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

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STATISTICAL ANALYSIS PLAN

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

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STATISTICAL ANALYSIS PLAN APPROVAL

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CONFIDENTIAL

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1. BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare, acquired, clonal, hematopoietic stem cell disorder in which hematopoietic cells acquire a somatic mutation in the gene encoding phosphatidylinositol glycan anchor biosynthesis class A located on chromosome X. As a result, 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. The current standard of care for treatment of patients with PNH with symptomatic hemolysis or thrombosis is component 5 (C5) inhibition with eculizumab or ravulizumab. Eculizumab significantly reduces intravascular hemolysis as measured by serum lactate dehydrogenase (LDH), stabilizes hemoglobin, reduces the need for red blood cells (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]).

While C5 inhibitors such as eculizumab are highly effective in the majority of patients in decreasing symptoms and complications of PNH, they do not affect the natural history of the disease because C5 inhibition does not affect the PNH clone (Brodsky et al. 2008; Brodsky 2009). Therefore, patients with PNH require lifelong treatment to prevent complications and symptoms. Patients treated with eculizumab (standard of care) are required to receive maintenance infusions every 2 weeks (Q2W). Approximately 10% to 15% of patients treated with labeled dose of eculizumab experience an increase in hemolysis near the end of the dosing interval and may require either a higher-than-approved dose of eculizumab or more frequent dosing to control Breakthrough Hemolysis (BTH; Kelly et al. 2011; Hillmen et al. 2013). In addition, approximately 35% to 50% of patients continue to require regular transfusions despite eculizumab treatment (Brodsky et al. 2008). Therefore, there remains a high unmet medical need in the treatment of PNH, despite recent significant improvements.

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 Sequential Monoclonal Antibody Recycling Technology-Immunoglobulin G (SMART-Ig) (Recycling Antibody®)

(Fukuzawa et al. 2017) with pH-dependent antigen binding allowing for efficient target disposal, and enhancement of neonatal fragment crystallizable receptor (FcRn) binding to improve antibody recycling efficiency, which results in a prolonged half-life and prolonged complement inhibition. The physicochemical properties of crovalimab support the development of high concentration formulation. The combination of the SMART-Ig and the high concentrated formulation enable every 4 weeks (Q4W) subcutaneous (SC) dosing. Based on clinical data, nonclinical pharmacology, and pharmacodynamic (PD) data, crovalimab has been shown to lead to consistent and complete complement protein C5 inhibition resulting in suppression of intravascular hemolysis at the targeted dosing regimens.

Crovalimab is currently being developed for the treatment of patients with PNH who have not previously been treated with complement inhibitors and who have been currently treated with complement inhibitors.

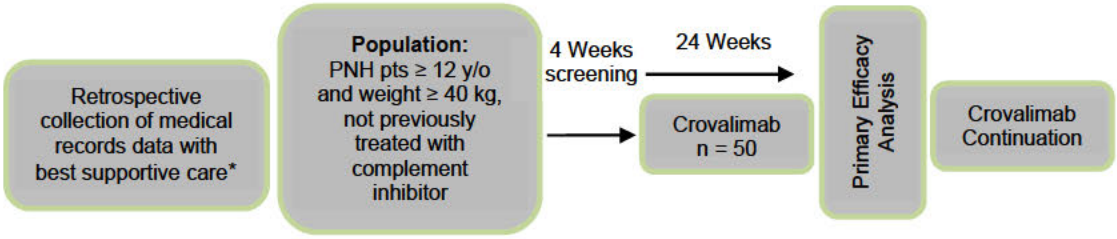
This Phase III, single-arm, multicenter study will evaluate the efficacy and safety, pharmacokinetics, and pharmacodynamics of crovalimab in patients with PHN not previously treated with complement inhibition.

2. STUDY DESIGN

This is a single-arm, multicenter, Phase III clinical study that will enroll Chinese 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 will be treated with crovalimab for at least 24 weeks.

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

Figure 1 Study Schema



PNH = paroxysmal nocturnal hemoglobinuria; pts= patients; n = number of patients enrolled; y/o = years or older.

*Note: Retrospective collection of medical data with best supportive care for the 24 months prior to enrollment

The screening period of the study will last up to 28 days. A maximum of two re-screenings, i.e., a total of three screenings, will be allowed. At screening, LDH testing

will be performed twice with at least 2 weeks interval between the measurements by the central laboratory.

The primary efficacy analysis will be performed when all enrolled patients have either completed 24 weeks of treatment in the study or discontinued from treatment, whichever occurs first. 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 (OLE) study (if available), 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 crovalimab on the study. All patients who discontinue from study treatment will return for a safety follow-up visit 24 weeks after treatment discontinuation. If these patients switch to a different C5 inhibitor, they should remain in safety follow-up and be monitored. For all patients, the day of the safety follow-up visit represents study discontinuation date.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 ENDPOINTS

2.2.1 Primary Efficacy Endpoints

The primary efficacy objective of this study is to evaluate the efficacy of crovalimab based on the following co-primary endpoints. Both co-primary endpoints need to be met to conclude the positive study results:

- The population proportion of patients with hemolysis control, measured by LDH $\leq 1.5 \times$ 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 transfusion avoidance (TA) from baseline through Week 25 (after 24 weeks of treatment) and the proportion of patients who achieve TA within 24 weeks prior to screening.
  - TA from baseline through Week 25 is defined as patients who are packed red blood cell (pRBC) transfusion-free and do not require transfusion per protocol-specified guidelines (Appendix 3).
  - TA within 24 weeks prior to screening is based on the blood transfusion history in the medical records.

2.2.2 Secondary Efficacy Endpoints

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 3 including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH $\geq 2\cdot\times$ ULN after prior reduction of LDH to $\leq 1.5\times$ 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. Baseline hemoglobin is defined as the latest available hemoglobin measurements prior to the first on-study crovalimab administration.
- Mean change from baseline to Week 25 in fatigue as assessed through the use of the FACIT-Fatigue (adults aged $\geq$ 18 years) (Yellen et al. 1997).

2.2.3 Exploratory Efficacy Endpoints

The exploratory 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
- The population proportion of patients with LDH $\leq 1\cdot\times$ 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 LDH levels by visit
- Time from baseline to first measurement of LDH $\leq 1\cdot\times$ ULN
- Time from baseline to first measurement of 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 (Appendix 3) 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 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)
  - Multidimensional Fatigue Scale (MFS)
  - Physical Functioning scale of the PedsQL Core

2.2.4 Supportive Historical Efficacy Endpoints

The supportive historical objectives are to characterize the efficacy of the best supportive care. These endpoints will be evaluated based on:

- 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 BTH and the proportion of patients who had MAVE as documented in the medical records within 24 weeks prior to screening.

2.2.5 Pharmacokinetic Endpoints

The pharmacokinetic (PK) objective for this study is to characterize the crovalimab, PK profile on the basis of the following endpoints:

- Serum concentrations of crovalimab over time
- Serum concentration of crovalimab at specified time points
- The relationship between PK and efficacy, safety or PD endpoints may be explored. Additional exploratory PK analyses may be conducted as appropriate.

2.2.6 Biomarker Endpoints

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

- Change over time in PD biomarkers, including complement activity measured by a liposome immunoassay (CH50) and total C5 concentration.
- Change over time in free C5 concentration.
- Observed value and absolute change from baseline to Week 25 in parameters reflecting hemolysis (e.g., reticulocyte count, free hemoglobin, haptoglobin).
- The other biomarker objectives for the study are:
  - To evaluate the change over time in PNH 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 extravascular hemolysis (e.g., C3d on RBCs).

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

2.2.7 Immunogenicity Endpoint

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.

Additional immunogenicity analyses may be performed to evaluate the potential effects of ADA on efficacy, safety, and PK endpoints.

2.2.8 Safety Endpoints

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 (AEs), 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 AEs leading to study drug discontinuation.

2.2.9 Health Status Utility Endpoints

The exploratory 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 (EQ-5D-5L) index based and visual analog scale (VAS) scores at specified time-points.

2.3 DETERMINATION OF SAMPLE SIZE

The sample size estimation is based on the assessment of the co-primary endpoints of hemolysis control and transfusion avoidance, approximately 50 patients will be enrolled in the study.

Table 1 presents the 95% confidence interval (CI) for a range of proportions of patients whose LDH $\leq$ 1.5 $\times$ULN at Week 25 based on a cohort of 50 patients. The proportion of patients with LDH normalization $\leq 1 \times$ULN in the eculizumab treated arm in study 301 is 49.4% (95%CI [41.7%, 57%]) (the 301 study, Lee et. al. 2019). Under the assumption of LDH being log-normally distributed, the expected proportion below 1.5$\times$ULN is 86%. Although it is unlikely that untreated patients have LDH levels below 1.5$\times$ULN, it's assumed 20% of untreated patients achieve this LDH level to be conservative when defining the efficacy threshold. With the above assumption, the minimum proportion of patients with LDH below 1.5$\times$ULN need to be crossing the efficacy threshold of 60% (i.e., point estimate of the proportion as 74%), to 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%.

Table 1 Summary of 95%CI (Wilson Method) for Potentially Observable Proportions of LDH ≤1.5× ULN Given N=50

No. of Patients with LDH ≤1.5 ×ULN at Week 25	Proportion of Patients with LDH ≤ 1.5 ×ULN at Week 25	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 the proportion of patients who reported 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 2-sided Type I error level of 0.05 using a paired McNemar test.

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) was transfusion free at Week 25.

Table 2 A 2 x 2 Table of Probabilities for McNemar's Test

		Post-treatment		
		Transfused	Transfusion Avoidance	
Pre-treatment	Transfused	$a(\pi_{00})$	$b(\pi_{01})$	$1-\pi_c$
	Transfusion Avoidance	$c(\pi_{10})$	$d(\pi_{11})$	π_c
		$1-\pi_t$	π_t	1

a = cell a; b = cell b; c = cell c; d = cell d ;π_t = response probability for the treatment; π_c= response probability for the control; π_{00} = response probability of cell a; π_{01} = response probability of cell b; π_{10} = response probability of cell c; π_{11} = response probability of cell d.

Note: Given the planned sample size of 50 patients, assuming that 50% of the patients are TA on crovalimab (π_t) and the proportion of patients with TA pre-treatment is 20% (π_c), with the proportions of discordant pairs taking values as 70%, 50%, 30% (e.g., sum of the proportions of patients with TA pre-treatment who received a blood transfusion on crovalimab and the patients who had a blood transfusion pre-treatment and had TA on crovalimab, $\pi_{10}+\pi_{01}$), there will be 77.5%, 91.2%, 99.6% power respectively to detect a significant difference of at least 30% between proportions of patients with TA pre-screening and post-baseline, with a 2-sided McNemar's test at a 5% significance level. The Power was calculated with EAST, Version 6.

2.4 ANALYSIS TIMING

The primary efficacy analysis will take place once the last patient on trial completes 24 weeks of treatment of crovalimab or discontinues early, whichever occurs first.

The final analysis will be performed at the end of study as defined in the protocol. The end of the study is defined as the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Study YO42311 is a single arm, open-label study. Patients with PNH who have never received treatment with a complement inhibitor prior to study entry will be enrolled to receive crovalimab.

3.1.1 Blinding

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

3.2 DATA MONITORING

There is no independent review facility or independent data monitoring committee in this study. No formal interim efficacy or safety analyses will be conducted.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

The analysis population for the primary and secondary efficacy analyses will be Primary Analysis Population as defined below.

4.1.1 Full Analysis Population

The Full Analysis Population will include all patients who were enrolled in the study.

4.1.2 Primary Analysis Population

The Primary Analysis Population (PAP) includes all enrolled patients receiving at least one dose of crovalimab and having at least one central LDH level assessment after the first intravenous (IV) infusion. The PAP will be used to evaluate the co-primary and secondary efficacy endpoints.

4.1.3 Pharmacokinetic-Evaluable Population

The PK-evaluable population includes all patients who received at least one dose, and have at least one post-dose crovalimab PK result.

Patients participating into the rich PK sampling collection to characterize crovalimab PK in Chinese patients (up to a maximum of 20 patients) will be excluded from this analysis if more than on PK sample is missing on Weeks 21 (Day 4), 22, 23, or 24. Excluded cases will be documented, including the reason for exclusion.

4.1.4 Immunogenicity-Evaluable Population

The immunogenicity analysis population will consist of all crovalimab treated patients with at least one ADA assessment post crovalimab administration.

4.1.5 Safety Population

Safety population will include all enrolled patients who have received at least one dose of crovalimab.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients who enroll, discontinue, or complete the study will be summarized and displayed in a CONSORT diagram. In addition, reasons of discontinuation from crovalimab and reasons for withdrawing from the study will be described. Major protocol deviations, major eligibility exceptions will be listed and evaluated for their potential effects on the interpretation of study results.

The potential disruptions caused by the coronavirus disease 2019 (COVID-19) pandemic will be addressed as recommended in the Statistical Issues and Recommendations for Clinical Trials Conducted during the COVID-19 Pandemic (Meyer et al.,2020) and strict internal Roche guidelines.

4.3 ANALYSIS OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic characteristics (including but not limited to age, sex, race, weight, height) and baseline characteristics (including but not limited to, proportion of patients of pRBCs transfusions in the past 12 months prior to the first dose administration, hemoglobin level, local and central LDH levels, PNH granulocytes (%*) and erythrocytes (%*), and history of aplastic anemia) will be summarized for the primary analysis population. For continuous variables, means, medians, ranges, and standard deviations will be presented. For categorical variables, the number and percentage of patients within each category will be presented. For each variable (continuous or categorical), the number of available observations will be reported.

4.4 EFFICACY ANALYSIS

The primary and secondary efficacy analyses will be based on the primary analysis population. For all endpoints, summary statistics (including means, median, range, standard deviations, and proportions where appropriate) will be presented.

4.4.1 Primary Efficacy Endpoints

Both co-primary endpoints (defined in Section 2.2.1) need to be met to conclude the positive study results. The primary efficacy analysis will be conducted once the last patient on trial completes 24 weeks of treatment of crovalimab or discontinues early, whichever happens first.

4.4.1.1 Definition of Primary Estimand

In alignment with the addendum to ICH E9, the primary efficacy study estimand is defined by the following four attributes:

- **Population**:

  The treatment-naive PNH population as defined through the inclusion and exclusion criteria, receiving at least one dose of crovalimab and providing at least one LDH sample post-baseline by central laboratory after the first IV infusion.

- **Variables**:
  - **Hemolysis control**: categorical indicator based on centrally processed bi-weekly LDH measured from Week 5 to Week 25, and taking value 1 when $LDH \leq 1.5 \times ULN$, 0 when $LDH > 1.5 \times ULN$, and missing where LDH was not measured.
  - **Transfusion Avoidance**: categorical indicator taking value 1 for lack of any transfusion from baseline to Week 25, and zero otherwise, and an indicator taking value 1 for lack of any transfusion within 24 weeks prior to the screening,

- **Inter-current event (ICE):**

  Withdrawal from study treatment for any reason before Week 25.

- **Population-level summary (estimate):**
  - **Hemolysis control**: The population proportion of patients with hemolysis control measured in patients with LDH $\leq 1.5 \times$ ULN from Week 5 through Week 25.
  - **Transfusion Avoidance**: The difference in the proportion of patients with TA from baseline through Week 25 and proportion of patients with TA within 24 weeks prior to screening.
- **Handling the Intercurrent events (ICEs):**

  Hypothetical strategy for the co-primary endpoint hemolysis control and composite strategy for the co-primary endpoint transfusion avoidance.

  - **Hemolysis control**: Hypothetical strategy will be used to estimate the treatment effect as if all patients had completed the assigned treatment at Week 25 without intercurrent events (ICEs). Any data missing due to an ICE will not be imputed for the primary analysis; rather, the Generalized Estimating Equation (GEE) model uses all observed data in order to provide estimates from Week 5 through Week 25.
  - **Transfusion Avoidance**: Composite strategy will be used to estimate the proportion of patients with TA from baseline through Week 25, i.e., patients with data missing due to an ICE will be assumed to have experienced an unfavorable outcome

If the assumption that data is missing completely at random (MCAR) is valid, then GEE results are unbiased. Little's test (Little 1988) will be used to assess MCAR and missing at random (MAR) assumptions, and sensitivity analyses may be conducted with consideration for the "missing not at random" assumption. For detailed information please refer to Section 4.7.

Prior to any analysis of the efficacy data, the assignment of all reasons for treatment discontinuation will be documented according to the Study Drug-related (SDR) and Non-Study Drug-Related (NSDR) categories. Table 3 lists possible classifications of treatment discontinuations. The Sponsor will encourage investigators to minimize withdrawals from treatment as well as withdrawal from the study. Also the importance of providing detailed reasons for study treatment discontinuation as well as discontinuation from the study will be emphasized to the investigators to allow appropriate assignment of any inter-current events to the SDR or NSDR category.

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

Table 3 Classification of Treatment Discontinuations

Non-Study Drug−Related (NSDR)	Study Drug−Related (SDR)
Pregnancy Protocol deviation	Lack of efficacy Adverse events Death Lost to follow-up Non-compliance with study drug Withdrawal by Subject Physician Decision

Reasons for discontinuation will include, but not be limited to the classifications above. The above classifications of treatment discontinuations are based on a conservative rationale, assuming that any non-specific treatment discontinuation is related to drug

4.4.1.2 Statistical Modelling

4.4.1.2.1 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 for LDH $> 1.5 \times$ ULN, and missing if LDH is not measured.

A GEE will be used to estimate the population-average proportion of the patients with hemolysis control from Week 5 to Week 25 taking account of the intra-patient and inter-patient correlation between LDH control statuses across visits. The dependent variable is the binary indicator for hemolysis control. Independent variables are categorical effects of visit, continuous baseline LDH. Further adjustments (baseline variables) may be explored in sensitivity analysis.

The primary analysis will apply an unstructured (UN) correlation matrix. This correlation structure imposes minimal assumptions but requires estimating a large number of parameters which may prevent model convergence. Other correlation structures will be applied if non-convergence happens, as described in the sensitivity analysis section. The primary analysis will use the standard GEE based on the available LDH assessments, assuming the missing data are MCAR.

The study aims to maintain 60% of eculizumab's treatment effect mentioned in Alexion 301 study (Lee et al. 2019). There will be no formal hypothesis testing for the hemolysis control. The efficacy endpoint will deem to be reached when the lower limit (LL) of the two-sided 95% CI for the mean proportion as estimated by generalized estimating equations to exclude the threshold of 60%.

4.4.1.2.2 Transfusion Avoidance

The difference in the proportion of patients with transfusion avoidance (TA) from baseline through Week 25 (after 24 weeks on treatment) and proportion of patients who with TA within 24 weeks prior to screening (refer to section 2.2.1) will be computed. From baseline to Week 25, patients who withdraw early from the treatment will be assumed to have undergone a transfusion. The intra-patient comparison will be made using a paired McNemar test with continuity correction at two-sided Type I error level of 0.05. The difference in the proportions of TA and the corresponding 95% CIs will be calculated with Wilson's method developed by Wilson (1927).

The transfusion related medical records will be collected to the fullest extent possible to ensure the robustness of the data.

4.4.2 Secondary Efficacy Endpoints

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

4.4.2.1 Breakthrough Hemolysis

The proportion of patients and its 95% CI for patients with BTH from baseline through Week 25 (see Section 2.2.2 for definition) will be calculated based on Wilson's method developed by Wilson (1927). As a conservative approach, patients withdrawing before Week 25 will be deemed to have experienced BTH in the unobserved period.

4.4.2.2 Hemoglobin Stabilization

The proportion of patients and its 95% CI for patients with stabilization of hemoglobin from baseline through Week 25 will be analyzed based on Wilson’s method (1927) similar as the secondary endpoint for BTH. As a conservative approach, patients who withdraw early will be assumed to not have hemoglobin stabilization.

Baseline hemoglobin is defined as the latest available hemoglobin measurement prior to the first on-study drug administration of crovalimab.

4.4.2.3 FACIT-Fatigue

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

Completion rates will be summarized by number and proportion of adults aged ≥18 years who complete the questionnaire at each time point.

4.4.3 Exploratory Efficacy Endpoints

Analyses for the exploratory efficacy objectives are described below.

- For assessment of mean change from baseline, the applicable endpoints and analyses are described below:
  - Mean change from baseline to week 25 in Physical Function, Role Function, and Global Health Status/QoL scales of the EORTC QLQ-C30 (for adults aged ≥18 years).
  - Mean change from baseline to Week 25 in PedsQL MFS, and the Physical Functioning scale of the PedsQL Core (for adolescents aged 12-17 years).
  - Mean change in LDH levels from baseline to Week 25.
  - *Percent change from baseline to Week 25 in LDH levels.

    *In this case, the mean percentage change will be treated similarly, with percentage change calculated at the patient level as:

    *(visit score - baseline score) / baseline score * 100*

    Baseline LDH is defined as the mean of all LDH values: 1) taken during screening, i.e., within 4 weeks prior to first crovalimab administration; and 2) the LDH value at Week 1 Day 1 collected prior to first crovalimab. All LDH values will be based on central LDH measurements.

- For the evaluation of the population proportion, the endpoint and analysis are described below:
  - Population proportion of patients with LDH ≤ 1 x ULN from Week 5 through Week 25 (as measured at the central laboratory).

  Similar method as for the co-primary endpoint hemolysis control will be used.

- With regard to assessment of proportion, the endpoints and analyses are described below:
  - Proportion of patients experiencing MAVE (Appendix 3) from baseline through Week 25.
  - 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.

  Proportions will be reported with 95% CI, and are calculated with the number of subjects as the denominator. As such, where multiple cases of the particular endpoint may be observed, the numerator of the calculation will be composed of subjects with one or more relevant instances. And, where applicable, plots depicting the proportions (95% CI) at each visit will be presented.
- For time to event, the endpoints and analyses are described below:
  - Time from baseline to the first time LDH ≤ 1 x ULN

– Time from baseline to the first time LDH ≤ 1.5 x ULN.

Time to event endpoints will be summarised with Kaplan-Meier curves and median times (if reached) and 95% CI. Time will be defined as the time from the first dose date to the date of the first LDH measurement less than or equal to the respective LDH criteria. Patients who do not reach the respective LDH criteria will be censored at the last LDH measurement. The extent of premature censoring will be monitored.

- For the following exploratory endpoint, summary statistics, including group mean, standard deviation, median, and ranges, will be presented at the stated visit time (i.e., not calculated relative to a baseline measure):
  – Total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25.

4.4.4 Supportive Historical Efficacy Endpoints

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 of the historical data. Given that historical data will be collected from the patients' medical records retrospectively, there will be some limitations to the interpretation of the intra-patient analysis results. In the clinical practice, patients are likely tested only if they experienced symptoms during the course of disease. Hence, we cannot rule out if there will be missing data as in the trial. Data from medical records were not collected for the purpose of this intra-patient analysis and might introduce bias due to uncontrolled confounding factors and limited information.

All the analyses will be exploratory based on available data. P-values are nominal and will not be adjusted for multiple analyses.

- Historical medical record data including LDH, hemoglobin, and PNH clone size (by erythrocytes, and white blood cells) within the past 24 weeks prior to screening will be summarized by the number of records. Summary statistics (N, mean, median, standard deviation, ranges) for normalized LDH and hemoglobin will be tabulated by nominal time points. Spaghetti plots (plots of individual patients over-laid with mean and median plots of the same individuals) for absolute value will be provided. Reference lines for the normal range of LDH should be displayed in all plots.
- The number of transfusions and number of packed RBC units in the past 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 after the first dose will be summarized by the average difference as well as the corresponding 95% CI calculated on the basis of the normal distribution. The comparison will also be tested using paired Student t-test.
- The proportion and its 95% CI of patients who had BTH, and the proportion and its 95% CI of patients who had MAVE as documented in the medical records in the past 24 weeks prior to screening will be provided if applicable.

4.4.5 Sensitivity Analyses

Sensitivity analyses will be performed to assess the robustness of the primary analysis results, based on different statistical model and model assumptions for the co-primary endpoints, and impact of missing data.

4.4.5.1 Missing Data

Details of how missing data will be addressed are provided in Section 4.7.

4.4.5.2 Statistical Model

If the model does not achieve the convergence in the primary analysis using the unstructured covariance matrix structure, different structures (in this order: Toeplitz, AR1 or CS) will be applied.

4.4.5.3 Historic Period

For endpoint of transfusion avoidance, we will perform the analysis to investigate the difference in the proportion of patients with TA from baseline through Week 25 and the proportion of patients with TA within 24 weeks prior to the baseline. Its corresponding 95% CIs will be calculated with Wilson's method developed by Wilson (1927).

4.4.5.4 Rescue Dosing

We will perform a sensitivity analysis to assess the effect of rescue dosing.

4.4.6 Subgroup Analyses

The analyses will be performed for the key efficacy endpoints. Due to the limited sample size, some subgroups will be highly sensitive to variability caused by individual patients. For each subgroup, the point estimates of crovalimab and the corresponding 95% CI will be provided.

The specified subgroups are:

- Age: <65, ≥65
- Sex: Male, Female
- History of pRBC units transfused in the 6 months prior to the baseline: 0, >0 to ≤6, and >6.
- Baseline LDH category (<4× ULN and ≥4 ×ULN).

Additional subgroups may be added based on emerging evidence.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

The PK analyses will be performed on the PK-evaluable population, as defined in Section 4.1.3.

For all patients, serum trough concentrations of crovalimab will be presented in individual listings, summary tables (including descriptive statistics: means, geometric

means, medians, ranges, standard deviations, and coefficients of variation) and graphs (including concentration versus time plots on linear and semi-logarithmic scales) as appropriate.

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.

4.6 SAFETY ANALYSES

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

Safety will be assessed through descriptive summaries of exposure to study treatment, AEs, changes in laboratory test results, and changes in vital signs and electrocardiogram (ECGs).

4.6.1 Exposure of Study Medication

Information on study drug administration will be summarized by duration of exposure and cumulative dose. Study treatment exposure (such as treatment duration, total dose received, dose interruption, delays and modifications) will be summarized.

Withdrawals of patients and deviations from study treatment will be reported as listings and summary tables.

4.6.2 Adverse Events

All verbatim AE terms will be mapped to Medical Dictionary of Regulatory Activities (MedDRA) thesaurus terms, and AE severity will be graded according to scale in NCI CTCAE v5. All AEs, serious AEs (SAEs), AEs leading to death, AEs leading to study treatment discontinuation/modification, AEs of special interest 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.

Details of deaths, if any, will be presented in the form of individual patient listings.

4.6.3 Laboratory Data

Relevant laboratories will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post baseline severity grade.

The numbers and proportions of ADA-positive patients and ADA-negative patients after drug administration (post-baseline incidence) will be summarized in the crovalimab arm. 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 post baseline 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).

4.6.4 Vital Signs

Relevant vital signs (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Changes in vital signs and ECGs will be summarized.

4.7 MISSING DATA

4.7.1 Transfusion Avoidance

Patients in whom is not possible to observe TA in the full treatment period (i.e., from baseline to Week 25), i.e., data missing due to an ICE, for example, due to withdrawal or death, will be hypothetically assumed to have experienced a transfusion.

4.7.2 Hemolysis Control

Missing assessments of LDH for an individual patient at a specific visit will not be imputed for the primary endpoint analysis. The proposed primary analysis GEE model is valid under the assumption that missing data are MCAR. Local LDH levels may be used to account for missing central LDH data in sensitivity analysis; however, given potential differences in local and central reads, this will only be considered where systematic loss of data is observed, and be considered exploratory only.

Sensitivity analysis will be performed to test the robustness of the MCAR assumptions that underlie the proposed model if the extent of missing data warrants (See Sensitivity analysis Section 4.4.5). The pattern of missingness will be explored using summary statistics.

Missing LDH values can be classified into the categories as following, which will determine how they will be imputed for sensitivity analyses:

4.7.2.1 Missing Baseline

Baseline LDH is defined as the mean of all centrally measured LDH values taken during screening up to Day 1 (Section 4.4.3). Baseline observations are therefore not expected to be missing.

4.7.2.2 Intermittent Missingness

This includes missing data for subjects reaching Week 25 assessment, but having one or more missing LDH assessments during the observed period. For sensitivity analysis, intermittent missing observations will be imputed through multiple imputation but simultaneously from the multivariate normal distribution using the Markov Chain Monte Carlo (MCMC) method. Continuous values will be imputed and converted to a categorical form in accordance with the definition of Hemolysis Control.

4.7.2.3 Withdrawal from Treatment

This includes missing observations resulting from subjects' premature end of study participation. In this case LDH values for one or more visits leading to (and including) Week 25 are not observed. These missing observations can further be classified into

- NSDR (defined in Section 4.4.1.1), or
- SDR

Frequencies of such reasons will be summarized in order to assess potential Missing Not at Random (MNAR). The following imputation approaches will be performed to assess robustness of the GEE model for the sensitivity analyses:

- Using multiple imputation if the dropout rate exceeds 5%, or in the presence of SDR withdrawal:
  - Using MCMC assuming missing data are missing at random, or
  - Using pattern mixture models to assess if data are MNAR and the impact of MNAR on inferences (in the presence of SDR missing)
- Including only data from fully compliant participants in the analysis (i.e., excluding patients with at least one missing LDH value).

For Hemolysis control, continuous LDH measurements will be imputed. The binary indicator for hemolysis control will then be derived from these values.

All imputations will be performed using SAS Procedure PROC MI and the results combined using PROC MIANALYZE.

In the presence of both intermittent missingness and missingness due to withdrawal from study, intermittent missing observations will be imputed first to create 1000 new datasets, the 1000 new datasets will then be imputed 1000 for observations missing due to early withdrawal from study.

Details of the proposed sensitivity analysis are provided in Section 4.4.5.

4.8 INTERIM ANALYSES

No efficacy interim analyses are planned for this study.

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Appendix 1 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**
PROTOCOL NUMBER:	YO42311
VERSION NUMBER:	2
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	Not Applicable
NCT NUMBER:	To be determined
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.

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.

- *Mean 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)

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 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 LDH levels *by visit*
- Time from baseline to first reach of LDH ≤1×ULN
- Time from baseline to first reach of 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)

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 breakthrough hemolysis and thrombotic event 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, and PK 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–and extra–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 visit 24 weeks 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 major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction, or history of pRBC transfusion because of PNH
- Vaccination against *Neisseria meningitidis* <3 years prior to initiation of study treatment (Day 1) *or within 7 days after the first drug administration*, in accordance with most

current local guidelines or standard-of-care as applicable in patients with complement deficiency.

- Vaccination against *Haemophilius influenzae type B* and *Streptococcus pneumonia* according to national vaccination recommendations
- 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
- Patients with known HIV infection are eligible, provided their CD4 counts are >200 cells/μL at time of screening and they meet all other criteria.
- 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 women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women 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 woman is considered to be of childbearing potential if she 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
- Platelet count <30000/mm^3 at screening
- Absolute neutrophil count <500/μL at screening
- History of allogeneic bone marrow transplantation
- History of *Neisseria 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 (≥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 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 6 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

The end of this study is defined as the date *at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later.*

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

Length of Study

The minimum length of the study (unless early discontinuation of treatment) for an individual patient will be 52 weeks, which includes:

- Screening period up to 4 weeks
- Treatment period, 24 weeks
- Safety follow-up visit, 24 weeks after discontinuing crovalimab

Patients who discontinue from the study and continue crovalimab treatment in a different study/program or via commercial supply do not need to return for a safety follow-up visit, since their safety reporting is done through the new study/program. The minimum length of study for these patients is 28 weeks.

Assuming an enrollment period of 10 months, the minimum length of the study, from screening of the first patient to the end of study, is expected to be approximately 1.5–2 years.

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 which is 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 or 170 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 will be permitted. This will require combining of crovalimab drug product solution (vial pooling) from up to two 1-mL vials into a single syringe. The detailed procedure for vial pooling is described in the Instructions for Use.

A single-use vial, which contains an extractable volume of 2 mL or 340 mg (nominal) crovalimab drug product is under development and may be introduced after the supportive technical information has been submitted and approved.

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.

The primary efficacy analysis population will consist of all enrolled patients who received at least one dose of crovalimab and have at least one central LDH level assessment after the first IV infusion.

The study will be regarded as successful when the co-primary endpoints listed below have reached the success criteria.

Hemolysis control

The co-primary endpoint of 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 adjusted proportion of hemolysis control, i.e., proportion of patients with 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.

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 2-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 2-sided Type 1 error level of 0.05 using a paired McNemar test.

Interim Analyses

There are no planned interim analyses for this study.

Appendix 2 Schedule of Assessments

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

	Screening	Crovalimab Treatment Period										Crovalimab Continuation [x]	Study Discontinuation/ Safety Follow-Up [w]
Study Week	−4 to −1	1		2	3	4	5	9	13	17	21	≥25 [x]	
Day		1	2										
Informed consent [a]	x												
N. meningitidis 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
12-Lead ECG [j]	x	x					x					x	
Concomitant medications and pRBC transfusions [k]	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [h, l]	x	x		x	x	x	x	x	x	x	x	x	x

Appendix 2 Schedule of Assessments (cont.)

	Screening	Crovalimab Treatment Period										Crovalimab Continuation [x]	Study Discontinuation/ Safety Follow-Up [w]
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]	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]	x	x	x	x	x	x	x	x	x	x	x	x	x
Plasma and serum sample set for biomarkers [t]		x		x	x	x	x	x	x	x	x	x	x
Serum ADA sample for crovalimab [h, t]		x		x	x	x	x	x	x	x	x	x	x
Serum PK sample for crovalimab [h, t, u]		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	

Appendix 2 Schedule of Assessments (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] *Neisseria meningitidis* vaccination *and Streptococcus pneumonia vaccination* (prior to initiation of the first drug administration on the study *or within 7 days after first drug administration*) may be administered any time between screening Day –28 and *within 7 days after first 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. *For patients who receive the vaccination within 7 days after first drug administration, prophylactic antibiotics should be started on Day 1 prior to the first drug administration and last for at least 2 weeks after the vaccination*.

[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.

[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.

Appendix 2 Schedule of Assessments (cont.)

[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. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[j] If screening ECG is abnormal, repeat at Week 1. If screening and Week 1 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 the end of the study. Report previous and concurrent pRBC transfusions.

[l] Hematology will be assessed locally. It includes RBC count, hemoglobin, hematocrit, platelet count, 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.

[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.

[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 24 weeks 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 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.

Appendix 2 Schedule of Assessments (cont.)

[t] 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 (*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.

[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 for assessments after Week 25. For patients who discontinue from crovalimab treatment, follow up safety assessments should 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.

[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 taken every 8 weeks (see Table 2 for schedule of activities for patients continuing crovalimab treatment at Weeks ≥25).

Appendix 2 Schedule of Assessments (cont.)

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	Study Discontinuation/ Safety Follow-Up [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
12-Lead ECG				
Concomitant medications [f]		x	x	x
pRBC transfusions [g]		x	x	x
Hematology [d, h]		x	x	x
Free hemoglobin, haptoglobin [d, i]		x	x	x
Coagulation [d, j]		x	x	x
Chemistry [d, k]		x	x	x
Urinalysis [d, l]		x	x	x
Adverse events [m]		x	x	x
Assessment and documentation of BTH [d, n]		x	x	x
Serum sample for central LDH and *potassium* [d, o]		x	x	x
Plasma and serum sample set for biomarkers [d, p]		x	x	x
Serum ADA sample for crovalimab [d, p]		x	x	x
Serum PK sample for crovalimab [d, p]		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
Crovalimab administration	Q4W			

Appendix 2 Schedule of Assessments (cont.)

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. 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 the end of the study.

[g] Report previous and concurrent pRBC transfusions.

[h] Hematology will be assessed locally. It includes RBC count, hemoglobin, hematocrit, platelet count, WBC count, and differential count.

[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.

Appendix 2 Schedule of Assessments (cont.)

[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 24 weeks 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.

Appendix 2 Schedule of Assessments (cont.)

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 first 20 enrolled Chinese patients only 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 3 Major Adverse Vascular Events

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

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 warrant a transfusion include angina, syncope, lightheadedness, confusion, severe or worsening shortness of breath, severe or worsening fatigue, stroke, or transient ischemic attack.

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 randomization 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.

The signs and symptoms associated with or that triggered 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.