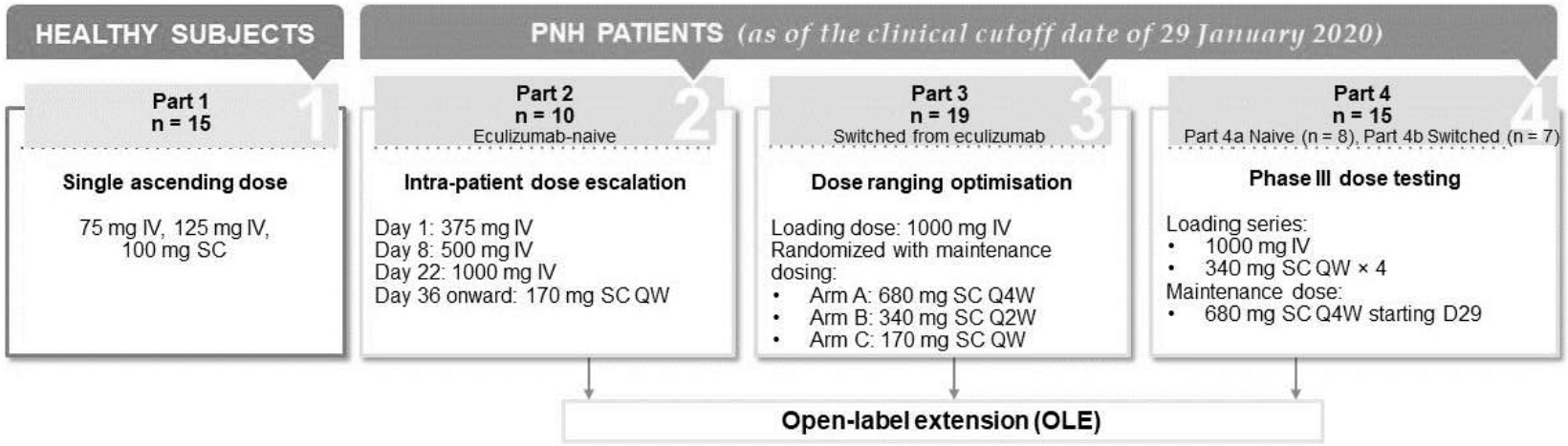
Additionally, crovalimab binds to a different C5 epitope than eculizumab or ravulizumab. In vitro studies with C5 variants (including Arg885His and also V145I, R449G, V802I, R928Q, D966Y, S1310N, and E1437D) have shown that crovalimab binds comparably with these as to wild-type C5 (Fukuzawa et al. 2017). 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. 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 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 (HVs) 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; IV = intravenous; PNH = paroxysmal nocturnal hemoglobinuria; QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

As of the clinical cutoff date (CCOD) of 29 January 2020, 15 HVs (9 HVs received crovalimab and 6 HVs received placebo) and 44 patients with PNH (all received crovalimab) have been enrolled in the study. Study BP39144 included a total of 9 healthy male subjects who received crovalimab, 18 treatment-naive (C5 inhibitors) patients with PNH who received crovalimab and 26 patients with PNH who were 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 data in HVs from Part 1, patients with PNH naïve 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. As of the CCOD 29 January 2020, 40 patients are participating in the OLE: 10 patients from Part 2, 15 patients from Part 3, and 15 patients from Part 4.

Additional clinical data are also available from Study YO42311 (this study), 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 (this study) 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.

Of 18 treatment-naive patients with PNH (10 patients in Part 2 and 8 patients in Part 4 [Arm A]) who *were* treated with crovalimab, 3 patients experienced seven serious adverse events; atrial fibrillation, abdominal pain, coronary artery stenosis, cardiac failure, bile duct stone, cholelithiasis, and hyperglycemia *(CCOD of 29 January 2020)*. All serious adverse events were assessed by the investigators as not related to crovalimab and were resolved at the CCOD. 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 [Arm B]) with PNH who had switched from eculizumab to crovalimab, 6 patients experienced five serious adverse events: hemolysis (2), erysipelas (1), upper respiratory tract infection (1), muscle injury (1), and nephrolithiasis (1); all resolved at the CCOD *(29 January 2020)*. All serious adverse events were assessed by the investigators as not related to

crovalimab except upper respiratory tract infection. All serious adverse events had resolved while on treatment.

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 of 29 January 2020)* 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 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 3.3.1 for details).

The identified dose and dosing regimen were investigated in Study BP39144 Part 4. 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.

1.2.2.2 Pharmacokinetic and Pharmacodynamic Data from Study BP39144 *and YO42311*

A population pharmacokinetic (*pop*PK) *model (legacy popPK model) was initially developed based on* data *from* Study BP39144 *including* the HVs, treatment-naïve 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 model, 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 3.3.1).* Age was also found as a significant covariate on the absorption rate and *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.

Pharmacodynamic data indicate that crovalimab can potently inhibit terminal complement activity in HVs 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).

PK profiles in patients who switched from eculizumab to crovalimab (Part 3) show a transient faster clearance that is not observed in HVs and treatment-naive patients with PNH, which is considered to be related to the formation of DTDCs. The formation of DTDCs presents a safety concern in patients who switched from eculizumab to crovalimab, which could lead to the development of type III hypersensitivity reactions. Dosing was optimized in Part 4 to minimize formation of large DTDCs and maintain crovalimab concentrations required for complement inhibition.

1.2.2.3 Immunogenicity and Anti-Drug Antibody from Study BP39144

Anti-crovalimab antibodies were detected in 6 of 10 HVs (60%), 10 of 18 treatment-naïve patients (56%), and 5 of 25 patients (20%) who switched from eculizumab to crovalimab, as of the CCOD of 29 January 2020. 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 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.

Thirteen patients who switched from eculizumab to crovalimab had detectable ADAs at baseline but were considered ADA-negative per protocol as described below:

- Patients are considered to be ADA-negative if they are ADA-negative at baseline and all postbaseline samples are negative, or if they are ADA-positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The presence of ADAs at baseline in these samples is likely due to an assay artifact resulting from the simultaneous presence of eculizumab and high C5 levels in these patients.

In the majority of ADA-positive patients, ADAs were detected at late timepoints, and there was no evidence of exposure loss, PD effect loss, nor correlation with observed adverse events. One patient was noted to have a decrease in crovalimab exposure and complement inhibition concomitant with ADA-positive titers from Weeks 12 to 36, which resolved by Week 52.

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 remaining of the study and was maintained during the OLE phase. 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 this was maintained through the open-label period (except on Day 29 for 1 patient in the context of an adverse event of hemolytic crisis with concurrent adverse event bronchitis). 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 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 ≥2×ULN after a prior decrease to LDH <1.5×ULN from 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, at Day 181). The BTH rate in patient-years was 0.18 (95% CI: 0.05–0.47). No BTH events in treatment-naive patients meeting the post-hoc criteria have been observed in Parts 2 and 4 (Arm A) at the CCOD.

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-naïve 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 (Part 3) achieved or maintained hemoglobin stabilization.

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

the 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. In China, eculizumab is not yet available. 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 prevent BTH events (Kelly et al. 2011; Hillmen et al. 2013).

The traditional treatment of PNH is aimed at protecting PNH clones, reducing complement attack and destruction, and alleviating hemolysis. Glucocorticoids are still the first-line drugs for the treatment of PNH to control hemolysis attacks, though there is significant inferiority to C5 inhibitors on reduced intravascular hemolysis, reduced or eliminated the need for transfusion, and improved anemia, fatigue, and the quality of life in patients with PNH. The most common adverse events that occurred during glucocorticoid treatment were Iatrogenic Cushing's syndrome, infection, osteoporosis, and hyperglycemia.

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. Crovalimab's 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 low-volume SC dosing Q4W. This has 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 HVs (Part 1 of Study BP39144) and treatment-naive patients with PNH (Parts 2 and 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 DTDC (that comprise eculizumab-C5-crovalimab) occurred transiently in all patients who switch from eculizumab to crovalimab (Parts 3 and 4 [Arm A]). Optimized dosing strategy and risk minimization strategy including patient selection, monitoring, and management of clinical manifestation of DTDC (see 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 discontinue crovalimab and switch to other C5 inhibitor *that* binds to a different C5 epitope.

1.3.3 Benefit and Risk

Crovalimab has shown promising clinical efficacy with effective reduction in intravascular hemolysis and effective terminal complement inhibition to patients with PNH in Study BP39144. Current clinical experience in patients treated with crovalimab indicate that the drug is well tolerated in PNH patients, with no significant adverse events observed. The potential class effect of meningococcal infections can be effectively managed with established risk mitigation strategies. Based upon the available data, crovalimab may provide a treatment option with promising efficacy and manageable safety in Chinese patients with PNH, where C5 inhibitors have demonstrated significant superiority compared with supportive care including glucocorticoid treatment. Moreover, crovalimab has shown promising efficacy in patients with C5 *R885* polymorphisms who do not benefit from treatment with eculizumab. In addition, the benefit of reduced treatment burden with optimal disease control could be substantial in many patients with PNH who require lifelong complement inhibition. In conclusion, the overall benefit-risk may be considered positive in Chinese treatment-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, multicenter, single-arm study designed to evaluate the efficacy, safety, pharmacokinetics, pharmacodynamics, and health status of crovalimab in patients with PNH aged ≥12 years and ≥40 kg who have not been previously treated with a complement-inhibitor therapy.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of crovalimab based on crossing the threshold of the co-primary endpoint hemolysis control and the superiority intra-patient assessment of the co-primary endpoint of TA on the basis of following endpoints:

- Mean proportion of patients with hemolysis control, measured by LDH ≤1.5×ULN from Week 5 through Week 25 (as measured at the central laboratory)
- The difference in the proportion of patients who achieve TA from baseline through Week 25 (after 24 weeks on treatment) and the proportion of patients who were TA within 24 weeks prior to screening

  TA is defined as patients who are packed red blood cell (pRBC) transfusion–free and do not require transfusion per protocol–specified guidelines.

  TA within 24 weeks prior to screening is based on the pRBC transfusion history in the medical records.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objectives for this study are to evaluate the efficacy of crovalimab on the basis 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 ≥2×ULN after prior reduction of LDH to ≤1.5×ULN on treatment.
- Proportion of patients with stabilized hemoglobin from baseline through Week 25

  Stabilized hemoglobin is defined as avoidance of a ≥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 through the use of the FACIT-Fatigue (adults aged ≥18 years)

2.1.3 Other Efficacy Objective

The other efficacy objective for this study is to evaluate the efficacy of crovalimab on the basis of the following endpoints:

- Total number of units of pRBCs transfused per patient from baseline to Week 25
- Mean proportion of patients with $central$ LDH $\leq$1$\times$ULN from Week 5 through Week 25 (as measured at the central laboratory)
- Mean LDH levels from baseline to Week 25 by visit
- Percent change from baseline to Week 25 in $central$ LDH levels by visit
- Time from baseline to first reach of $central$ LDH $\leq$1$\times$ULN
- Time from baseline to first reach of $central$ LDH $\leq$1.5$\times$ULN
- 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 from baseline to Week 25.
- Proportion of patients with MAVE from baseline to Week 25
- Mean change from baseline to Week 25 in Physical Function, Role Function, and Global Health Status/Quality of Life (QoL) scales of the European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 (EORTC QLQ-C30) (for adults aged $\geq$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 adolescents aged 12–17 years)
- Proportion of patients with a $\geq$5-point improvement from baseline in the FACIT-Fatigue at Week 25 (for adults aged $\geq$18 years)

2.1.4 Supportive Historical Objective

The supportive historical objectives are to characterize the efficacy of best supportive care and intra-patient comparison based on the following endpoints:

- Mean LDH, and hemoglobin within 24 weeks prior to screening
- Mean number of blood transfusion and number of units of pRBC transfused within 24 weeks prior to screening
- Proportion of patients who had MAVE as documented in the medical records within 24 weeks prior to screening

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the overall safety of crovalimab 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, (CTCAE), 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

2.3 PHARMACOKINETIC OBJECTIVES

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

- Trough serum concentrations of crovalimab over time
- Serum concentrations of crovalimab at specified timepoints

The other PK objective for this study is as follows:

- To evaluate potential relationships between drug exposure and the efficacy and safety of crovalimab

2.4 IMMUNOGENICITY OBJECTIVES

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

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

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

2.5 BIOMARKER OBJECTIVE

The biomarker objective for this study is to identify and/or evaluate biomarkers that can provide evidence of crovalimab activity (i.e., PD biomarkers) on the basis of the following endpoints:

- Change over time in PD biomarkers, including complement activity measured by LIA
- Change over time in total and free C5 concentration
- Observed value and absolute change from baseline to Week 25 in parameters reflecting hemolysis (reticulocyte count, free hemoglobin, haptoglobin)

The other biomarker objectives for this study are as follows:

- To evaluate the change over time in red cell clone size by flow cytometry and markers from the coagulation system (D–dimer)
- To evaluate the change over time in additional biomarkers of the complement system and markers for intra- and extra-vascular hemolysis (e.g., C3d on RBCs).

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

2.6 HEALTH STATUS UTILITY OBJECTIVE

The health status utility objective for this study is to evaluate health status utility scores of adolescent and adult patients treated with crovalimab on the basis of the following endpoint:

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

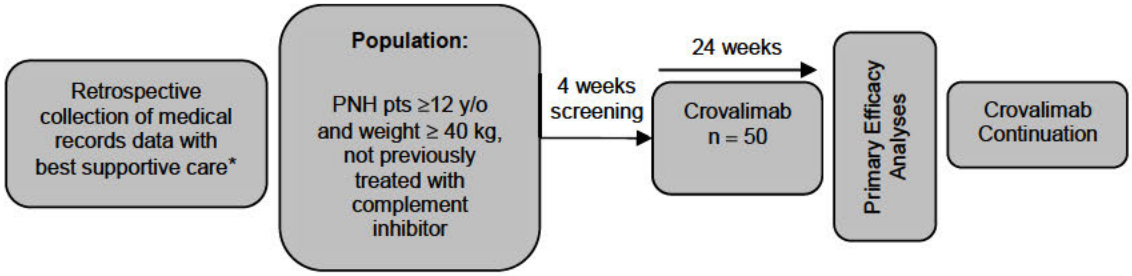
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This single-arm, multicenter, China Phase III clinical study will enroll patients aged 12 years or older, with a body weight ≥40 kg, diagnosed with PNH, who have not been previously treated with a complement-inhibitor therapy. Approximately 50 patients with PNH will be treated with crovalimab for at least 24 weeks.

Figure 2 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 2 Study Design



PNH = paroxysmal nocturnal hemoglobinuria; pts = patients.
*Note: Retrospective collection of medical data with best supportive care for the 24 weeks prior to enrollment.

At screening, all the medical records should be provided to the investigators in the site for eligibility check and medical history data collection. The screening period of the study will last up to 28 days in length for each screening. A maximum of two re-screenings, for a total of three screenings, will be allowed. At screening, LDH testing will be performed two times with at least 2 weeks interval between the measurements by central laboratory.

Patients enrolled should have a history of transfusion events of at least four transfusions in the past year. If necessary, patients may be transfused prior to enrollment to reach a hemoglobin level above the specified transfusion threshold (see Section 4.5.7).

The study will aim to evaluate the efficacy, safety, pharmacokinetics, pharmacodynamics, and health status of crovalimab in patients with PNH aged 12 years

or older, with a body weight ≥40 kg, diagnosed with PNH, who have not been previously treated with a complement-inhibitor therapy. The primary efficacy analysis will be performed when all patients have either completed 24 weeks of treatment with crovalimab or discontinued from the treatment, whichever occurs first. Patients must have received at least one dose of treatment with crovalimab and have at least one central LDH level assessment after the first crovalimab administration to be included in the primary efficacy analysis.

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 study treatment. All patients who receive crovalimab as part of this study will do so according to a weight-based tiered dosing approach schedule (see Table 1). Additional PK samples will be drawn in up to a maximum of 20 patients to characterize crovalimab PK profiles in Chinese patients. More details are provided in Section 6.6. After completing 24 weeks of treatment with crovalimab (i.e., Week 25 visit), patients will be allowed to continue crovalimab Q4W until they can switch to an OLE study (if available), to a commercial product, or receive crovalimab as per the Roche Global Policy on Continued Access to Investigational Medicinal Products.

The 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*. If these patients switch to a different C5 inhibitor, they should remain in safety follow-up and be monitored as detailed in Section 5.1.1.2. More details are provided in Section 4.6.

At selected sites, the Sponsor may propose and conduct exploratory substudies associated with the YO42311 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 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 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Crovalimab Dose and Schedule

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

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

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

3.3.2 Rationale for Patient Population

3.3.2.1 Primary Population

Patients with PNH who were never treated with a C5-inhibitor therapy prior to study entry will comprise the primary population for this Phase III study. Patients will be included if their LDH at screening is at least 2×ULN and have had at least four transfusions in the 12 months prior to screening. The requirements were 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.

3.3.2.2 Inclusion of Adolescents

PNH onset during adolescence is rare. However, when occurring, PNH in adolescents 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. Therefore, the clinical manifestations and the response to treatment with C5 inhibitors is similar in patients with PNH across the age continuum justifying inclusion of adolescents in this trial. Importantly, for these young individuals the potential for reduced treatment burden offered by crovalimab may be particularly meaningful. Adolescents will be included in the primary efficacy population.

The Sponsor anticipates that, because of the rarity of disease among adolescents, only a few of them will be enrolled. Their data will be aggregated with data from adult patients given 1) similar disease process, 2) similar response to intervention, and 3) anticipated similar crovalimab PK and PD in adolescents and adults. The inclusion of adolescent patients in the crovalimab Phase III studies will also provide an important age-specific safety experience.

3.3.3 Rationale for Co-Primary Endpoints

The goal of the study is to demonstrate that in previously C5-inhibitor therapy untreated patients with PNH crovalimab can establish control of hemolysis. This will be done through complementary co-primary endpoints. TA is a disease-related event for patients with PNH and is a clinically significant measure of disease control, has high clinical interpretability, and can be used by physicians and patients to make treatment decisions. 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.

LDH normalization (defined as patients achieving LDH ≤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% to 74% of the patients achieved TA and only 4% to 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 ≤1.5×ULN was the most sensitive and specific predictor of mortality (standard mortality ratio [SMR] of 4.81 for patients with PNH compared to 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 reduced 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.

Using TA and hemolysis control (LDH level ≤1.5×ULN) as co-primary endpoints and supplementing secondary endpoints (BTH, hemoglobin stabilization and FACIT-Fatigue) provides a complete and meaningful picture of drug efficacy, integrating the assessment of the effect on hemolysis with that on clinical outcomes.

3.3.4 Rationale for Biomarker Assessments

Inadequate C5 inhibition and detectable hemolytic activity have been reported in patients with PNH during standard-of-care 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. Moreover, plasma free hemoglobin and serum haptoglobin will also be examined to complement the LDH end point in evaluating intravascular hemolysis prevention.

Additional other biomarkers, including red cell clone size, markers from the complement system, and markers for intra- and extra-vascular hemolysis (e.g., C3d on RBCs) may

be measured in blood samples. An interplay between the complement and coagulation systems may contribute to thrombosis in PNH (Keragala et al. 2018). Thus, D-dimer, the marker from the coagulation system, may also be measured.

3.3.5 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). 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 in adolescent patients, respectively. The EQ-5D-5L will be administered for the purpose of producing health utility scores for economic modeling.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 50 patients with PNH will be enrolled in this study.

4.1.1 Inclusion Criteria

All patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards
- Age ≥12 years at time of signing ICF or Assent Form
- Body weight ≥40 kg at screening
- Willingness and ability to comply with all the 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 screening
- LDH level ≥2×ULN at screening (as per central assessment)

- Patients who have at least four transfusions during 12 months prior to screening (documented in the medical record)
- Presence of one or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), history of a MAVE (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 (Day 1). *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 pneumonia* according to national vaccination recommendations
- Patients who have been vaccinated (partially or in full) against SARS-CoV-2 with a locally approved vaccine are eligible to be 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 ≥30,000/mm^3 at screening without transfusion support within 7 days of lab testing.
- ANC >500/μl 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 ≥28 days prior to screening and up to the first drug administration

- Adequate hepatic function, with ALT ≤3×ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine ≤2.5×ULN and creatinine clearance by Cockcroft-Gault formula ≥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.

  A female patient is considered to be of childbearing potential if the patient is postmenarcheal, has not reached a postmenopausal state (≥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.

4.1.2 Exclusion Criteria

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

- Current or previous treatment with a complement inhibitor
- History of allogeneic bone marrow transplantation
- History of *N. meningitidis* infection within 6 months prior to screening and up to first drug administration
- Known or suspected immune deficiency (e.g., history of frequent recurrent infections)
- Known or suspected hereditary complement deficiency
- Known HIV infection with CD4 count<200 cells/μL within 24 weeks prior to screening

  Patients with HIV infection who have CD4>200 cells/μL and meet all other criteria are eligible

- Infection requiring hospitalization or treatment with intravenous (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
- Splenectomy <6 months before screening
- 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, including hypersensitivity to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product
- Pregnant, breastfeeding, or intention of becoming pregnant during the study or within *46 weeks (or approximately 10.5* months*)* after the final dose of the study treatment

    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

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a single-arm study. Patients with PNH who have never received anti C5 treatment prior to study entry and fulfill the entry criteria at screening will be enrolled to receive crovalimab treatment.

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/Web Response System (IxRS). For those patients who are eligible for enrollment, the study site will obtain the patient's identification number 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 enrolled in this study, they cannot be re-screened.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is crovalimab.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Crovalimab

Crovalimab will be supplied by the Sponsor in a formulation suitable for IV and SC administration. For information on the formulation and handling of crovalimab, see the pharmacy manual and the Crovalimab Investigator's Brochure.

Crovalimab for IV Infusion and SC Administration

Crovalimab vials will be supplied by the Sponsor as a solution for infusion (IV)/solution for injection (SC) from a single-use vial, which contains 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 pharmacy manual.

- The 2 mL (340 mg) configuration will not require the vial-pooling step. The pharmacy manual will be adapted accordingly.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The study treatment is 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.

Guidelines for discontinuation for patients who experience adverse events are provided in Section 5.1.2.

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

IV=intravenous; QW=every week; Q4W=every 4 weeks; SC=subcutaneous.

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 provider (HCP) 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 HCP for 60 minutes following the drug administration.

For all patients, weight will be assessed at screening, at Weeks 13, 25, 33, and every 8-12 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 5.1.2.1).

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.

Training for At-Home 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 will be trained in SC administration of crovalimab by a 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 will gain proficiency in the correct and safe self-administration of SC crovalimab.

Crovalimab is intended to be self-administered as an SC injection Q4W in the home setting, after in-clinic training and supervised self-administration. The SC administrations should be performed by the patient under the observation of a HCP prior to starting home administration. At that time, the HCP will evaluate the self-injection capability of each patient and/or caregiver. Self-injection by the patient or injection by the caregiver will be allowed only once the HCP certifies that adequate proficiency was achieved. At Week 9, SC injections may be self-administered at home by the patient or caregiver if the HCP has confirmed proficiency. Additional training and guidance by a HCP will be available to each patient, at the discretion of the patient or the investigator. Patients have the option to come to the clinic for treatment administration, if he/she prefers.

Patient compliance with at-home-administration will be assessed in two ways during the study: 1) patients 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 will bring their used drug vials in their boxes (including the labels) to each clinic visit for verification of use.

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 or reduction of patient burden and/or obligation in attending study site(s) for the sole purpose of drug administration.

The schedule of activities is provided in Appendix 1.

4.3.3 Rescue Dosing: Crovalimab IV

If a patient 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. 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.

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 Handling and Accountability

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

The IMP 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 IMP 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
- pRBC transfusion

Patients may receive other concomitant medication which must be recorded in 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 strongly not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies may be used during the study at the discretion of the investigator and in consultation with the Medical Monitor.

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

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 the Week 46 safety follow-up telephone call, female patients of childbearing potential will independently conduct a home pregnancy study assessment within two days prior

to 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). ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. Adolescent patients aged 12–17 years will complete and sign an Informed Assent Form, and their parent or a legally authorized representative will complete 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. 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

All the medical records should be provided to the investigators in the site for eligibility check and medical history data collection, including data of PNH history, covering the date of diagnosis, and clone size by high sensitivity flow cytometry within 6 months prior to screening (if available) should be recorded, as well as documentation of the details of transfusion treatment, transfusion episodes, number of pRBC units used and dates of transfusion within the past 12 months prior to screening. Transfusion history should meet the transfusion criteria specified in Section 4.5.7. Records of LDH, hemoglobin, BTH and thrombotic events with dates within 24 weeks prior to screening will also be collected.

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, immunization history, use of alcohol and drugs of abuse, will be recorded at screening. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by the patient from when the Informed Consent Form is signed 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 will be performed at screening in all patients and 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, and every 8–12 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 as detailed in the Crovalimab Investigator's Brochure.

Limited, symptom-directed physical examinations should be performed at post–baseline 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, temperature, and systolic and diastolic blood pressure while the patient is in a seated position. 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 *N. meningitidis*, *H. influenzae* Type B, and *S. pneumonia* Vaccinations

Vaccination against *N. 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 the most current local guidelines or SOC as applicable in patients with complement deficiency.

In the absence of clear local guidelines for N. 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.

H. infuenzae type B, and *S. pneumonia* vaccinations should be done in accordance with current local guidelines or standard of care as applicable in patients with complement deficiency. These vaccinations may be administered any time between Screening Day –28 and one week after the first drug administration.

Patients who receive the vaccines within 2 weeks prior to initiating study treatment or after the start of study treatment must receive appropriate prophylactic antibiotics from initiation of study treatment, continuing for at least 2 weeks after the vaccination. Additional infection prevention measures per local guidelines are permissible.

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, hemoglobin, total and direct bilirubin results, once available, in the eCRF.

In addition, as soon as possible, blood samples will have to be drawn for central testing: LDH, free hemoglobin and haptoglobin, pharmacokinetics, ADA, and PNH clone size. Biomarkers from the complement system, and biomarkers for intra and extra-vascular hemolysis (e.g., C3d on RBCs) as well as the marker of endothelial cell activation and markers from the coagulation system (e.g., D–dimer) may be also tested. If blood transfusions are required, the number of units of pRBCs will be 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.

Prior to enrollment and within 5 days of Week 1 Day 1 of study drug administration, the patient's hemoglobin will be evaluated. At that time, if the patient's hemoglobin value meets the criteria above for transfusion, the patient must be transfused with pRBCs to a hemoglobin level above the transfusion thresholds as specified above. The patient's post-transfusion hemoglobin value should be confirmed to be above the transfusion threshold.

For transfusions 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 in the eCRF.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Laboratory assessments for LDH, potassium, hematology, chemistry, 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: RBC count, hemoglobin, hematocrit, platelet count, reticulocytes absolute count (percentage count may be reported if the absolute count is not available), WBC count and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): 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

- Coagulation: partial thromboplastin time (PTT)/activated PTT (aPTT), prothrombin time (PT)/international normalized ratio (INR)
- Screening PNH clone size
- LDH levels

  This 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 5.1.2.1), they must be recorded on the eCRF.
- 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 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.

  For patients randomized or enrolled to receive crovalimab treatment, during the first 10 weeks on crovalimab, a urine sample should be sent directly 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, to the Sponsor, or to a designee for analysis:

- Serum sample for measurement of LDH and potassium levels
- Serum sample for measurement of total and free C5 concentration
- Serum sample for measurement of LIA
- Serum sample for measurement of haptoglobin levels
- Plasma sample for measurement of free hemoglobin
- Blood sample for PNH clone size with C3d on RBC for all post-screening measurements
- Plasma sample for D-dimer testing
- Serum ADA sample for crovalimab immunogenicity analysis

- Serum PK sample for crovalimab PK analysis

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 other research, biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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 will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of other 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 electrocardiogram (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 (except PROs) scheduled at that same time (e.g., vital sign measurements, blood draws) 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 5.1. 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 addition, PRO instruments (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, EORTC QLQ-C30 (select scales)
- For adolescent patients (aged 12-17 years): PedsQL Core and the PedsQL MFS (Physical Functioning scale)
- EQ-5D-5L

4.5.10.1 Data Collection Methods for Patient-Reported Outcomes

PRO instruments will be self-administered at the clinic at the 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 and validated as appropriate, will be provided by the Sponsor in pre-printed 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; Cella et al. 2005; Lai et al. 2011; 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.

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, 13–18 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 adolescent self-report version with a 1-week recall period (i.e., acute adolescent version) will be used for patients 12–17 years old, as the wording is the same for this scale in the 8–12 and 13–17 self-report versions.

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 (e.g., 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, 13–18 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 adolescent self-report version with a 1-week recall period (i.e., acute adolescent version) will be used for patients 12–17 years old, as the wording is the same in the 8–12 and 13–17 self-report versions.

EQ-5D-5L

The EQ-5D-5L, is a validated self-reported 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 will be administered to

adult and adolescent patients and takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

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 after treatment discontinuation *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.

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.

Patients who discontinue crovalimab without switching to another complement inhibitor should be monitored for signs and symptoms of serious intravascular hemolysis for at least 20 weeks (see details in Section 5.1.1.7).

Hemolysis occurring after treatment discontinuation and until completion of the safety follow-up visit should be recorded in the eCRF.

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.

Several 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 (see Section 5.1). Details regarding safety reporting for this study are provided in Section 5.4.

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 final dose of crovalimab. 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 Summary of Product Characteristics [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 4.5.5.1.

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

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate subjects immediately if an infection is suspected and treat with antibiotics if necessary. Monitoring of subjects 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 the 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

To those patients who have access and switch to other C5-inhibitors after discontinuation of crovalimab, Type III hypersensitivity may occur due to the transient formation of DTDCs made of other C5-inhibitor, C5 and crovalimab (more details of DTDCs could be found in the Crovalimab Investigator's Brochure v4 Section 6.7.2). To minimize the risk, monitoring and management guidelines are provided and only applicable to patients who discontinued crovalimab and switched to other C5–inhibitors. 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)

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

Generic signs and symptoms of Type III hypersensitivity reactions can include fever, malaise, enlarged and tender lymph nodes, enlarged spleen, arthralgias, neuralgias, vasculitis, urticarial rashes, purpura, gastrointestinal distress, and glomerulonephritis. Laboratory findings could include leukopenia, leukocytosis with eosinophilia, proteinuria, and lowered serum C3, C4, and complement hemolytic activity (from consumption).

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 crovalimab to other C5 inhibitor. 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 Week 7 and Week 9 after switching from crovalimab to another C5 inhibitor (as detailed in

Appendix 2). Biopsies of skin manifestations can be done, if considered clinically indicated.

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.

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 first IV infusion and the first four SC injections, crovalimab should be administered in a clinical environment where resuscitation equipment is available for immediate use.

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 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.

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 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).

Hemolysis occurring after treatment discontinuation and until completion of the safety follow-up visit should be recorded in the eCRF.

5.1.2 Management of Patients Who Experience Adverse Events

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

5.1.2.1 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 $\geq$2 ULN measured at 3 consecutive assessments and persisting for at least 4 weeks, where each LDH$\geq$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 $\geq$40 kg to $<$100 kg would increase their maintenance dose from 680 mg Q4W to 1020 mg Q4W
- Patients with body weight $\geq$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 and 2):

- 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.

5.1.2.2 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 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.

5.1.2.3 Management Guidelines

Crovalimab (for the initial IV infusion and the first five vial-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 Reactions	
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.
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 pruritus and rash, administer antihistamines and topical corticosteroids. • Monitor kidney function and perform urinalysis (Section 4.5.8). • Continue crovalimab.

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

Event	Action to Be Taken
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 the 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 the Medical Monitor for Grade 3 infections that persist for >7 days. • Discuss continuation of crovalimab with the 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.

IRR=infusion-related reaction; ISR=injection-site reaction; IV=intravenous.

[a] Grade 3 ISRs 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 5.4.

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 for definitions) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 through Section 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 crovalimab, 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 after the final dose of crovalimab.

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 (v5.0), 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 (see also Table 4):

- 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

Table 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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×ULN) in combination with either an elevated total bilirubin (>2×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×ULN in combination with total bilirubin >2×ULN
- Treatment-emergent ALT or AST >3×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.

5.4 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 Institutional Review Board (IRB)/ Ethics Committee (EC).

5.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day,

7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all 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 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. 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 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 *>46* weeks *(approximately 10.5 months)* after the final dose of crovalimab 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 within *46* weeks *(approximately 10.5 months)* after the final dose of crovalimab. 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 event 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.

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), 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 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.

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).

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 primary efficacy objective for this study is to evaluate the effect of crovalimab based on crossing the threshold of the co-primary endpoint hemolysis control and the superiority intra–patient assessment of the co-primary endpoint of TA. The study will be

regarded as successful when the co-primary endpoints have reached the success criteria.

Approximately 50 patients with PNH will be enrolled in the study.

Table 5 shows the 95% CI for potentially observable proportions of patients with LDH ≤ 1.5×ULN while on the study. The proportion of patients with LDH normalization (LDH≤1×ULN) in the eculizumab treated arm in study 301 is 49.4% (95% CI: 41.7% to 57%) (Lee et al. 2019). Under the assumption of LDH being log-normally distributed, the expected proportion of patients with LDH ≤1.5×ULN is 86%. Although it is unlikely that untreated patients have LDH levels below 1.5×ULN, it's assumed 20% of untreated patients achieve this LDH level to be conservative when defining the efficacy threshold. With these assumptions, the minimum proportion of patients with LDH ≤1.5xULN being crossing the efficacy threshold of 60% will preserve about 60% of the effect of eculizumab with sample size of 50. The study will be regarded as reaching the co–primary endpoint of hemolysis control (based on LDH≤ 1.5×ULN) if the 95% CI lower bound is at least 60%.

Table 5 Summary of 95% CI (Wilson method) for Potentially Observable Proportions of LDH ≤1.5xULN Given N=50

No. of Patients with LDH ≤1.5xULN	Proportion of Patients with LDH ≤1.5xULN	Lower 95% CI	Upper 95% CI
35	70%	56%	81%
36	72%	58%	83%
37	74%	60%	84%
38	76%	63%	86%
39	78%	65%	87%
40	80%	67%	89%
41	82%	69%	90%
42	84%	71%	92%
43	86%	74%	93%
44	88%	76%	94%
45	90%	79%	96%

CI=confidence interval; LDH=lactate dehydrogenase; N=no. of patients; ULN=upper limit normal.

Proportion of patients who achieve TA from baseline through Week 25 will be compared with proportion of patients who were TA within 24 weeks prior to screening. The study will be regarded as reaching the co-primary endpoint of TA if the intra-patient difference of proportions of patients with TA is significant at the two-sided Type 1 error level of 0.05 using a paired McNemar test.

Table 6 shows the 95% CI around a potential range in the percentage of patients that would avoid transfusions while on the study. In the TRIUMPH study (Hillmen et al. 2006), TA was achieved in 22 of 43 of patients (51%) in the eculizumab treated arm and none of the patients from the Placebo arm (n=44) were transfusion free at Week 25.

Table 6 Summary of 95% CI (Wilson method) for Potentially Observable TA Proportions Given N=50

No. of Patients with TA	Proportion of Patients with TA	Lower 95% CI	Upper 95% CI
20	40%	28	54
22	44%	31	58
25	50%	37	63
26	52%	39	65
28	56%	40	67
30	60%	46	72

CI=confidence interval; N=no. of patients; TA=transfusion avoidance.

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, total number of pRBC transfused, and baseline LDH category) will be summarized 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 will include all enrolled patients who received at least one dose of crovalimab and have at least one *centrally processed* 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 patients who have met* the inclusion and exclusion criteria (Section 4.1), *received* at least one dose of crovalimab, and *have* at least one *centrally processed* LDH *level assessment after the first IV infusion*.

- Variable: $central$ LDH measured at pre-specified hospital visits from Week 5 to Week 25 and any transfusion event from 24 weeks prior to the screening 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 5.1.2.1 on dose modifications) will be included in the primary analysis.
- Population-level summary (estimate): Mean proportion of patients with hemolysis control, i.e., LDH≤1.5×ULN from Week 5 through Week 25 and the difference in the proportion of patients with TA from baseline through Week 25 and the proportion of patient who were TA within 24 weeks prior to screening.

6.4.2 Primary Efficacy Analyses

The primary efficacy analysis will take place when all patients have either completed 24 weeks of treatment with crovalimab or have discontinued the study drug, whichever occurs first.

6.4.2.1 Hemolysis Control

The co-primary endpoint of the mean proportion of patients with hemolysis control is defined as LDH≤1.5×ULN from Week 5 through Week 25 (as measured at the central laboratory).

For each patient at each visit, a binary variable will be created with the value of 1, if LDH ≤1.5×ULN, and 0, otherwise. A Generalized Estimating Equation (GEE) will be used to estimate the mean proportion of hemolysis control (i.e., LDH≤1.5×ULN from Week 5 through Week 25 and 95% confidence interval).

The primary analysis will use the standard GEE based on the available LDH assessments, assuming the missing data are missing completely at random (MCAR).

Sensitivity analyses will be performed based on different missing data handling rules to assess the robustness of the primary analysis results. These sensitivity analyses will be described in more detail in the Statistical Analysis Plan (SAP).

6.4.2.2 Transfusion Avoidance

The co-primary endpoint of proportion of patients who achieve TA consists of proportion of patients who achieve TA from baseline through Week 25 (after 24 weeks on treatment) and proportion of patients who were TA within 24 weeks prior to screening. TA is defined as patients who are pRBC transfusion-free and do not require transfusion per protocol-specified guidelines.

The intra-patient comparison between proportion of patients with TA from baseline through Week 25 and proportion of patient who were TA within 24 weeks prior to screening will be made using a paired McNemar test at two-sided Type 1 error level of 0.05. The proportion of TA and the corresponding 95% CIs based on Wilson's method (1927) will be provided.

For the primary analysis, patients who withdrew early before Week 25 independent of the reason for withdrawal will be included in the analysis as non–responders (i.e., requiring transfusion).

Sensitivity analyses will be performed according to the causes for dropping out of the study before Week 25. These sensitivity analyses will be described in more detail in the SAP.

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 stabilized hemoglobin from baseline through Week 25
- Mean change from baseline to Week 25 in fatigue as assessed through the use of the FACIT-Fatigue (adults aged ≥18 years)

The definitions of BTH and stabilized hemoglobin are provided in Section 2.1.2.

Proportion of patients with BTH will be reported with 95% CI, and are calculated with the number of subjects as the denominator.

The proportion of patients with stabilization of hemoglobin will be analyzed using the same methodology as the secondary efficacy endpoint of BTH.

Change from baseline in FACIT-Fatigue total scores (range of 0–52) will be summarized over time with means, standard deviations, medians, and ranges. Graphs of the mean changes and standard errors over time will also be provided.

6.4.4 Other Efficacy Analyses

All other efficacy endpoints have been defined in Section 2.1.3.

Continuous data, including total number of units of pRBC transfused from baseline to Week 25 will be summarized by the group mean, standard deviation, median, and range.

Time from baseline to first reach of LDH $\leq 1 \times$ULN and LDH $\leq 1.5 \times$ULN will be analyzed using Kaplan-Meier methodology.

Mean proportion of patients with LDH $\leq 1 \times$ULN from Week 5 through Week 25 (as measured at the central laboratory) will use the same method as co-primary endpoint hemolysis control.

Proportion of patients with MAVE and 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 from baseline to Week 25 will use the same method as the second efficacy endpoint BTH.

The other endpoints regarding absolute value and change from baseline will be summarized over time with means, standard deviations, medians, and ranges. Graphs of the mean absolute value and changes and standard errors over time from the baseline assessment will provide visual description. Details will be provided in the SAP.

6.4.5 Supportive Historical Analyses

Historical medical record data from the study population will be used to characterize the efficacy of crovalimab versus best supportive care via intra-patient analyses. Before any intra-patient comparison, data collection frequency, consistency and completeness of the medical history data will be examined to assess the quality. The intra-patient comparison other than TA between historical data and post baseline data will be used as supportive evidence only, as the different methods of data collection (retrospective vs prospective) might limit the interpretability of the statistical analysis results.

Historical medical record data including LDH, and hemoglobin within 24 weeks prior to screening will be presented by summary statistics (N, mean, median, standard deviation, range) by nominal timepoints. Spaghetti plots (plots of individual patients over-laid with mean and median plots of the same individuals) with reference lines for the normal

range for absolute value will be provided for LDH and hemoglobin collected both within 24 weeks prior to screening and 24 weeks post baseline.

Number of transfusions and number of RBC units in 24 weeks prior to screening will be summarized using number of records, means, standard deviations, medians, and ranges. The comparison between 24 weeks prior to screening and 24 week post baseline will be summarized by the average difference as well as the corresponding 95%CI calculated on the basis of the t-distribution.

The proportion of patients who had MAVE as documented in the medical records within 24 weeks prior to screening will be provided if applicable. The comparison between 24 weeks prior to screening and 24 week post baseline will be provided with a difference between the proportions and 95% CI on the basis of a normal approximation to the binomial distribution.

The comparison between historical data and post-baseline data will be described in detail in the SAP.

6.4.6 Handling Missing Data

For the co-primary endpoint of hemolysis control (based on LDH $\leq$1.5xULN), the primary analysis will use the standard GEE based on the available LDH assessments, assuming missing data are MCAR. For the co-primary endpoint of TA, patients who withdrew early from baseline through Week 25 independent of the reason for withdrawal will be included in the analysis as non-responders (i.e., requiring transfusion) for the primary analysis.

The detailed missing data handling rules will be described in the SAP.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety evaluable population, defined as all enrolled patients who received at least one dose of crovalimab.

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.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (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 sign (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 worst post baseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

The pharmacokinetic analyses will be performed on the PK-evaluable population, defined as all patients who received at least one dose of crovalimab and who took at least one PK blood sample, as data allow and where appropriate.

Patients may be excluded from the PK analysis population if, in the opinion of the clinical pharmacologist, they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete, where the PK analysis might be influenced. Excluded cases will be documented, including the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

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

To characterize crovalimab steady state pharmacokinetics in Chinese patients, additional PK samples will be collected at Weeks 21 (Day 4), 22, 23, and 24 in up to a maximum of 20 patients. Summary descriptive statistics of serum PK parameters including maximum concentration observed at steady state ($C_{max, SS}$), area under the concentration–time curve at steady state (AUC_{SS}) derived using non–compartmental analysis will be presented including means, geometric means, standard deviation, coefficient of variation, medians and ranges.

Non-linear mixed effects modeling will be used to analyze the dose-concentration-time profiles of crovalimab and evaluate the potential influence of ethnicity on population PK parameters, such as clearance and volume of distribution. Data will be pooled with data from other studies that enrolled patients from different ethnic groups to investigate the influence of ethnicity on population PK parameter estimates.

The influence of other covariates such as age, sex and body weight on population PK parameter estimates will also be investigated. Inter-patient variability will be evaluated. The relationship between PK and efficacy or safety endpoints may also be explored.

Additional PK analysis may be conducted as appropriate. 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.

The numbers and proportions of ADA–positive patients and ADA–negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized. 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 post–baseline 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 post-baseline 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.

6.8 BIOMARKER ANALYSES

Change over time in PD parameters (e.g., complement inhibition by LIA, C5 levels) and other biomarkers will be presented using summary statistics (e.g., arithmetic and geometric means, median, range, standard deviations, and coefficients of variation). 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.

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 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.

7.4 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 into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 9.6.

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.

7.5 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 at least 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).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form 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 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 a legally authorized representative 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. 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.

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 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 managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management (involving clinical research organization), data management, and medical monitoring.

Approximately 10 sites will participate to enroll approximately 50 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.

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 healthcare 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 healthy 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: Overall Schedule of Activities for Patients Until Study Discontinuation/Safety Follow-Up

	Screening	Crovalimab Treatment Period										Crovalimab Continuation [x]	Safety Follow-Up *Site Visit* [w]	*Safety Follow-Up Telephone Call*
Study Week	–4 to –1	1		2	3	4	5	9	13	17	21	≥25 [x]		
Day		1	2											
Informed consent [a]	x													
Neisseria meningitidis, *Haemophilus influenzae type B*, and *Streptococcus pneumonia* vaccinations [b]	x													
Medical history and baseline conditions [c]	x													
Demographic data [d]	x													
Blood sample for PNH clone size [e]	x	x							x			x	x	
Complete PE [f]	x													
Limited PE [f]		x	x	x	x	x	x	x	x	x	x	x	x	
Vital signs [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Pregnancy test [h, i]	x	x					x	x	x	x	x	x	x	*x*
12-Lead ECG [j]	x	x					x					x		
Concomitant medications [k]	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*
pRBC transfusions [k]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Hematology [h, l, y]	x	x		x	x	x	x	x	x	x	x	x	x	

Appendix 1: Schedule of Activities

Table 1: Overall Schedule of Activities for Patients Until Study Discontinuation/Safety Follow-Up (Cont.)

	Screening	Crovalimab Treatment Period										Crovalimab Continuation [x]	Safety Follow-Up *Site Visit* [w]	*Safety Follow-Up Telephone Call*
Study Week	–4 to –1	1		2	3	4	5	9	13	17	21	≥25 [x]		
Day		1	2											
Free hemoglobin, haptoglobin [h, m]		x		x	x	x	x	x	x	x	x	x	x	
Coagulation [h, n]	x	x					x		x		x	x	x	
Chemistry [h, o, y]	x	x		x	x	x	x	x	x	x	x	x	x	
Urinalysis [h, p]	x	x						x		x		x	x	
Adverse events [q]	x													
Assessment and documentation of BTH [h, r]		x	x	x	x	x	x	x	x	x	x	x	x	
Serum sample for LDH and potassium [h, s, y]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Plasma and serum sample set for biomarkers [t, y]		x		x	x	x	x	x	x	x	x	x	x	
Serum ADA sample for crovalimab [h, t, y]		x		x	x	x	x	x	x	x	x	x	x	
Serum PK sample for crovalimab [h, t, u, y]		x	x	x	x	x	x	x	x	x	x	x	x	
FACIT-Fatigue, EORTC QLQ–C30 scales (adults only) [v]		x		x			x	x		x			x	
PedsQL Core and PedsQL MFS (adolescents only) [v]		x		x			x	x		x			x	
EQ-5D-5L [v]		x		x			x	x		x			x	
Crovalimab administration		x	x	x	x	x	x	x	x	x	x	x		

Table 1: Overall Schedule of Activities for Patients Until Study Discontinuation/Safety Follow-Up (Cont.)

ADA = anti-drug antibody; ALP=alkaline phosphatase; aPTT=activated partial thromboplastin time; BTH = breakthrough hemolysis; BUN=blood urea nitrogen; ECG=electrocardiogram; eCRF = electronic Case Report Form; EoI = end of injection; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire; EQ-5D-5L= EuroQoL 5-Dimension Questionnaire, 5–level; FACIT = Functional Assessment of Cancer Therapy; INR=international normalized ratio; IV=intravenous; LDH=lactate dehydrogenase; LIA=liposome immunoassay; MFS=Multidimensional Fatigue Scale; PD=pharmacodynamic; PE = physical examination; PedsQL=Pediatric Quality of Life; PK=pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed red blood cell; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; QW = every week; Q4W = every 4 weeks; Q8W = every 8 weeks; Q16W = every 16 weeks; Screen = screening.

Note: All assessments should be performed within ±2 days of the scheduled visit for the first 24 weeks 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.

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

[b] *Vaccination against* ***N. 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* ***S. pneumonia*** *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.*. Patients who receive a vaccine less than 2 weeks before initiating treatment must receive treatment with appropriate prophylactic antibiotics until 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.*

[c] For the collection of medical historical data and baseline condition, refer to Section 4.5.2 for details.

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

[e] Blood sample to determine PNH clone size. At screening only, historical data collected no more than 6 months prior to screening 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, PNH RBC clone size and C3d on RBCs may be measured centrally.

[f] 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. Height and weight will be recorded at screening and at Weeks 13 and 25.

Table 1: Overall Schedule of Activities for Patients Until Study Discontinuation/Safety Follow-Up (Cont.)

[g] 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.

[h] To be collected prior to study drug dose administration. Prior to enrollment and within 5 days of Week 1 Day 1 of study drug administration, the patient's hemoglobin will be evaluated.

[i] 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.

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

[k] 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*. Report previous and concurrent pRBC transfusions.

[l] Hematology will be assessed locally. It includes RBC count, hemoglobin, hematocrit, platelet count, reticulocytes count (or percentage count if absolute count is not available, WBC count, and differential count.

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

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

[o] Chemistry panel (serum or plasma) will be assessed locally. It includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care 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 if it 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.

[p] 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.

Table 1: Overall Schedule of Activities for Patients Until Study Discontinuation/Safety Follow-Up (Cont.)

[q] 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. 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 time point (see Section 5 for additional details and reporting requirements).

[r] Symptoms of BTH and confirmation of blood sampling for local LDH, 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, free hemoglobin, haptoglobin, pharmacokinetics, ADA*s,* and biomarkers (may be included). If blood transfusions are required, the number of units of pRBCs will be also documented in the eCRF.

[s] At screening, LDH and potassium testing will be performed for 2 times with at least 2 weeks interval between the measurements by central laboratory. Additional LDH and potassium samples for all the visits will be obtained and sent to a central laboratory for analysis.

[t] In case of an adverse event of BTH or a hypersensitivity reaction on a patient treated with crovalimab, an additional sample *for pharmacokinetics*, ADAs, and biomarkers (total free C5 D-dimer and liposome) should be drawn as close as possible to the onset of the event. In the event of BTH accompanied by an IV rescue dose of crovalimab, the sampling should occur prior to the drug administration.

[u] See Table 3 of Appendix 1.

[v] 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.

[w] Only for patients who discontinue at or before Week 25. All other patients should follow schedules in Table 2 of Appendix 1 for assessments after Week 25. For patients who discontinue from crovalimab treatment, 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.

[x] Patients continue to receive crovalimab. At the Week 25 visit (after completion of 24 weeks of study treatment), crovalimab will be administered every 4 weeks. Assessments will be taken Q8W or Q12W following Week 25 (see Table 2 of Appendix 1 for schedule of activities for patients continuing crovalimab treatment at Weeks ≥25).

[y] 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), ADAs (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.

Appendix 1: Schedule of Activities

Table 2: Schedule of Activities for Patients Continuing Treatment with Crovalimab 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)*[r]	*Safety Follow-Up Telephone Call (46 Weeks after Last Dose)* [r]
Blood sample for PNH clone size [a]	Follow Table 1 Week 25 Schedule for each corresponding row			x	
Limited PE [b]		x	x	x	
Vital signs [c]		x	x	x	
Pregnancy test [d, e]		x	x	x	*x*
12-Lead ECG					
Concomitant medications [f]		x	x	x	*x*
pRBC transfusions [g]		x	x	x	
Hematology [d, h, s]		x	x	x	
Free hemoglobin, haptoglobin [d, i]		x	x	x	
Coagulation [d, j]		x	x	x	
Chemistry [d, k, s]		x	x	x	
Urinalysis [d, l]		x	x	x	
Adverse events [m]		x	x	x	*x*
Assessment and documentation of BTH [d, n]		x	x	x	
Serum sample for central LDH and potassium [d, o, s]		x	x	x	
Plasma and serum sample set for biomarkers [d, p, s]		x	x	x	
Serum ADA sample for crovalimab [d, p, s]		x	x	x	
Serum PK sample for crovalimab [d, p, s]		x	x	x	
FACIT-Fatigue, and EORTC QLQ-C30 scales, (adults only) [q]		x	x	x	
PedsQL Core and PedsQL MFS (adolescents only) [q]		x	x	x	
EQ-5D-5L [q]		x	x	x	

Appendix 1: Schedule of Activities

Table 2: Schedule of Activities for Patients Continuing Treatment with Crovalimab at Weeks ≥25 (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)*[r]	*Safety Follow-Up Telephone Call (46 Weeks after Last Dose)* [r]
Crovalimab administration	Q4W				

ADA = anti-drug antibody; aPTT=activated partial thromboplastin time; BTH = breakthrough hemolysis; BUN=blood urea nitrogen; DTDC = drug–target-drug complex; ECG=electrocardiogram; eCRF = electronic Case Report Form; EoI = end of injection; EORTC QLQ–C30 = European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire; EQ–5D–5L=EuroQoL 5-Dimension Questionnaire, 5–level; FACIT = Functional Assessment of Cancer Therapy; INR=international normalized ratio; LDH=lactate dehydrogenase; MFS = Multidimensional Fatigue Scale; PD = pharmacodynamic; PE = physical examination; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed red blood cell; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q4W = every 4 weeks; Q8W = every 8 weeks;.

Note: 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.

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

[b] Height and weight will be recorded at each specified assessment.

[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] To be collected prior to study drug dose administration.

[e] 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.

[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] Hematology will be assessed locally. It includes RBC count, hemoglobin, hematocrit, platelet count, reticulocytes count (or percentage count if absolute count is not available), WBC count, and differential count.

Table 2: Schedule of Activities for Patients Continuing Treatment with Crovalimab at Weeks ≥25 (cont.)

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

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

[k] Chemistry panel (serum or plasma) will be assessed locally. It includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard-of-care 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 if it 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.

[l] 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.

[m] 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.

[n] Symptoms of BTH and confirmation of blood sampling for local LDH, hemoglobin, and bilirubin measurement, 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, free hemoglobin, haptoglobin, pharmacokinetics, ADA, and biomarkers (may be included). If blood transfusions are required, the number of units of pRBCs will be also documented in the eCRF.

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

[p] In case of an adverse event of BTH or a hypersensitivity reaction on a patient treated with crovalimab, an additional sample of PK, ADA, and biomarkers should be drawn as close as possible to the onset of the event. In the event of BTH, accompanied by an IV rescue dosing of crovalimab, the sampling should occur prior to the drug administration.

[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.

[r] Follow-up safety assessments to be taken 24 weeks 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.

Table 2: Schedule of Activities for Patients Continuing Treatment with Crovalimab at Weeks ≥25 (cont.)

[s] 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.

Appendix 1: Schedule of Activities

TABLE 3: SCHEDULE OF ACTIVITIES FOR PHARMACOKINETIC PARAMETERS FROM WEEK 1 THROUGH WEEK 25

	Screen	Crovalimab Treatment Period														
Study Week	–4 to –1	1		2	3	4	5	9	13	17	21	21 [a]	22 [a]	23 [a]	24 [a]	25
Day		1	2	1	1	1	1	1	1	1	1	4	1	1	1	1
Serum PK sample [b, c]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

PK=pharmacokinetic.

[a] PK samples at Week 21 Day 4, Weeks 22, 23, and 24 is limited for the enrolled Chinese patients (maximum of 20 patients) in addition to the other PK sampling from Weeks 1 through Week 25. PK samples (Week 21 Day 4, Day 1 of Week 22, 23, 24) for crovalimab at these visits should be collected ±24 hours.

[b] At Week 1 Day 1 visit, the PK samples for crovalimab IV should be collected before the start of infusion (within 2-hour pre-dose) and within 30 minutes after the end of infusion.

[c] PK samples at Day 1 of Week 2, 3, 4, 5, 9, 13, 17, 21, and 25 visits should be collected within 2 hours before the administration.

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

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 24 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. 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 infusion:

- 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 infusion, 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

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