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

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STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS**
PROTOCOL NUMBER:	BO42162
STUDY DRUG:	Crovalimab (RO7112689)
VERSION NUMBER:	3
IND NUMBER:	131343
EUDRACT NUMBER:	2019-004931-21
SPONSORS:	F. Hoffmann-La Roche Ltd. Chugai Pharmaceutical Co. Ltd.
PLAN PREPARED BY:	[redacted], M.Sc.
DATE FINAL:	Version 1: 4 September 2020 Version 2: 8 June 2021
DATE(S) AMENDED	See electronic date stamp below on the last page of this document.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan (SAP) for Study BO42162 has been amended to incorporate the following changes:

- The 30% cap for any country was removed to allow potential enrollment flexibility in an ultra-rare condition while maintaining generalizability of the study results (Section 2).
- The threshold for the improvement in FACIT-Fatigue scores has been revised from 3 points to 5 points to reflect recent research supporting its use in a paroxysmal nocturnal hemoglobinuria patient population (Section 2.2.3).
- Sample size determination has been aligned with text in the study protocol (Section 2.3). Also, the lower bound of the confidence interval for Transfusion Avoidance has been corrected to reflect the numbers in the cited article of Lee et al., (2019).
- To explicitly state the endpoints assessed in patients randomized to eculizumab in Arm B and who switch to crovalimab following the primary treatment period (24 weeks of treatment) (Section 2.2.4), and in descriptive Arm C (Section 2.2.5).
- Pharmacodynamic endpoint was added to evaluate potential effects of ADAs (Section 2.2.8).
- Subsections of Section 4.1 have been updated to clarify the analysis population definitions in Arm B patients switching from eculizumab to crovalimab, and in descriptive Arm C.
- The criteria for Per Protocol population has been modified to align with protocol language with regards to transfusion guidelines. The protocol does not mandate transfusions. However, patients not meeting the inclusion/exclusion hemoglobin levels at enrollment may be transfused to reach the required hemoglobin levels prior to enrollment (Section 4.1.3).
- The Intercurrent Event (ICE) language has been updated to align with protocol v5 and v6, which document the condition under which a dose increase may be administered in response to suspected neutralizing antibodies and breakthrough hemolysis. Such a dose modification is considered an ICE for the hemolysis control primary efficacy endpoint (Section 4.4.1).
- An amendment has been made (Section 4.4.1.2), correcting stratification factor from History of transfusion to number of pRBC units administered within the 6 months prior to randomization.
- The term 'valid' has been removed from 'valid post-baseline LDH sample' in Sections 4.1.2 and 4.4.1.1. Instead, language has been added to explicitly clarify that LDH samples affected by tabletop hemolysis will be excluded from the analysis. The criteria for identification of tabletop hemolysis affected LDH samples has also been added (Section 4.4.1.2).

- To avoid the bias that may arise from using only scheduled LDH assessments in the analysis models (Section 4.4.1.2), language has been added to clarify that unscheduled LDH assessments will be included in the analysis via windowing.
- Sections 4.4.4 and 4.4.5 have been added to introduce language on exploratory efficacy analyses in Arm B patients switching from eculizumab to crovalimab , and in descriptive Arm C.
- Body weight has been added to the pre-planned subgroup analyses based on health authority feedback (Section 4.4.7).
- Language on analyses to assess the proportion of patients experiencing a clinically meaningful change on the EQ-5D-5L has been removed from Section 4.7 in order to better align with the corresponding health status endpoint wording.
- A clarification has been made in the definition of positive ADA subcategories; in addition the definition of persistent/transient ADAs was clarified to align this definition with other crovalimab studies (Section 4.8.4).
- An option to perform tipping-point sensitivity analyses had been Section 4.9.1.3.

Additional minor changes have been made to improve clarity and consistency.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AEs	adverse events
AR1	autoregressive
BTH	Breakthrough Hemolysis
C5	component 5
COVID-19	Coronavirus Disease 2019
CS	Compound Symmetry
CSR	Clinical Study Report
DTDC	drug-target-drug complex
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire
EQ-5D-5L	Euro Qol-5 dimesions-5 level
FACIT	Functional Assessment of Chronic Illness Therapy
FcRn	neonatal fragment crystallizable receptor
GEE	generalized estimating equation
GPI	glycosylphosphatidylinositol
HLA	human leukocyte antigen
HRQoL	health-related quality of life
ICEs	Inter-current events
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LL	lower limit
MAC	membrane attack complex
MAR	missing at random
MAVE	major adverse vascular event
MCAR	missing completely at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Multidimensional Fatigue Scale
MMRM	mixed model for repeated measures
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse

	Events
NIM	non-inferiority margin
NSDR	non-study drug-related
OLE	open-label extension
OR	odds ratio
PAP	Primary Analysis Population
PD	pharmacodynamic
PedsQL	Pediatric Quality of Life
PGIS	Patient Global Impression of Severity Survey
PK	pharmacokinetic
PNH	Paroxysmal nocturnal hemoglobinuria
pRBC	packed RBC
Q2W	every 2 weeks
Q4W	every 4 weeks
QLQ-AA/PNH	Quality of Life Questionnaire-Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria
QoL	quality of life
RBC	red blood cells
SAP	Statistical Analysis Plan
SC	subcutaneous
SDR	study-drug related
SMART-Ig	Sequential Monoclonal Antibody Recycling Technology-Immunoglobulin
TA	transfusion avoidance
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
TTH	tabletop hemolysis
UL	upper limit
ULN	upper limit of normal
VAS	visual analog scale
vWF	von Willebrand factor

1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods that will be used to evaluate the efficacy and safety for Study BO42162. The analyses described in this SAP will supersede those specified in the Study BO42162 protocol if there is any inconsistency between the two documents.

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 Organization 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). There, therefore, 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 (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.

2. STUDY DESIGN

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

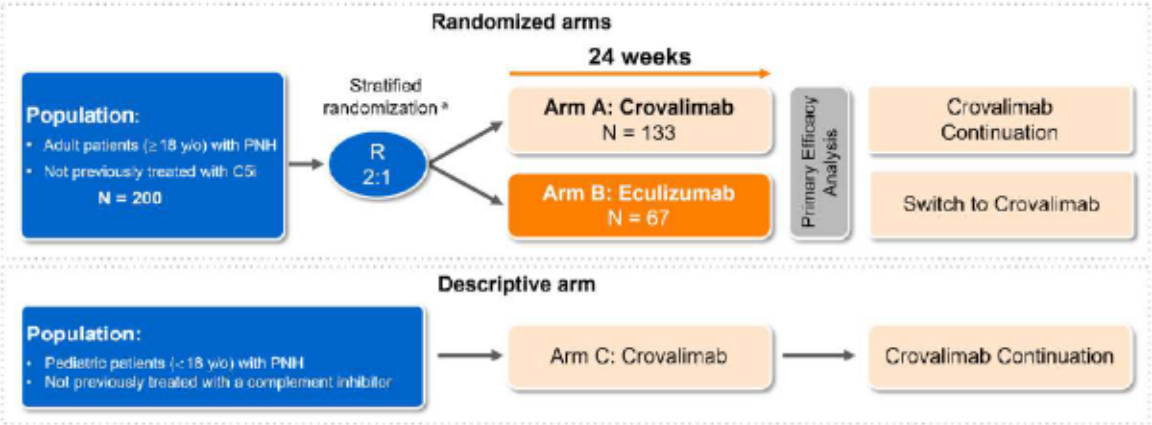
This study is divided into two parts: randomized arms (Arms A and B), consisting of adult patients (≥18 years old), that will contribute to the primary analysis; and a descriptive analysis arm (Arm C), consisting of pediatric patients (<18 years old), that will contribute to the exploratory analysis.

Approximately 200 patients in Arms A and B will be randomized in a 2:1 ratio to the following regimens:

- Crovalimab
- Eculizumab

A central randomization procedure will be used for all patients that fulfill the entry criteria at screening. A block-based randomization method will be used, stratified by the most recent LDH value (2–4 x upper limit of normal [ULN], and >4 x ULN) and by the transfusion history (0, >0 to 6, and >6 packed RBC [pRBC] units administered within 6 months prior to randomization). The proposed randomization method is designed to balance treatment group assignment within the prognostic stratification factors. Figure 1 represents an overview of the study design. The schedule of activities is provided in Appendix 2.

Figure 1 Study Design



C5i = C5 inhibitor; LDH = lactate dehydrogenase; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed red blood cells; Q4W = every 4 weeks; R = randomization; ULN = upper limit of normal; y/o = years old.

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

The screening period of the study will last up to 28 days. Enrollment of patients without a history of transfusion in the past year will be capped at 20%. If necessary, patients may be transfused prior to randomization to reach a hemoglobin level above the specified transfusion threshold. Randomization will be stratified according to the following factors:

- LDH level (most recent value prior to randomization, locally performed): 2 – ≤4×ULN, and >4×ULN
- Number of pRBC units administered within 6 months prior to randomization: 0 units, >0 – ≤6 units or >6 units

The study will aim to demonstrate the efficacy of crovalimab compared with eculizumab, based on the non-inferiority assessment of both transfusion avoidance (TA) and hemolysis control; superiority will be evaluated for both endpoints provided that non-inferiority has first been demonstrated.

The primary efficacy analysis will be performed when all randomized patients have either completed 24 weeks of treatment in the study or discontinued from treatment, whichever occurs first. To obtain additional efficacy and safety data, patients who are randomized to eculizumab will have the opportunity to switch to crovalimab once they have completed 24 weeks of treatment with eculizumab, if the treating physician determines that this is in their best interest.

All patients who receive crovalimab as part of the study (those randomized to crovalimab and those who switch to crovalimab after completing 24 weeks of eculizumab treatment) will continue to do so until they can switch to an open-label extension (OLE) 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 study crovalimab treatment while on the study will return for a safety follow-up site visit 24 weeks after treatment discontinuation and a safety telephone call 46 weeks (approximately 10.5 months) after treatment discontinuation, unless they continue crovalimab outside of the study. If these patients switch to a different C5 inhibitor, they should remain in safety follow-up and be monitored. Patients who discontinue from study eculizumab treatment will return for a safety follow-up visit 10 weeks after treatment discontinuation date. For all patients, the day of the last safety follow-up visit represents study discontinuation date.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis and the Schedule of Activities are provided in Appendix 1 and Appendix 2, respectively.

2.2 ENDPOINTS

2.2.1 Co-Primary Efficacy Endpoints (Randomized Arms)

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

- Proportion of patients who achieve TA, from baseline through Week 25 (after 24 weeks on treatment), with TA defined as patients who are pRBC transfusion-free and do not require transfusion per protocol-specified guidelines (Appendix 3).
- Proportion of patients with hemolysis control, defined as LDH $\leq 1.5 \times$ ULN, from Week 5 through Week 25 (as measured at the central laboratory).

2.2.2 Secondary Efficacy Endpoints (Randomized Arms)

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

- Proportion of patients with BTH, from baseline through Week 25
  - BTH is defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], a major adverse vascular event (MAVE); [as defined in Appendix 3, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH $\geq 2 \times$ ULN after prior reduction of LDH to $\leq 1.5 \times$ ULN on treatment.
- Proportion of patients with stabilization of hemoglobin, from baseline through Week 25

- Stabilized hemoglobin is defined as avoidance of a ≥2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion. With baseline hemoglobin defined as the latest available hemoglobin measurements prior to the first on-study drug administration.

- Mean change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue (for adults aged ≥18 years) will be scored according to the questionnaire specific algorithm, with higher values indicating less fatigue (Yellen et al. 1997).

2.2.3 Exploratory Efficacy Endpoints (All Arms)

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

The endpoints analyzed for Arm B patients switching from eculizumab to crovalimab after the primary treatment period are described in the following section.

- Total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25
- Proportion of patients with central LDH ≤1×ULN from Week 5 through Week 25
- Time from baseline to the first time central LDH ≤1×ULN
- Time from baseline to the first time central LDH ≤1.5×ULN
- Percent change from baseline to Week 25 in central LDH levels
- Proportion of patients who reach a hemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in the absence of a transfusion
- Proportion of patients experiencing MAVE (Appendix 3) from baseline through Week 25
- Mean change from baseline to Week 25 in the following functional domains and symptoms scales of European Organization for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire (EORTC QLQ-C30) (for adults aged ≥18 years):
  - Functioning scales (higher values indicative of a high level of functioning)
    1. Physical functioning
    2. Role functioning
    3. Global Health Status/quality of life (QoL)
  - Symptom scales (higher values indicative of higher levels of symptoms)
    1. Abdominal pain
    2. Headaches
    3. Dyspnea
    4. Dysphagia
    5. Chest pain
    6. Erectile dysfunction

- Mean change from baseline to Week 25 in Pediatric Quality of Life (PedsQL)
  - Multidimensional Fatigue Scale (MFS)
  - Physical Functioning scale of the PedsQL Core
- Proportion of patients with a ≥5 point improvement from baseline in the FACIT-Fatigue at Week 25 (for adults aged ≥18 years)
- Mean treatment satisfaction with crovalimab or eculizumab, as assessed by the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) at Week 25 (for adults aged ≥18 years)
- Mean change over time in quality of life, as assessed by Quality of Life Questionnaire-Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria (QLQ-AA/PNH), and in overall health status, as assessed by Patient Global Impression of Severity Survey (PGIS) (for adults aged ≥18 years

2.2.4 Exploratory Efficacy Endpoints (Arm B Patients Switching from Eculizumab To Crovalimab)

Patients randomized to receive eculizumab in Arm B have the opportunity to switch to crovalimab after completing 24 weeks of study treatment with eculizumab.

The following efficacy endpoints will be explored for the time period under crovalimab treatment (separate from exploratory efficacy analyses performed for the time period under eculizumab treatment):

- Proportion of patients with central LDH ≤1.5×ULN from the first dose of crovalimab through 24 weeks of treatment with crovalimab
- Proportion of patients who achieve TA from the first dose of crovalimab through 24 weeks of treatment with crovalimab
- Proportion of patients with BTH from the first dose of crovalimab through 24 weeks of treatment with crovalimab
- Proportion of patients with stabilization of hemoglobin from the first dose of crovalimab through 24 weeks of treatment with crovalimab
- Mean change in fatigue from the first dose of crovalimab through 24 weeks of treatment with crovalimab, as assessed by the FACIT-Fatigue
- Proportion of patients with preference for crovalimab or eculizumab at Week 41, for patients randomized to eculizumab who switch to crovalimab after 24 weeks of eculizumab treatment, as assessed through use of the Patient Preference Questionnaire developed by the Sponsor (see Protocol Section 4.5.10)

2.2.5 Exploratory Efficacy Endpoints (Descriptive Arm C)

For patients in the descriptive analysis arm (Arm C), with the exception of FACIT-Fatigue endpoint which is intended for adults only, the exploratory efficacy endpoints also include the primary and secondary endpoints as defined in Section 2.2.1 and Section 2.2.2, as well as the endpoints listed in Section 2.2.3.

2.2.6 Pharmacokinetic Endpoints

The pharmacokinetic (PK) objective for this study is to evaluate the pharmacokinetics of crovalimab and eculizumab based on the following endpoint:

- Serum concentrations of crovalimab and eculizumab over time

The relationship between PK and efficacy, safety or PD endpoints may be explored. Additional exploratory PK analyses may be conducted as appropriate.

The exploratory PK objectives for this study are as follows:

- To evaluate potential relationships between drug exposure and the efficacy and safety of crovalimab (patients randomized to crovalimab)
- To evaluate potential relationships between drug exposure and the efficacy and safety of eculizumab (patients randomized to eculizumab)
- To evaluate relationship between drug-target-drug complex (DTDC) size and kinetics and PK parameters of crovalimab and eculizumab (for patients randomized to eculizumab who switch to crovalimab after completion of eculizumab treatment)

2.2.7 Biomarker Endpoints

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

- Change over time in PD biomarkers, including complement activity (CH50) measured by a liposome immunoassay and total C5 concentration.
- Change over time in free C5 concentration in crovalimab-treated patients.
- Observed value and absolute change from baseline to Week 25 in parameters reflecting hemolysis (e.g., reticulocyte count, free hemoglobin, haptoglobin).
- Change over time in additional exploratory biomarkers, including PNH clone size, markers from the complement system, and markers for intra- and extra-vascular hemolysis (e.g., C3d on RBCs, and sC5b9 complex), as well as markers of endothelial cell activation and markers from the coagulation system (e.g., von Willebrand factor [vWF], P-selectin, D-dimer, thrombin-anti-thrombin complexes, thrombin generation) may also be evaluated.
- To investigate potential treatment resistance mechanisms, Arg885 and additional polymorphisms in C5 and in other complement-related genes may be analyzed. Human leukocyte antigen typing to investigate potential mechanisms of immunogenicity may also be performed.

Additional analysis may be performed to evaluate the potential relationship between blood biomarkers and efficacy, safety, pharmacokinetics, and immunogenicity.

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

2.2.9 Safety Endpoints

Safety will be assessed based on the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE v5)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results
- Incidence and severity of injection-site reactions, infusion-related reactions, hypersensitivity, and infections (including meningococcal meningitis)
- Incidence of adverse events leading to study drug discontinuation
- Incidence of DTDC formation over time by DTDC size in patients who switched to crovalimab treatment from eculizumab treatment

2.2.10 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 compared to eculizumab 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 timepoints

2.3 DETERMINATION OF SAMPLE SIZE

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

The sample size estimation for the randomized portion of the study (Arms A and B) is based on the non-inferiority assessment of the co-primary endpoints of hemolysis control, as assessed by centrally measured LDH, and the proportion of patients who achieve TA during the efficacy period. The final target sample size corresponds to the endpoint that requires the larger number of patients, i.e., TA from baseline to Week 25. Approximately

200 adult patients will be randomly assigned in a 2:1 ratio to receive either crovalimab (n=133) or eculizumab (n=67), to ensure approximately 180 evaluable patients, assuming a 10% drop-out rate. This sample size will provide 80% power to demonstrate the non-inferiority of crovalimab to eculizumab with respect to TA, using a non-inferiority margin (NIM) of -20%, and one-sided Type 1 error rate of 2.5%.

The NIM for TA was determined based on the data reported in protocol ALXN1210-PNH-301, comparing eculizumab-treated patients with untreated patients from the global PNH Registry for eculizumab-treated patients, i.e., patients treated with eculizumab showed a benefit over untreated patients, with a difference of approximately 40% (TA proportion of 57.1% and 18.6%, respectively), after adjustment for history of transfusions 12 months prior to enrollment. Hence, a difference in proportions of -20%, the NIM, would preserve at least 50% of the control treatment effect. This NIM was also defined based on operational considerations, given the rarity of PNH. A more conservative NIM would have resulted in the estimated sample size being too large and infeasible. Lee et al., (2019) reported a proportion of patients with TA of 66.1% (95%CI: 57.7% to 74.6%) in treatment-naive patients in eculizumab.

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

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

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

2.4 ANALYSIS TIMING

The primary analysis will be performed once the last randomized patient on trial completes 24 weeks of study treatment or discontinues early, whichever happens first.

The final analysis will occur at the end of the study, as defined in the protocol.

3. STUDY CONDUCT

3.1 RANDOMIZATION

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

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 by treatment until the time of primary analysis.

3.2 DATA MONITORING

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

All the analyses for review by the iDMC that will take place before the primary analysis will be prepared by an independent Data Coordinating Center (iDCC) that is independent of the Sponsor. The iDCC will perform unblinded analyses and provide tables and listings to support the iDMC data review.

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

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

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

The analysis population for the primary and secondary efficacy analyses to evaluate the non-inferiority of crovalimab compared with eculizumab will be the Primary Analysis Population as defined below.

4.1.1 Randomized Population

The randomized population (intent-to-treat [ITT]) is defined as all randomized patients, with analyses performed as randomized.

4.1.2 Primary Analysis Population

The Primary Analysis Population (PAP) to evaluate the non-inferiority of crovalimab compared with eculizumab includes all randomized patients receiving at least one dose of the assigned treatment and having at least one centrally processed LDH level assessment after the first intravenous (IV) infusion.

4.1.3 Efficacy Analysis Population for Patients Switching from Eculizumab to Crovalimab

For patients in Arm B switching from eculizumab to crovalimab after completing the primary treatment period, the efficacy analysis population is defined as all patients receiving at least one dose of crovalimab and having at least one centrally processed LDH level assessment after the first crovalimab IV infusion.

4.1.4 Efficacy Analysis Population for Descriptive Arm C

For patients in Arm C, the efficacy analysis population is defined as all patients receiving at least one dose of the crovalimab treatment and having at least one centrally processed LDH level assessment after the first IV infusion.

4.1.5 Per Protocol Population

In order to assess the criteria stated below prior to study unblinding at the primary analysis, protocol deviations will be reviewed and a determination of the definition of the population for per protocol analysis will be made in accordance with the Sponsor's Guidance for Per-Protocol Population Derivation v1.0.

Per protocol population is comprised of all randomized patients who fulfil the following criteria:

- Received only assigned treatment per randomized schedule, i.e., never received incorrect randomized treatment
- Received all planned doses in full within ±3 days of the scheduled day of administration
- Met required hemoglobin level at enrollment, and where applicable followed protocol-specified baseline transfusion guidelines

- Have met the following inclusion criteria:
  - LDH $\geq 2 \times$ ULN at screening (as per local assessment)
  - Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of white blood cells (WBCs), with granulocyte or monocyte clone size $\geq 10\%$, within 6 months prior to randomization
  - Body weight ≥ 40 kg at screening
- Have not met the following exclusion criteria:
  - Major adverse vascular event in the 6 months prior to Study Day 1
  - Current or previous treatment with a complement inhibitor
  - Platelet count $< 30{,}000/mm^3$ (30×10^9/L) at screening
  - Absolute Neutrophil Count $< 500/\mu L$ (0.5×10^9/L) at screening
  - History of bone marrow transplantation

The primary efficacy endpoint analyses and the secondary endpoint analyses may be repeated on the per protocol population as sensitivity analyses.

4.1.6 Pharmacokinetic-Evaluable Population

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

The PK-evaluable population for analyses of Arm B patients who switch from eculizumab to crovalimab after the primary treatment period is defined as all patients who received at least one dose of crovalimab, and have at least one post-dose concentration result.

The PK-evaluable population for the descriptive arm (Arm C) is defined as all pediatric patients who received at least one dose of study drug, and have at least one post-dose concentration result.

4.1.7 Immunogenicity-Evaluable Population

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

The immunogenicity evaluable population for analyses of Arm B patients who switch from eculizumab to crovalimab after the primary treatment period is defined as all patients who received at least one dose of crovalimab, and have at least one ADA assessment.

The immunogenicity evaluable population for the descriptive arm (Arm C) is defined as all pediatric patients who received at least one dose of study drug, and have at least one ADA assessment.

4.1.8 Safety Population

Safety analyses will be performed on the safety evaluable population, defined as all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

The safety evaluable population for analyses of Arm B patients who switch from eculizumab to crovalimab after the primary treatment period is defined as all patients who received at least one dose of crovalimab.

The safety evaluable population for the descriptive arm (Arm C) is defined as all pediatric patients who received at least one dose of study drug.

4.2 ANALYSIS OF STUDY CONDUCT

Flow of patients through the study will be displayed in a CONSORT diagram. A clear account of all patients who entered the study, who were randomized, and who entered and completed each phase of the study will be displayed. In addition, reasons discontinuation from study treatment and reasons for withdrawing from the study will be described.

Major eligibility exceptions, major protocol deviations, reasons for study discontinuation and exposure will be summarized by treatment group for all randomized patients.

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 TREATMENT GROUP COMPARABILITY

Demographic characteristics (e.g., age, sex, race, and weight) and baseline characteristics (including proportion of subjects with pRBCs transfusion in the past 12 months, local and central LDH levels, PNH granulocytes (%*) and erythrocytes (%*), and history of aplastic anemia will be summarized by treatment arm for the ITT and for the primary analysis population.

*percentage of PNH clones

4.4 EFFICACY ANALYSIS

The efficacy analyses will be based on primary analysis population.

For all endpoints, summary statistics (including means, median, range, standard deviations, and proportions where appropriate) will be presented by treatment arm using tables, listings, and graphs as appropriate. Proportions will be reported with 95% CIs. In graphs, CIs will only be displayed for a treatment group when the treatment group sample size is at least 10.

4.4.1 Co-Primary Efficacy Endpoints

Both of the following co-primary endpoints need to be met in order to conclude non-inferiority of crovalimab to eculizumab: proportion of patients achieving TA, and hemolysis control.

The primary efficacy analysis will be conducted once the last patient randomized on trial completes 24 weeks of study treatment or discontinues early, whichever happens first.

4.4.1.1 Definition of Primary Estimands

In alignment with the addendum to International Council for Harmonisation (ICH) E9, the primary efficacy estimand is defined by the following four attributes:

- **Population:** The treatment-naive PNH population, as defined through the inclusion and exclusion criteria, randomized either to crovalimab or to eculizumab, receiving at least one dose of the assigned treatment and providing at least one centrally processed LDH level assessment after the first intravenous (IV) infusion.
- **Variables:**
  - Transfusion avoidance: categorical indicator taking value 1 for lack of any transfusion event from baseline to Week 25, and zero otherwise.
  - 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.
- **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 the 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 generalized 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 Protocol Section 5.1.3.1 on dose modifications) will be included in the primary analysis.
- **Population-level summary (estimate):**
  - **Transfusion avoidance:** the difference in proportion of TA, from baseline through Week 25, between crovalimab and eculizumab arms.
  - **Hemolysis control:** the odds ratio for hemolysis control between crovalimab and eculizumab arms, as assessed from Week 5 through Week 25.

If the assumption that data are missing completely at random is valid, then GEE results are unbiased. Little's test (Little 1988) will be used to assess missing completely at random (MCAR) and missing at random (MAR) assumptions, and sensitivity analyses may be conducted with consideration for the "missing not at random" assumption. For details see Section 4.4.4 and Section 4.8.

Prior to any analysis of the efficacy data, all reasons for treatment discontinuation will be documented according to the study-drug related (SDR) and non-study drug-related (NSDR) categories.

Table 1 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 ICEs 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 1 Classification of Treatment Discontinuations

Non-Study Drug–Related	Study Drug–Related
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 Model for Hemolysis Control

A GEE model will be used to estimate the adjusted log-odds ratio of LDH $\leq 1.5 \times$ ULN due to treatment, and taking account of the intra-individual correlation between LDH control statuses across visits. The dependent variable is the binary indicator for hemolysis control. Independent covariates are categorical effects of treatment and visit, visit by treatment interaction, continuous baseline LDH, and number of pRBC units administered within the 6 months prior to randomization. Data hierarchy is specified at the patient (subject ID) level. Further adjustments (baseline variables) may be explored in sensitivity analyses.

Baseline LDH is defined as the mean of all central LDH values: 1) taken during screening, i.e., within 28 days prior to first on study drug administration of either crovalimab or eculizumab; and 2) the LDH value at Week1 Day 1 collected prior to first dose administration of either crovalimab or eculizumab.

The primary analysis will apply an unstructured (UN) correlation matrix. This correlation structure imposes minimal assumptions; however, it requires estimating a large number of parameters which may prevent model convergence. If this is the case, other structures will be applied, as described in the sensitivity analysis section (Section 4.4.4).

All centrally processed LDH measurements, i.e., taken Q2W from Week 5 up to Week 25, will be used in the statistical model assessing non-inferiority of crovalimab compared with eculizumab. Unscheduled central LDH measurements will be mapped to the nearest scheduled assessment using windowing. Where more than one measurement is attributed to a visit window, then the average will be taken.

It is anticipated that a small proportion of central LDH samples will be affected by tabletop hemolysis (TTH), and such samples will be excluded from analyses. Samples

suspected to be affected by TTH will be identified via potassium concentration ≥ 6 mmol/L and LDH ≥ 2 x ULN.

4.4.1.3 Hypothesis Testing

4.4.1.3.1 Transfusion Avoidance

The percentage of patients with TA will be computed for the two randomized arms. Note that, as a conservative approach, patients who prematurely withdraw from study treatment will be assumed to have undergone a transfusion. A difference in the percentage of patients with TA in the two treatment arms will be calculated, along with a 95% CI for the difference using the stratified Newcombe CI method (Yan and Su 2010). The difference between the two treatment arms will be computed as a weighted combination of the differences between crovalimab and eculizumab arms within the stratification indicators of transfusion history and baseline LDH categories using Mantel-Haenszel weights (Agresti 2013).

Non-inferiority with respect to TA will be concluded if the lower limit (LL) of the 95% CI for the difference between crovalimab and eculizumab for TA is greater than the NIM of −20%:

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

versus

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

4.4.1.3.2 Hemolysis Control

LDH will be evaluated as scheduled in Appendix 1. Measures taken Q2W from Week 5 through Week 25 correspond to the period of stability in treatment-naive patients and will be used in the statistical analysis, as treatment-naive patients are expected to reach a stable LDH plateau by the end of the first month of treatment. For each patient at each visit, a binary variable will be created with the value of 1 if LDH $\leq 1.5 \times$ ULN, and 0 for LDH $> 1.5 \times$ ULN, and missing if LDH is not measured.

The non-inferiority hypothesis between crovalimab relative to eculizumab will be tested by comparing the LL of the two-sided 95% CI for the OR to the non-inferiority margin of 0.2:

$$H_0: \text{LL 95\% CI (OR)} \leq 0.2$$

versus

$$H_1: \text{LL 95\% CI (OR)} > 0.2$$

The null hypothesis will be rejected if the LL of the confidence interval (CI) is above 0.2 and crovalimab can be declared non-inferior to eculizumab with respect to hemolysis control.

4.4.2 Secondary Efficacy Endpoints

If non-inferiority is established for the co-primary endpoints then the secondary endpoints, including superiority testing of primary and secondary endpoints, will be tested using the hierarchical order tabulated below, with [c] denoting co-primary endpoints, which will be tested together. The strict testing hierarchy ensures family-wise Type I error rate is controlled at 2.5% level.

Test	Endpoint
Non-inferiority	[c]Proportion of patients with TA from baseline through Week 25
Non-inferiority	[c]Hemolysis control from Week 5 through Week 25
Non-inferiority	Proportion of patients with BTH from baseline through Week 25
Non-inferiority	Proportion of patients with stabilization of hemoglobin from baseline through Week 25
Superiority	Proportion of patients with TA from baseline through Week 25
Superiority	Hemolysis control from Week 5 through Week 25
Superiority	Proportion of patients with BTH from baseline through Week 25
Superiority	Proportion of patients with stabilization of hemoglobin from baseline through Week 25
Non-inferiority	Mean change from baseline to Week 25 in fatigue as assessed through use of the FACIT-Fatigue scale (for adults aged ≥ 18 years)
Superiority	Mean change from baseline to Week 25 in fatigue as assessed through use of the FACIT-Fatigue scale (for adults aged ≥ 18 years)

BTH= Breakthrough Hemolysis; TA= transfusion avoidance; FACIT-Fatigue= Functional Assessment of Chronic Illness Therapy- Fatigue

[c] Co-primary endpoints which will be tested together

Due to the hierarchical testing order being specified, no adjustment for the type I error is required. However, a closed testing procedure will be used and lack of significance of an endpoint in the hierarchy precludes the analysis of subsequent endpoints.

The choices of NIMs for the secondary endpoints are based on those used in ALXN1210-PNH-301 study (Lee et al. 2019). Additional details on the NIM and statistical analyses are described below.

4.4.2.1 Breakthrough Hemolysis

The proportion of patients with BTH from baseline through Week 25 will be analyzed using the same methodology as TA. As a conservative approach, patients withdrawing before Week 25 will be deemed to have experienced BTH in the unobserved period.

If the upper limit (UL) of the 95% CI for the difference between crovalimab and eculizumab in the proportion of patients with BTH is less than the NIM of 20%, then crovalimab will be declared non-inferior to eculizumab and the next endpoint will be tested.

4.4.2.2 Hemoglobin Stabilization

The proportion of patients with stabilization of hemoglobin from baseline through Week 25 will be analyzed using approaches similar to TA. As a conservative approach, patients who withdraw early will be assumed to not have hemoglobin stabilization.

If the LL of the 95% CI for the difference between crovalimab and eculizumab in the proportion of patients with stabilized hemoglobin is greater than the NIM of −20%, then crovalimab will be declared non-inferior to eculizumab and the next endpoint will be tested.

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

4.4.2.3 FACIT-Fatigue

Fatigue will be assessed if NI and then superiority are concluded for the co-primary and secondary endpoints above.

The change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue questionnaire will be analyzed using a mixed model for repeated measures (MMRM) assuming normally distributed scores, with adjustment for stratification factors, and baseline FACIT-Fatigue score. An unstructured covariance matrix will be used to model the within-patient errors. In the event that the model does not converge with unstructured covariance matrix, a more parsimonious structure will be considered in the following order until model convergence is achieved: Toeplitz, First order Autoregressive (AR1) and Compound Symmetry (CS).

The NIM will be a -5 point score, where higher scores indicate less fatigue, and hence non-inferiority hypothesis will be tested comparing the LL of the 95% CI for the difference with a non-inferiority margin of -5 points (Cella et al. 2002). The summary statistics for score will be presented by treatment group for baseline and treatment visits.

Non-inferiority of crovalimab compared to eculizumab will be declared if the null hypothesis of inferiority is rejected.

4.4.3 Exploratory Efficacy Endpoints

Analyses for the exploratory efficacy objectives are described below.

Time to event endpoints will be summarized with Kaplan-Meier curves and median times (if reached) with 95% CI. Time will be measured as the number of days between randomization /enrollment and the first observation of 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.

With regard to assessment of Mean Change from baseline, the applicable endpoints and analyses that will be applied for are described below:

- Mean change from baseline to Week 25 in selected EORTC QLQ-C30 (EORTC IL17) scales (for adults aged ≥18 years)
  - Functioning scales (Positive value indicative of a high level of functioning/QoL):
    1. Physical
    2. Role
    3. Global Health Status/QoL
- Mean change from baseline to Week 25 in EORTC IL40 symptoms (for adults aged ≥18 years)
  - Disease-related symptoms (Positive value indicative a high level of symptoms):
    1. Abdominal pain
    2. Headaches
    3. Dyspnea
    4. Dysphagia
    5. Chest pain
    6. Erectile dysfunction
- Mean change from baseline to Week 25 in PedsQL MFS and Physical Functioning scale of the PedsQL Core (for pediatric patients aged 8−17 years)
- Mean change over time in health-related quality of life according to QLQ-AA/PNH and PGIS (for adults aged ≥18 years)
- *Percent change from baseline to Week 25 in LDH levels

Change from baseline is calculated at the patient level as each visit score minus the value at baseline. Summary statistics will describe the raw scores and mean change (95% CI) from baseline at each visit. Plots of average scores with dispersion bars will be presented over time and by treatment arm.

*in this case the percentage change will be calculated at the patient level as:

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

Proportions will be reported with 95% CI, and are calculated with the number of patients as the denominator. As such, where multiple cases of the particular endpoint may be observed, the numerator of the calculation will be comprised of patients with one or more relevant instances and, where applicable, plots depicting the proportions (95% CI) at each visit will be presented by treatment arm.

As with other binary endpoints, a conservative assumption of failure with be applied for missing data.

For the proportion of patients with a ≥5 point improvement from baseline in the FACIT-Fatigue at Week 25 (for adults aged ≥18 years), percentage of patients will be summarized per treatment arm.

For patient preference for crovalimab or eculizumab, the percentage of patients preferring each treatment and the reasons for preference will be summarized per treatment arm.

Mean treatment-satisfaction with crovalimab or eculizumab at Week 25, as assessed through use of the TSQM-9 (for adults aged ≥18 years) will be presented by visit for treatment arm.

For other exploratory endpoints, applicable summary statistics will be presented by treatment arm.

4.4.4 Analysis of Arm B Patients Switching from Eculizumab to Crovalimab

Exploratory efficacy data from Arm B patients switching from eculizumab to crovalimab after 24 weeks of treatment will be summarized separately for the time period under crovalimab treatment. For analysis of endpoints defined over 24 weeks treatment intervals (see Section 2.2.4), only patients with at least 24 weeks of crovalimab treatment will be included. However, listings and by visit summary analysis of efficacy endpoints will include all available efficacy data.

4.4.5 Analysis of Descriptive Arm C

All exploratory efficacy endpoints listed in Section 2.2.5 will be descriptively analyzed separately for descriptive Arm C. If the number of patients in the descriptive arm is fewer than 10 then production of listings only, rather than summary tables, may be considered.

4.4.6 Sensitivity Analyses

Sensitivity analyses will include different analysis population definitions, statistical model and model assumptions for the primary endpoint, and impact of missing data as described below.

4.4.6.1 Analysis Populations

The primary efficacy endpoint analysis may be repeated using:

- ITT population (if PAP is markedly different to the randomized patient population) (as defined in Section 4.1.2)
- Per protocol population (as defined in Section 4.1.5)

4.4.6.2 Impact of Missing Data

Details of how missing data will be addressed are provided in Section 4.9.

4.4.6.3 Statistical Modelling

In the event that convergence is not achieved in the primary analysis using the unstructured covariance matrix structure, different structures (in this order: Toeplitz, AR1 or CS) will be applied.

Further sensitivity analyses may also include, based on the contribution of covariates assessed by Akaike Information Criterion (AIC), adjustment for continuous (age, PNH clone size of granulocytes and weight) and categorical (aplastic anemia) variables at baseline.

Additional sensitivity analyses adjusting for further covariates may be performed if new evidence arises.

4.4.6.4 Transfusion Avoidance

To supplement the primary analysis for Transfusion Avoidance which is performed applying the composite strategy for ICE handling, a sensitivity analysis will be performed in which failure is assumed where discontinuation is concluded to be SDR, and patients with non-SDR discontinuation will not be deemed a failure, for example in cases of pregnancy.

4.4.7 Subgroup Analyses

Comparative subgroup analyses describing the co-primary endpoints, and mean percent change in LDH levels from baseline to Week 25 will be conducted for the primary analysis population. Due to the limited sample size, some subgroups will be highly sensitive to variability caused by individual patients. No p-values will therefore be calculated. For each subgroup, the point estimates of the difference of crovalimab versus eculizumab and the associated 95% CI will be presented via Forest plots.

The specified sub-groups are:

- Age: <18, ≥ 18 – <65, ≥ 65 years
- Sex: Male, Female
- Region: North America, Central and South America, Europe, Africa and Middle East, Japan, Rest of Asia Pacific
- Eculizumab availability: Yes, No (see Appendix 4)

- Race: Asian, Black or African American, White, Other
- [stratification factor] transfusion history of total pRBC units administered in the 6 months prior to randomization: 0, >0 to ≤ 6, and >6
- [stratification factor] LDH value (2=$\leq 4 \times$ ULN, and $>4 \times$ ULN)
- Aplastic anemia: Yes, No
- Body weight (kg): 40 to <60, 60 to <100, ≥ 100

Additional subgroups may be added based on emerging evidence.

4.5 PHARMACOKINETIC ANALYSES

PK concentration data and calculated PK parameters for crovalimab and eculizumab 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.

In addition, non-linear mixed effects modeling will be used to analyze the PK concentration-time data for crovalimab and eculizumab. Population and individual PK parameters will be estimated and the influence of various covariates (such as age, race, gender and body weight) on these parameters will be investigated.

The relationship between PK and efficacy, safety or PD endpoints may be explored. Additional exploratory PK analyses may be conducted as appropriate.

Details of the mixed effects modeling and exploratory PK analyses and results of these will be reported in a document separate from the Clinical Study Report.

4.6 PHARMACODYNAMIC AND BIOMARKER ANALYSES

The change over time in PD biomarkers (e.g., C5 concentration, complement activity (CH50) measured by a liposome immunoassay) will be presented using summary statistics, including means, median, range, standard deviations, and coefficients of variation. The association of C5 polymorphisms and other complement-related gene polymorphisms, including human leukocyte antigen (HLA) types, with safety, efficacy, PK, PD, and immunogenicity endpoints may be explored and reported descriptively. No formal statistical analysis of exploratory biomarkers will be performed.

4.7 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.

4.8 SAFETY ANALYSES

Safety analyses will be performed on the safety evaluable population (defined as in Section 4.1.8). All safety endpoints will be analyzed descriptively and grouped by treatment received. Data will be presented separately for the randomized Arms A and B, and for the descriptive Arm C. Comparative summaries for randomized Arms A and B will be presented for the primary treatment period.

For Arm B, safety data occurring during the eculizumab treated period or during the safety follow-up period will be attributed to eculizumab. In patients that switch to crovalimab, safety data occurring on or after the first dose of crovalimab will be attributed to crovalimab. Data from patients in Arm B switching from eculizumab to crovalimab will be summarized separately for the time period under eculizumab treatment and under crovalimab treatment.

Safety analysis will include all available data up to the time of clinical cut-off date (CCOD).Safety will be assessed through descriptive summaries of exposure to each study treatment, adverse events (AEs), changes in laboratory test results, and changes in vital signs and electrocardiogram (ECG).

4.8.1 Exposure of Study Medication

Information on study drug administration will be summarized by duration and cumulative dose. In addition, treatment exposure will be summarized, including delays and interruptions. The number of patients whose dose was modified will be summarized.

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

4.8.2 Adverse Events

To evaluate the overall safety of crovalimab compared with eculizumab, the incidence of adverse events (AEs) will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade for each treatment period.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and AE severity will be graded according to NCI CTCAE v5. All AEs, serious AEs, AEs leading to death, AEs of special interest, and AEs 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 (worst) grade will be used in the summaries. Deaths and cause will be summarized.

4.8.3 Laboratory Data

Relevant laboratory tests will be summarized using mean change from baseline and shift-tables where appropriate.

4.8.4 Immunogenicity Analyses

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence); and the numbers and proportions of ADA-positive patients and ADA-negative patients after drug administration (post-baseline incidence) will be summarized in patients receiving crovalimab by arm (A, C and B after switch) (Section 4.1.7). 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).

ADA-positive responses may be further classified as neutralizing antibody and non-neutralizing antibody responses. In addition, treatment induced ADA response will be further classified as transient ADA response or persistent ADA response as follows and summarized using descriptive statistics:

- Transient ADA response
  - Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which ought to be considered persistent unless shown to be undetectable at a later time) or
  - Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.
- Persistent ADA response
  - Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or
  - Treatment-induced ADA incidence only in the last sampling time point of the treatment study period

The relationship between ADA status and safety, efficacy, PK, and PD endpoints may be analyzed and reported via descriptive statistics.

4.8.5 Vital Signs/ECG

Vital signs (including pulse rate, respiratory rate, blood pressure, and temperature) and ECG will be summarized by treatment arm using mean change from baseline.

4.9 MISSING DATA

The endpoint definitions of Section 4.4.1.3.1 describe handling of data for patients in whom it is not possible to observe TA in the full treatment period, e.g., due to withdrawal or death.

Missing assessments of LDH for an individual patient at a specific visit will not be imputed for the primary endpoint analysis of hemolysis control. The proposed primary analysis GEE model is valid under the assumption that missing data are missing completely at random. This assumption is likely to apply in this disease setting since a missing LDH value that depends on data that were not observed is unlikely to occur.

Local LDH levels may be used to account for missing central LDH data; 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 4.4.4).

The pattern of missingness will be explored using summary statistics (summary of reasons of discontinuations by treatment arm) and Kaplan-Meier plots showing the probability of remaining in the study over time by treatment arm.

4.9.1 Imputation of Missing Data

Missing LDH values can be classified into three categories, which will determine how they will be imputed for sensitivity analysis.

4.9.1.1 Missing Baseline

Baseline LDH is comprised of the average of all centrally processed screening LDH values up to Day 1. Baseline observations are therefore not expected to be missing.

4.9.1.2 Intermittent Missingness

This includes missing data for patients 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 within each treatment group 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.

4.9.1.3 Withdrawal from Treatment

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

classified into 1) NSDR or 2) SDR. Frequencies of such reasons will be summarized in order to assess potential MNAR.

The following imputation approaches will be performed to assess robustness of the GEE model:

- Using multiple imputation if the dropout rate exceeds 5% in any arm, if there is a 5% difference in dropout rate between arms, or in the presence of SDR withdrawal:
  - Using MCMC assuming missing data are missing at random
  - Using pattern mixture models or tipping point analyses to assess if data are Missing Not at Random (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 HC will then be derived from these values.

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 times for observations missing due to early withdrawal from study.

Details of the proposed sensitivity analysis are provided in Section 4.4.4.

4.10 INTERIM ANALYSES

No interim efficacy analysis is planned.

5. REFERENCES

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Appendix 1 Protocol Synopsis

TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS**
PROTOCOL NUMBER:	BO42162
VERSION NUMBER:	*6*
EUDRACT NUMBER:	2019-004931-21
IND NUMBER:	131343
NCT NUMBER	NCT04434092
TEST PRODUCT:	Crovalimab (RO7112689)
PHASE:	Phase III
INDICATION:	Paroxysmal nocturnal hemoglobinuria
SPONSORS:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd

Objectives and Endpoints

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

This study is divided into two parts as follows:

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

Primary Efficacy Objective (Randomized Arms)

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

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

  TA is defined as patients who are packed RBC (pRBC) transfusion-free and do not require transfusion per protocol-specified guidelines.
- Proportion of patients with hemolysis control, measured by *lactate dehydrogenase* (LDH) ≤1.5 × upper limit of normal (ULN) from Week 5 through Week 25 (as measured at the central laboratory)

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

Secondary Efficacy Objective (Randomized Arms)

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

- Proportion of patients with 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 stabilization of 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 by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue

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

Exploratory Efficacy Objective (All Arms)

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

- Total number of units (based on local equivalent) of pRBCs transfused per patient by Week25
- Proportion of patients with *central* LDH ≤1 ULN from Week 5 through Week 25
- Time from baseline to the first time *central* LDH ≤1 ×ULN
- Time from baseline to the first time *central* LDH ≤1.5 ×ULN
- Percent change from baseline to Week 25 in *central* LDH levels
- Proportion of patients who reach a hemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in the absence of a transfusion
- Proportion of patients experiencing MAVE from baseline through Week 25
- Mean change from baseline to Week 25 in Physical Functioning, Role Functioning, and Global Health Status/Quality of Life scales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life–Core 30, and select disease-related symptoms (abdominal pain, headaches, dyspnea, dysphagia, chest pain, and erectile dysfunction) of the EORTC Item Library (for patients aged ≥ 18 years)
- Mean change from baseline to Week 25 in Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale, and the Physical Functioning scale of the PedsQL Core (for patients aged 8–17 years)
- Proportion of patients with a ≥5-point improvement from baseline in the FACIT-Fatigue at Week 25 (for adults aged ≥18 years)
- Mean treatment satisfaction with crovalimab or eculizumab, as assessed by the Treatment Satisfaction Questionnaire for Medication-9 at Week 25 (for patients aged ≥18 years)
- Proportion of patients with preference for crovalimab or eculizumab at Week 41, for patients randomized to eculizumab who switch to crovalimab after 24 weeks of eculizumab treatment, as assessed through use of the Patient Preference Questionnaire developed by the Sponsor (for patients aged ≥18 years)
- Mean change over time in quality of life, as assessed by Quality of Life Questionnaire – Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria, and in overall health status, as assessed by Patient Global Impression of Severity Survey (for patients aged ≥18 years)

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

Safety Objective

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

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results
- Incidence and severity of injection-site reactions, infusion-related reactions, hypersensitivity, and infections (including meningococcal meningitis)
- Incidence of adverse events leading to study drug discontinuation
- Incidence and severity of clinical manifestations of drug-target–drug complex (DTDC) formation in patients who switched to crovalimab treatment from eculizumab treatment

Pharmacokinetic Objectives

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

- Serum concentrations of crovalimab and eculizumab over time

The exploratory PK objectives for this study are as follows:

- To evaluate potential relationships between drug exposure and the efficacy and safety of crovalimab (patients randomized to crovalimab)
- To evaluate potential relationships between drug exposure and the efficacy and safety of eculizumab (patients randomized to eculizumab)
- To evaluate relationship between DTDC size and kinetics and PK parameters of crovalimab and eculizumab (for patients randomized to eculizumab who switch to crovalimab after completion of eculizumab treatment)

Immunogenicity Objectives

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

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

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

Biomarker Objective

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

- Change over time in PD biomarkers, including complement activity measured by a liposome immunoassay and total component 5 (C5) concentration.
- Change over time in free C5 concentration in crovalimab-treated patients.
- Observed value and absolute change from baseline to Week 25 in parameters reflecting hemolysis (e.g., reticulocyte count, free hemoglobin, haptoglobin).
- Change over time in additional exploratory biomarkers, including but not limited to PNH clone size, markers from the complement system, and markers for intra- and extra-vascular hemolysis (e.g., C3, C4, C3d on RBCs, and sC5b9 complex), as well as markers of endothelial cell activation and markers from the coagulation system (e.g., vWF, P-selectin, D-dimer, thrombin-anti-thrombin complexes, thrombin generation) may also be evaluated.

- To investigate potential treatment resistance mechanisms, Arg885 and additional polymorphisms in C5 and in other complement-related genes may be analyzed. Human leukocyte antigen typing to investigate potential mechanisms of immunogenicity may also be performed.

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

Health Status Utility Objective

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

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

Study Design

Description of Study

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

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

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

Randomized Arms

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

- Crovalimab
- Eculizumab

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

Randomization will be stratified according to the following factors:

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

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

For patients who are randomized to crovalimab, an initial IV loading dose will be administered on Week 1 Day 1, followed by four weekly crovalimab SC doses on Week 1 Day 2, then on Weeks 2, 3, and 4. Maintenance dosing will begin at Week 5 and will continue every 4 weeks thereafter, for a total of at least 24 weeks of primary treatment period, followed by the treatment

extension period of no more than 5 years. All patients who receive crovalimab as part of this study will do so according to a weight-based tiered dosing approach schedule.

For patients who are randomized to eculizumab, dosing will follow local prescribing information or, if enrolled in a country without access to commercial eculizumab, the pharmacy manual. Initial weekly doses for 4 weeks will be followed by every 2-week administrations starting on Week 5. To obtain additional efficacy and safety data, patients who are randomized to eculizumab will have the opportunity to switch to crovalimab as part of the extension period of the study, once they have completed 24 weeks of treatment with eculizumab, if the treating physician determines that this is in their best interest.

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

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

Descriptive Analysis Arm (Arm C)

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

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

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

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

Exploratory Substudies

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

Number of Patients

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

Target Population

Inclusion Criteria for All Arms

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards
- Body weight ≥40 kg at screening
- Willingness and ability to comply with all study visits and procedures

- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of WBCs with granulocyte or monocyte clone size of ≥10%, within 6 months prior to randomization
- LDH level ≥2 × ULN at screening (as per local assessment)
- Presence of one or more of the following PNH-related signs or symptoms within 3 months prior to screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion because of PNH
- Vaccination against *Neisseria meningitidis serotypes A, C, W, and Y* < 3 years prior to initiation of study treatment. *Vaccination against serotype B should be administered in accordance with the most current local guidelines or standard of care (SOC), as applicable in patients with complement deficiency. If not previously administered or no longer current,* vaccination *must be completed* no later than *1* week after the first study drug administration. Vaccination currency *with vaccination against serotypes A, C, W, Y and B* should be maintained throughout the study, *according to* local guidelines or *SOC* as applicable in patients with complement deficiency. *In the absence of clear local guidelines for Neisseria meningitidis, the Advisory Committee on Immunization Practices 2020 Guidelines are recommended.*

  If vaccination is completed < 2 weeks prior to initiation or after the start of study treatment, appropriate antibiotic prophylaxis must be maintained from first study drug administration, continuing for at least 2 weeks after completion of vaccination or according to local SOC as applicable in patients with complement deficiency, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to the first dose of study drug. Patients who refuse vaccination against Neisseria meningitidis are not eligible for the study.
- Vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* according to national vaccination recommendations (e.g., *Advisory Committee on Immunization Practices* guidelines). If not previously *administered or no longer current,* vaccination should be *completed* no later than *1* week after the first study drug administration. *If vaccination is completed < 2 weeks prior to initiation or after the start of study treatment, appropriate antibiotic prophylaxis must be maintained from first study drug administration, continuing for at least 2 weeks after completion of vaccination or according to local SOC, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to enrollment. Patients who refuse vaccination against Haemophilus influenzae type B and Streptococcus pneumoniae when recommended are not eligible for the study.*
- Patients who have been vaccinated (partially or in full) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with a locally approved vaccine are eligible to be randomized/enrolled in the study, 3 days or longer after inoculation. Patients who have not been vaccinated against SARS-CoV-2 are also eligible to be in the study.
- Platelet count ≥ 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 the first study 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 and 3 months after the final dose of eculizumab (or longer if required by the local product label, e.g., 5 months after the final dose of eculizumab in the United Kingdom and the European Union according to the Summary of Product Characteristics).

  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.

Additional Inclusion Criteria for Patients in the Randomized Arms

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

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

Additional Inclusion Criteria for Patients in the Descriptive Arm

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

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

Exclusion Criteria

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

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

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

- Know HIV infection and with a $CD4^+$ cell count <200 cells/μL within 24 weeks prior to screening
- Patients with HIV infection who have a $CD4^+$ cell count >200 cells/μL and meet all other criteria are eligible.
- Infection requiring hospitalization or treatment with IV antibiotics within 28 days prior to screening and up to the first drug administration, or oral antibiotics within 14 days prior to screening and up to the first drug administration
- Active systemic bacterial, viral, or fungal infection within 14 days before first drug administration
- Presence of fever ($\geq$38°C) within 7 days before the first drug administration
- Immunized with a live attenuated vaccine within 1 month before first drug administration
- History of malignancy within 5 years prior to screening and up to the first drug administration, with the following exceptions:

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

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

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

  Female patients of childbearing potential must have a negative serum pregnancy test result within 28 days prior to initiation of study drug.
- Participation in another interventional treatment study with an investigational agent or use of any experimental therapy within 28 days of screening or within 5 half-lives of that investigational product, whichever is greater
- Substance abuse within 12 months prior to screening, in the investigator's judgment
- Concurrent disease, treatment, procedure or surgery, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose any additional risk for the patient, or would, in the opinion of the investigator, preclude the patient's safe participation in and completion of the study
- Splenectomy $\leq$6 months prior to screening
- Positive for hepatitis B surface antigen at screening
- Positive for hepatitis C virus (HCV) antibody at screening
- Patients who are seropositive for HCV but without detectable HCV RNA are eligible.
- History of or ongoing cryoglobulinemia at screening

End 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.

Investigational Medicinal Products

Test Product (Investigational Drug).

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

Crovalimab for IV Infusion and SC Administration

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

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

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

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

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

Eculizumab

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

Statistical Methods

Primary Analysis

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

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

Primary Estimand

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

- Population: *All randomized patients in Arms A and B who have met* the inclusion and exclusion criteria, *have received* at least one dose of *study drug* and *have* at least one *centrally processed* LDH *level assessment after the first IV infusion.*
- Variables: *central* LDH measured at prespecified hospital visits from Week 5 to Week 25, and any transfusion event from baseline to Week 25.
- Intercurrent events (ICEs):
  - TA: early withdrawal from study
  - Hemolysis control:

- Early withdrawal from study treatment
- Dose modification due to experiencing two or more qualifying intravascular hemolysis 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 or sustained intravascular hemolysis: treatment policy strategy

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

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

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

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

Primary Efficacy Analyses

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

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

Transfusion Avoidance

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

The difference in proportion of patients with TA between crovalimab and eculizumab arms, together with its 95% CI will be calculated as a weighted combination across stratification factors of transfusion history and baseline LDH using Mantel-Haenszel weights (Agresti 2013)

and the Newcombe Confidence Interval method (Yan and Su 2010). The non-inferiority hypothesis for the difference in proportions between crovalimab and eculizumab will be tested by comparing the lower limit (LL) of the 95% CI for the difference in proportions to the non-inferiority margin of −20%:

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

vs.

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

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

Hemolysis control

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

H_0: LL 95% CI (OR) ≤ 0.2

vs.

H_1: LL 95% CI (OR) > 0.2

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

Determination of Sample Size

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

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

The NIM for TA was determined based on the data reported in protocol ALXN1210-PNH-301, comparing eculizumab-treated patients with untreated patients from the global PNH Registry for eculizumab-treated patients, i.e., patients treated with eculizumab showed a benefit over untreated patients, with a difference of approximately 40% (TA proportion of 57.1% and 18.6%, respectively), after adjustment for history of transfusions 12 months prior to enrollment. Hence, a difference in proportions of −20%, the NIM, would preserve at least 50% of the control treatment effect. This NIM was also defined based on operational considerations, given the rarity of PNH. A more conservative NIM would have resulted in the estimated sample size being too large and infeasible. Lee et al. (2019) reported a proportion of patients with TA of 66.1% (95%CI: 65.9% to 74.6%) in treatment-naive patients in eculizumab.

With regard to hemolysis control, 116 patients are required in a 2:1 ratio to test the non-inferiority of crovalimab vs. eculizumab, with a non-inferiority margin of 0.2 in the OR scale, 80% power, and 1-sided test at 0.025 Type I error rate. Incidentally, a similar sample size was required to test for non-inferiority in the probability scale when the NIM is −0.2. Lee et al. (2019) also reported a proportion of LDH normalization below 1 × ULN of 49.4%. Under the

assumption of LDH being log-normally distributed, the expected proportion below 1.5x ULN is 86%. The same proportion was assumed for crovalimab. The NIM in the OR scale was obtained as $1/OR^{0.5}$, where OR = 24.6 assuming 86% of patients receiving eculizumab will reach LDH ≤1.5 × ULN compared to an upper bound of the 95% CI of the proportion among placebo-treated patients of 20%. Note that both proportions are approximately twice the ones used in protocol ALXN1210-PNH-301 for LDH ≤1 × ULN), and a fraction of 0.5 of that effect is retained (Ng 2008). Assuming a 10% drop-out, the total needed sample size would be 128 patients (85 randomized to crovalimab and 43 to eculizumab). With 180 evaluable patients expected in the study, the power for this endpoint will be 94%. Hence, the joint power for both TA and LDH would be 75% if they were uncorrelated. It is likely that co-primary endpoints are correlated and hence joint power would be higher. If there were no drop-outs and all 200 patients contributed at least one LDH sample then the power for TA would be 84% and for LDH 96%.

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

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

TA = transfusion avoidance; ULN = upper limit of normal.

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

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

Interim Analyses

No interim efficacy analysis is planned.

Appendix 2 Schedule of Activities

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

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

Appendix 2: Schedule of Activities (cont.)

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

Appendix 2: Schedule of Activities (cont.)

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

Appendix 2: Schedule of Activities (cont.)

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

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

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

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

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

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

[b] Only for patients who discontinue at or before Week 25. All other patients should follow schedules in Appendix 1 of Protocol version 6. Table 2 or Table 3 of the Protocol v6 for assessments after Week 25. For patients who discontinue from crovalimab, follow-up assessments should be taken 24 weeks *(site visit) and 46 weeks (safety telephone call)* after the final dose of crovalimab. Note that patients who continue crovalimab after discontinuation from the study treatment do not need to return for the safety follow-up visit. For patients who discontinue from eculizumab treatment, follow-up assessments should be taken 10 weeks after the final dose of eculizumab.

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

[d] Vaccination against *Neisseria meningitidis serotypes A, C, W, and Y* must be administered <3 years prior to initiation of study treatment. *Vaccination against serotype B* must be administered in accordance with most current local guidelines or *SOC as applicable for patients with complement deficiency. Vaccination currency with vaccination against serotypes A, C, W, Y and B should be maintained throughout the study according to local guidelines or SOC* as applicable in patients with complement deficiency. *Vaccination against Haemophilus influenzae type B and Streptococcus pneumoniae should be administered according to national vaccination recommendations. If not previously administered or no longer current, vaccination must be completed no later than one week after the first study drug administration. See Section 4.5.5.1 of the Protocol v6 for further details.* Patients who receive the vaccine within 2 weeks prior to initiating study treatment or after start of study treatment must receive appropriate prophylactic antibiotics from initiation of study treatment, continuing for at least 2 weeks after

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

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

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

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

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

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

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

[k] Vital signs include measurements of blood pressure (systolic and diastolic) while the patient is in a seated position, pulse rate, respiratory rate, and body temperature.

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

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

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

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

[p] Report previous and concurrent pRBC transfusions.

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

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

[s] Samples will not be collected *at some timepoints* from pediatric patients to ensure the drawn blood volumes will not exceed the limits described in Section 4.5.8 of the Protocol v6.

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

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

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

[w] After informed consent has been obtained but prior to initiation of the study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. Subsequently, all adverse events will be reported until *46* weeks *(approximately 10.5 months)* after the final dose of the study drug, unless the patient continues crovalimab treatment as part of an open-label extension study, or as per the Roche Global Policy on Continued Access to Investigational Medicinal Products or as commercial product. For patients randomized to eculizumab who do not switch to crovalimab after 24 weeks of treatment, all adverse events will be reported until 10 weeks after the final dose of the study drug. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to crovalimab at any timepoint. See Section 5 (Protocol v6) for additional details and reporting requirements.

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

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

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

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

[aa] Exploratory biomarker sample for central coagulation tests will not be collected from pediatric patients in all visits to ensure the drawn blood volumes will not exceed the limits described in Section 4.5.8 of the Protocol v6.

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

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

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

[ee] A local hemoglobin assessment must be performed within 5 days prior to Week 1 Day 1 (Days –4 to Day 1). The measurement can also be taken on Day 1 prior to randomization/enrollment, if randomization/enrollment takes place on Day 1), as an eligibility criterion. If the hemoglobin assessment taken at the screening visit is within this time interval, *and patient meets the hemoglobin eligibility requirement,* it does not need to be repeated. *Patient may* be transfused with pRBCs *to meet hemoglobin eligibility requirement. They must have their hemoglobin re-assessed for eligibility* with a post-transfusion hemoglobin *assessment prior to* randomization/enrollment (see Section 4.1.2 of the Protocol v6).

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

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

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

Appendix 2: Schedule of Activities (cont.)

Study Week	Week 25	Week 33 and Q8W Thereafter	Week 49 and Q12W Thereafter	Safety Follow-Up *Site Visit (24 Weeks After Last Dose)* [a]	*Safety Follow-Up Telephone Call (46 Weeks After Last Dose)* [a]
Plasma and serum sample set for PD biomarkers [e, q, u, v]	Follow Table 1 (Protocol v6) Week 25 Schedule for each corresponding row	X	x	x	
Serum ADA sample for crovalimab [e, q, u]		X	x	x	
Serum PK sample for crovalimab [e, q, u]		X	x	x	
FACIT-Fatigue, EORTC QLQ-C30 scales, and EORTC Item Library symptoms (patients aged ≥18 years) [r]		X	x	x	
PedsQL Core and PedsQL MFS (patients aged 8-17 years) [r]		X	x	x	
EQ-5D-5L (patients aged ≥12 years) [r]		X	x	x	
TSQM-9 (patients aged ≥18 years) [r]			x [s]		
QLQ-AA/PNH and PGIS (patients aged ≥18 years) [r]		x [t]			
Crovalimab administration	Q4W				

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

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.

Note: After 24 weeks in the primary treatment period, patients may continue/switch to crovalimab for a maximum of 5 years on the study (extension

period) and then continue crovalimab according to the Roche Global Policy on Continued Access to Investigational Medicinal Products.

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

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

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

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

[d] Vital signs include measurements of blood pressure (systolic and diastolic) while the patient is in a seated position, pulse rate, respiratory rate, and body temperature.

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

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

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

[h] Report previous and concurrent pRBC transfusions.

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

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

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

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

[m] Urinalysis will be performed through dipstick (pH, specific gravity, glucose, protein, ketones, and blood). If there is a clinically significant positive result (i.e., confirmed by a positive repeat sample), urine will be sent to the laboratory for microscopy and culture (sediment, RBCs, WBCs, casts,

crystals, epithelial cells, bacteria). If there is a known explanation for the positive dipstick result (e.g., menses), it should be recorded, and there is no need to perform laboratory for microscopy and culture.

[n] All adverse events will be reported until *46* weeks *(approximately 10.5 months)* after the final dose of the study drug, unless the patient continues crovalimab treatment as part of an open-label extension study, or as per the Roche Global Policy on Continued Access to Investigational Medicinal Products or as commercial product. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to crovalimab at any timepoint. See Section 5 of Protocol version 6 for additional details and reporting requirements.

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

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

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

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

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

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

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

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

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

Overall Study Week (Day)	Crovalimab Treatment										Week 49 and Q12W Thereafter	*Safety* Follow-Up Site Visit (24 Weeks After Last Dose)[a]	*Safety Follow-Up Telephone Call (46 Weeks After Last Dose)* [a]
	25 (Day 1)	25 (Day 2)	26	27	28	29	31	33	37	41	45			
Limited physical examination [b]	Follow Table 1 (Protocol v6) Week 25 Schedule for each corresponding row	x	x	x	x	x	x	x	x	x	x	x	x	
Vital signs [c]		x	x	x	x	x	x	x	x	x	x	x	x	
Pregnancy test [d, e]						x		x	x	x	x	x	x	*x*
12-Lead ECG						x								
Concomitant medications [f]		x	x	x	x	x	x	x	x	x	x	x	X	*x*
pRBC transfusions [g]		x	x	x	x	x	x	x	x	x	x	x	X	
Blood sample for PNH clone size [h]									x				X	
Hematology [d, i]			x	x	x	x	x	x	x	x	x	x	X	
Free hemoglobin, haptoglobin [d, j]			x	x	x	x	x	x	x	x	x	x	X	
Coagulation [d, k]						x			x			x	X	
Chemistry [d, l]			x	x	x	x	x	x	x	x	x	x	X	
Urinalysis [d, m]		x	x	x	x	x	x	x		x		x	X	
Adverse events [n]		x	x	x	x	x	x	x	x	x	x	x	X	*x*

Appendix 2: Schedule of Activities (cont.)

Overall Study Week (Day)	Crovalimab Treatment											Week 49 and Q12W Thereafter	*Safety* Follow-Up Site Visit (24 Weeks After Last Dose)[a]	*Safety Follow-Up Telephone Call (46 Weeks After Last Dose)* [a]
	25 (Day 1)	25 (Day 2)	26	27	28	29	31	33	37	41	45			
Assessment and documentation of BTH [d, o]	Follow Table 1 (Protocol v6) Week 25 Schedule for each corresponding row	x	x	x	x	x	x	x	x	x	x	x	X	
Serum sample for central LDH and central potassium [d, p, v]		x	x	x	x	x	x	x	x	x	x	x	X	
Plasma and serum for PD biomarkers [d, s, v, w]			x	x	x	x	x	x	x	x	x	x	X	
FACIT-Fatigue, EORTC QLQ-C30 scales, and EORTC Item Library symptoms [q]			x			x		x		x		x	x	
EQ-5D-5L [q]			x			x		x		x		x	x	
TSQM-9 [q]												x [r]		
Serum ADA sample for crovalimab [d, s, v]	x		x	x	x	x		x	x	x	x	x	x	
Serum PK sample for crovalimab [d, s, t, v]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum DTDC sample [d, u]	x	x	x	x	x	x	x	x	x	x	x		x	
QLQ-AA/PNH and PGIS [q]							x							

Appendix 2: Schedule of Activities (cont.)

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

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

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

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

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

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

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

[c] Vital signs include measurements of blood pressure (systolic and diastolic) while the patient is in a seated position, pulse rate, respiratory rate, and body temperature.

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

[e] Serum or urine pregnancy tests will be locally performed for patients of childbearing potential prior to dosing and Q4W thereafter. *A urine*

pregnancy test will also be performed by the patient within 2 days prior to the final telephone call follow-up (i.e., 46 weeks [approximately 10.5 months] after the final dose of crovalimab). The patient should report the result of the pregnancy test during the telephone call. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

[g] Report previous and concurrent pRBC transfusions.

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

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

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

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

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

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

[n] All adverse events will be reported until *46* weeks *(approximately 10.5 months)* after the final dose of crovalimab, unless the patient continues crovalimab treatment as part of an open-label extension study, or as per the Roche Global Policy on Continued Access to Investigational Medicinal Products or as commercial product. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to the study drug. See Section 5 of Protocol version 6 for additional details and reporting requirements.

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

documented in the eCRF.

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

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

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

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

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

[u] On Day 1 of Week 25, DTDC sample is to be collected before and after the end of infusion of the first dose of crovalimab. Subsequent DTDC samples are to be collected before the crovalimab dose.

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

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

Schedule of Activities for Patients Who Discontinue Crovalimab and Switch to Other C5 Inhibitors

	Treatment with Other C5 Inhibitor						
Week	1	2	3	4	5	7	9
Physical examination [a, b]	x	x	x	x	x	x	x
Vital signs [b, c]	x	x	x	x	x	x	x
Safety laboratory assessments [b, d]	x	x	x	x	x	x	x
Urinalysis [b, e]	x	x	x	x	x	x	x
Adverse events [f]	x	x	x	x	x	x	x

BTH=breakthrough hemolysis; C5=component 5.

[a] Only a limited physical examination is required.

[b] Assessment/sampling should be performed before the C5 inhibitor dose.

[c] Vital signs include measurements of blood pressure (systolic and diastolic) while the patient is in a seated position, pulse rate, respiratory rate, and body temperature.

[d] Safety laboratory assessments include hematology and chemistry panels as per investigator's judgement in order to monitor the safety of a patient.

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

[f] All adverse events will be reported until *46* weeks *(approximately 10.5 months)* after the final dose of the study drug. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to crovalimab at any timepoint. See Section 5 of Protocol version 6 for additional details and reporting requirements.

Appendix 3 Clinical Definitions

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.

Appendix 4 Eculizumab Availability Definition

Regions in which eculizumab is available (yes/no) are listed in the table below.

Eculizumab's Availability

Regions	Eculizumab Access Y/N
Argentina	N
Australia	Y
Austria	Y
Belgium	Y
Brazil	Y
Canada	Y
China	N
Colombia	Y
Czech Republic	Y
France	Y
Germany	Y
Greece	Y
Hong Kong	Y
Hungary	Y
Italy	Y
Malaysia	N
Mexico	Y
Netherlands	Y
Peru	N
Poland	Y
Portugal	Y
Romania	N
Singapore	Y
South Africa	N
Spain	Y
Sweden	Y
Thailand	N
Turkey	Y
United Kingdom	Y
United States	Y

Signature Page for SAP Study BO42162 (Crovalimab_Naive) v3 - Published
System identifier: RIM-CLIN-455475

Approval Task	[redacted] Company Signatory 19-Oct-2022 16:44:45 GMT+0000

CHARTER FOR THE INDEPENDENT DATA MONITORING COMMITTEE

TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN ADULT AND ADOLESCENT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS**
PROTOCOL:	BO42162
AUTHOR:	[redacted] M.Sc.
IND NUMBER:	131343
EUDRACT NUMBER:	2019-004931-21
SPONSORS:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd
DATE FINAL:	26 October 2020
DATES AMENDED:	Version 2: 3 June 2021 Version 3: Please see electronic date stamp below.

FINAL CHARTER APPROVAL

[redacted]

Data Review Board [redacted] Ph.D.
Genentech, Inc.

21-Nov-2022
Date

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF APPENDICES

iDMC Charter BO42162, Version 3
Administrative Update

Effective 31 August 2022, the Data Review Board Chair responsibilities for F. Hoffmann-La Roche Ltd will transfer from [redacted] Ph.D. to [redacted], Ph.D.

[redacted] **Ph.D.**
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
USA
[redacted]
Mobile Phone No.: [redacted]

Electronic signature clause has been added to the signature pages.

INDEPENDENT DATA MONITORING COMMITTEE MEMBER SIGNATURES

TITLE: **A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN ADULT AND ADOLESCENT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS**

PROTOCOL: BO42162

I have read this Charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the independent Data Monitoring Committee.

Independent Data Monitoring Committee [redacted] M.D.
Hematology Clinic

Date

[redacted] Ph.D.
[redacted], Statistik und Dokumentation
Medizinische Universität Graz

Date

The Parties agree that in order to fulfill the written form requirement of this Agreement, as alternative to handwritten signatures on a hard copy, electronic signatures ("eSignature[s]") of duly authorized representatives of the Parties may be used. eSignature shall mean a signature that consists of one or more letters, characters, numbers or other symbols in digital form incorporated in, attached to or associated with the electronic document, that (a) is unique to the person executing the signature; (b) the technology or process used to make the signature is under the sole control of the person making the signature; (c) the technology or process can be used to identify the person using the technology or process; and (d) the electronic signature can be linked with an electronic document in such a way that it can be used to determine whether the electronic document has been changed since the electronic signature was incorporated in, attached to or associated with the electronic Document.

INDEPENDENT DATA MONITORING COMMITTEE MEMBER SIGNATURES

TITLE: **A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN ADULT AND ADOLESCENT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS**

PROTOCOL: BO42162

I have read this Charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the independent Data Monitoring Committee.

[redacted] M.D. Date

[redacted]

University Children's Hospital Basel

[redacted] M.D., Ph.D. Date

[redacted]

Saint-Louis Hospital

The Parties agree that in order to fulfill the written form requirement of th s Agreement, as alternative to handwritten signatures on a hard copy, electronic signatures ("eSignature[s]) of duly authorized representatives of the Parties may be used. eSignature shall mean a signature that consists of one or more letters, characters, numbers or other symbols in digital form incorporated in, attached to or associated with the electronic document, that (a) is unique to the person executing the signature; (b) the technology or process used to make the signature is under the sole control of the person making the signature; (c) the technology or process can be used to identify the person using the technology or process; and (d) the electronic signature can be linked with an electronic document in such a way that it can be used to determine whether the electronic document has been changed since the electronic signature was incorporated in, attached to or associated with the electronic Document.

1. INTRODUCTION

This Phase III, randomized, open-label, active-controlled, multicenter study is designed to evaluate the efficacy of crovalimab compared with eculizumab in patients that have not been previously treated with a complement-inhibitor therapy, based on the non-inferiority assessment of both TA and hemolysis control.

Approximately 200 patients aged 12 years or older, with a body weight ≥40 kg, will be randomized 2:1 to crovalimab or eculizumab.

For further study details, please refer to the protocol.

This iDMC Charter defines the roles and responsibilities of the iDMC, including its membership, scope, timing of meetings, and communication plan.

Terms and abbreviations used in this Charter are defined in Table 1.

Table 1 Terms and Abbreviations

Term	Definition
Blinded data	Data for which treatment assignment is not identified.
CRO	Contract Research Organization
DRB	Roche's Data Review Board, consisting of employees of the Sponsor authorized to make critical decisions, such as whether to accept a recommendation from the iDMC to stop the clinical trial(s). For this study, the DRB is composed of the Chief Medical Officer (CMO), the Global Head of Regulatory, the Global Head of Safety Risk Management, the Hematology Global Clinical Development Head, and the Global Head of Data Sciences (DRB Chair). The DRB Chair is the Sponsor's point of contact for the iDMC members after the iDMC has reviewed unblinded data.
iDCC	independent Data Coordinating Center, wherein external data analysts are responsible for preparing current, accurate, and unblinded analyses for iDMC review. Independence hereby refers to the role being independent from the individuals involved in the execution of the clinical trial and independent from Roche.
iDMC	independent Data Monitoring Committee.
IxRS	Interactive Voice or Web-Based Response System
Scientific Responsible	Sponsor employee who is overall responsible for the scientific content and conduct of a clinical trial.

Term	Definition
Sponsor Statistician	Sponsor employee responsible for statistical aspect of a clinical trial.
Study Management Team (SMT)	Team composed of Sponsor representatives directly involved with the trial; includes Scientific Responsible, Statistician, and Study Lead.
PK	pharmacokinetic
Pooled data	data for which treatment arms are combined
Roche Group	The Roche Group includes, among others, the following entities: Roche Holding Ltd (Basel, Switzerland), F. Hoffmann-La Roche AG (Basel, Switzerland), Roche Translational Clinical Research Center (New York, USA), Roche Products Limited (Welwyn, United Kingdom), Genentech, Inc. (South San Francisco, USA), and Shanghai Roche Pharmaceuticals Limited (Shanghai, China).
Sponsor	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd.
Unblinded data	data for which treatment assignment is identified

2. ROLE OF THE COMMITTEE

2.1 SAFETY

The independent Data Monitoring Committee (iDMC) shares with the Sponsor the responsibility to monitor overall patient safety of the Investigational Medicinal Product (IMP). By carefully reviewing overall safety profile, including rates of deaths, all adverse events, and other specified safety events, the iDMC will help the Sponsor minimize patient exposure to unnecessary risk. If appropriate, the iDMC may also evaluate benefit and risk by reviewing relevant efficacy data together with safety data during the review meetings. Pharmacokinetic (PK) data will also be available to the iDMC. Safety analyses will be conducted according to the schedule below:

- The first analysis will be done when approximately 30 patients randomized in BO42162 reach 10 weeks of treatment on the study, or when 40 patients randomized in BO42161 reach 10 weeks of treatment on the study, or when 5 ravulizumab patients have switched to crovalimab have completed the first 8 weeks of treatment in study BO42161 (see BO42162 iDMC charter). All patients enrolled in the BO42162 and BO42161 studies at that time will be evaluated.
- Additional safety reviews may be planned depending on the speed of enrollment and the emerging safety profile from either study.

After each safety review, the iDMC will make a recommendation to continue the study without modification, to continue the study with recommended modifications, to stop the study, or to put enrollment on hold pending further iDMC recommendation.

2.2 EFFICACY

There is no pre-planned efficacy interim analysis that could lead to early stopping of the study. However, the iDMC may request any relevant efficacy data for review.

2.3 STUDY CONDUCT

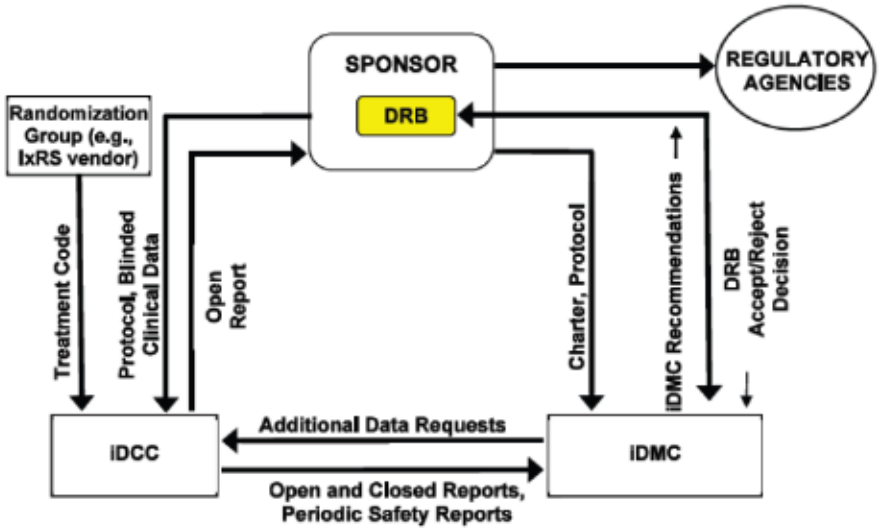
The iDMC may alert the Sponsor to possible concerns related to the conduct of the trial. These include but are not limited to concerns about the appropriateness of the study population on the basis of characteristics of enrolled patients, adequacy of the randomization process, protocol violations and deviations, problems with protocol compliance, and problems with data completeness and quality.

3. ORGANIZATIONAL FLOW

Figure 1 illustrates the relationships among the Sponsor, the iDMC, the independent Data Coordinating Center (iDCC), the interactive voice or web-based response system (IxRS) vendor, the Data Review Board (DRB), and regulatory agencies.

When the iDMC issues recommendations, the Sponsor's Data Review Board (DRB) makes the final decision as to whether to accept the iDMC's recommendations. The DRB Chair is the Sponsor's single point of contact for the iDMC members after the iDMC members have reviewed unblinded data.

Figure 1 Organizational Flow



DRB = Data Review Board; iDCC = independent Data Coordinating Center; iDMC = independent Data Monitoring Committee; IxRS = Interactive Voice or Web-Based Response System.

4. COMMITTEE MEMBERSHIP

4.1 MEMBERS

Chair: [redacted], M.D.
Huntsman Caner Hospital
[redacted]
1950 Circle of Hope
Salt Lake City, UT 84112

Members: [redacted], Ph.D.
[redacted]
Medizinische Universität Graz
Auenbruggerplatz 2, A-8036 Graz

[redacted], M.D.
[redacted]
University Children's Hospital Basel
Spitalstrasse 33
4056 Basel

[redacted], M.D., Ph.D.
[redacted]
16 Boulevard Vital Bouhot
92200 Neuilly-sur-Seine, France

Each member's curriculum vitae is available in the Sponsor's files and will be provided to regulatory agencies and institutional review boards (independent ethics committees) upon request.

4.2 FINANCIAL DISCLOSURE AND CONFLICT OF INTEREST

iDMC members may not be employees of the Sponsor or any CRO that works with the Sponsor on this study. No iDMC member may participate in the study as an investigator, co-investigator, subinvestigator, patient, or in any other capacity that might compromise his or her privileged activities on the iDMC.

iDMC members are strongly discouraged from owning any stock in Roche (such as bearer shares, non-voting equity security [NES or Genussscheine], or American Depository Receipts [ADR]) or owning any stock in Chugai Pharmaceutical Co. Ltd. or any other Sponsor of the study. In no event may iDMC members own stock in Roche or any other Sponsor of the study in excess of U.S.$50,000.

iDMC members must disclose any payments they or their immediate family members may have received from the Roche Group or Chugai Pharmaceutical Co. Ltd. in excess of U.S.$25,000 or its equivalent in the 12 months prior to the ratification of the Charter.

Such payments may include any combination of consulting fees, honoraria, donations of equipment, grants to fund ongoing research, or other payments exclusive of reimbursements to support the costs of conducting clinical trials.

At the time of signing the contract with the Sponsor, iDMC members must disclose whether they serve on other iDMCs or are engaged in activities with other sponsors that relate to products or molecules under investigation in the same disease area as the studies covered under this charter.

All members of the iDMC will disclose new conflicts of interest in the closed session of each meeting and document these in the meeting minutes. The template provided in Appendix 5 may guide this discussion. The iDMC Chair will be responsible for deciding whether possible conflicts of interest disclosed by any of the other members of the iDMC do materially affect their objectivity or whether there is a reasonable belief that a member's objectivity may be in doubt. The decision taken by the iDMC Chair will be documented in the minutes of the closed session.

Any new conflicts of interest disclosed by the iDMC Chair will also be reported in writing to the DRB Chair. If required, the DRB Chair will then consult with other members of the Sponsor and share the final decision with the iDMC Chair.

Members of the iDMC who develop potential or significant perceived conflicts of interest that may materially affect objectivity will be asked to resign from the iDMC and will be replaced.

4.3 DURATION OF IDMC MEMBERSHIP

iDMC membership will extend for the duration of the trial, up to the time the database for primary analysis is locked and the study is unblinded to the Sponsor. If a member leaves the iDMC, the Sponsor will select a replacement.

5. COMMITTEE MEETINGS

5.1 ORGANIZATIONAL MEETING

The first meeting of the iDMC will be an organizational meeting. This meeting will formally establish the iDMC and thoroughly acquaint the iDMC with the protocol and interim analysis plan. It also affords the iDMC an opportunity to recommend final revisions to the Charter and to the communication plan between the iDMC and the Sponsor.

Attendees:

- iDMC members
- iDCC statistician
- Sponsor representatives: Study Medical Monitor, Study Biostatistician, Study Clinical Pharmacologist, Clinical Safety Responsible, and other designees, as appropriate

Documents to be provided by the Sponsor:

- ☐ Final protocol
- ☐ Data collection specification (e.g., Case Report Form)
- ☐ Draft iDMC charter
- ☐ Statistical Analysis Plan (SAP)

Meeting objectives:

- ☐ Provide feedback on the iDMC charter
- ☐ Reach agreement on the safety monitoring plan
- ☐ Outline the logistics of interactions between the iDMC and the Sponsor for the predefined updates
- ☐ Review future meeting timelines

5.2 SCHEDULED INTERIM ANALYSIS MEETINGS

A minimum of one interim analysis is scheduled for the review of the accrued safety and PK data. Additional safety analyses may be conducted at the request of the iDMC or the Study Team.

5.2.1 Open Session

The open session will serve as a general study update and will provide a forum for iDMC members to question the Sponsor about the trial and to seek additional information deemed relevant to the interim analysis. Attendees will be the iDMC members, the iDCC Statistician, the Sponsor Scientific Responsible, the Sponsor Clinical Safety Responsible, the Sponsor Clinical Pharmacologist, and the Sponsor Statistician, and others as appointed by the Sponsor. This will be the only portion of the meeting during which the Sponsor representatives discuss the trial with the iDMC.

5.2.2 Closed Session

At the closed session, the iDMC will discuss the unblinded data and make recommendations regarding the study. Only iDMC members and the iDCC Statistician will attend the closed session. The Sponsor will not have access to the closed reports until the primary analysis.

Any meetings between the Sponsor and the iDMC immediately after the closed session are strongly discouraged.

5.3 UNSCHEDULED MEETINGS

In addition to the regularly scheduled safety reviews, an unscheduled review of the data may be performed at the request of the iDMC or Study Team, on the basis of a perceived concern for patient safety. The iDCC Statistician will prepare the necessary reports to which the Sponsor will remain blinded.

6. COMMUNICATION

iDMC members are to treat all communications regarding this clinical study, including reports, data, review meeting discussions, teleconferences, and meeting minutes, as confidential material.

6.1 OPEN REPORTS

The open reports will be prepared by the iDCC and distributed to the open session attendees within 5 business days prior to each interim analysis meeting. The open reports will include the data displays as described in Appendix 1.

6.2 CLOSED REPORTS

The closed reports will be prepared by the iDCC and provided to the iDMC within 5 business days prior to each interim analysis meeting. Closed reports will be reviewed at closed sessions and will include unblinded PK and safety data, as well as unblinded baseline characteristics and protocol deviation data, as described in Appendix 2.

6.3 iDMC MINUTES

The iDCC Statistician or another individual designated by the iDMC Chair will prepare minutes of the open and closed sessions within one week following each iDMC meeting. Minutes of the open session will be shared with the open session attendees and the DRB Chair. Minutes of the closed session will be distributed to the iDMC members and the iDCC Statistician only.

At the conclusion of the study, a complete set of the minutes of the closed sessions and the closed reports will be sent to the Sponsor Statistician.

6.4 iDMC RECOMMENDATIONS

At each interim analysis, the iDMC will recommend that the trial either continues or stops. The iDMC may also recommend change(s) to study conduct via a protocol amendment. The recommendations will be based on the guidelines outlined in Section 2.

The iDMC Chair, the iDCC Statistician, and an additional medical member of the iDMC must be present for the meeting to be quorate. The iDCC Statistician does not have a vote but needs to be present at the meeting to help the iDMC interpret the data. The iDMC Chair will make efforts to build a consensus among the members before the final decision on the iDMCs recommendation is issued. If it is deemed impossible to come to a consensus, the iDMC may agree on voting; in this case, if there is a tie, the iDMC Chair has the casting vote.

The iDMC Chair will notify the DRB Chair of the iDMC's recommendations, in a meeting or by telephone (email may also be used if time zones make either a meeting or a

telephone call unfeasible), immediately after the closed session and will follow up with a written communication, using the topline recommendation template within 72 hours.

6.5 SPONSOR DECISIONS

Upon receipt of the iDMC's recommendations, the DRB will review the recommendations, obtain input or additional data as deemed necessary from the iDMC, Study Team, Steering Committee, regulatory agencies, or other bodies such as the Ethics Committee/Institutional Review Board, and, on behalf of the Sponsor, accept or reject the recommendations.

If the iDMC and the DRB agree to amend the protocol or to stop the trial, the Sponsor will inform regulatory agencies of the decision prior to notifying the investigational centers. Public disclosure of the decision, as appropriate, will be made by the Sponsor.

If the iDMC recommends that the trial be stopped prematurely, the DRB may request unblinded data from the iDCC upon which to base its decision. If the DRB decides to continue the trial, the DRB Chair will first discuss with the iDMC Chair the rationale for the decision and, thereafter, will provide a written explanation of the decision to the iDMC within three business days. At no point in the trial will the clinical team have access to the unblinded interim data.

The DRB Chair will communicate all iDMC recommendations that are accepted by the DRB and any other DRB decisions to the iDMC Chair and the Sponsor Statistician. If required, the Sponsor's DRB regulatory representative or designee will communicate the Sponsor's decisions to regulatory agencies as appropriate. The iDMC Chair will communicate the Sponsor's decision to the rest of the iDMC.

Appendix 1
Data Displays for Open Reports

The iDMC may request analyses of additional data at any time in order to perform its duties effectively. Similarly, the Sponsor may request that the iDMC review additional data should a particular safety concern be identified.

Pooled, blinded data:

- ☐ Summary of Patient Enrollment
- ☐ Summary of Patient Disposition
- ☐ Summary of Reasons of Withdrawal from Study
- ☐ Summary of Reasons for Treatment Discontinuation
- ☐ Summary of Protocol Deviations
- ☐ Summary of Patient Demographics and Baseline Characteristics

Appendix 2
Data Displays for Closed Reports

The iDMC may request analyses of additional data at any time in order to perform its duties effectively. Similarly, the Sponsor may request that the iDMC review additional data should a particular safety concern be identified.

Standard interim outputs

Unblinded data by treatment:

- Summary of Patient Enrollment
- Summary of Patient Disposition
- Summary of Reasons of Withdrawal from Study
- Summary of Reasons for Treatment Discontinuation
- Summary of Protocol Deviations
- Summary of Patient Demographics and Baseline Characteristics
- Summary of Deaths
- Summary of Adverse Events
- Summary of Adverse Events by Intensity
- Summary of Related Adverse Events
- Summary of Serious Adverse Events
- Summary of All Adverse Events Leading to Treatment Discontinuation
- Listings and Summary for Adverse Events of Special Interest
- Summary and Listings of Anti-Drug Antibody (ADA; and nADA if available)
- Listing of BTH
- Listing of Transfusions
- Listing of C_{trough}
- Listings and Summary of Study Drug Exposure
- Summary tables, plots, and listings for abnormal laboratory data including:
    - Hematology
    - Biochemistry
    - LDH
- Summary tables and listings for:
    - Vital signs
    - ECG

Appendix 3 iDMC Recommendation

TO: [redacted], Ph.D.
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
USA
[redacted]
Mobile Phone No.: [redacted]

FROM: [redacted], M.D.

DATE: "{Date of communication}"

MOLECULE: Crovalimab

PROTOCOL: BO42162

SUBJECT: Recommendation following iDMC review of "{e.g., first interim efficacy analysis, safety review, etc.}"

The iDMC met by "{Teleconference/Face to Face}" on "{Date of meeting}" for protocol BO42162: A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN ADULT AND ADOLESCENT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS.

Based on review of the data and the meeting discussion, it is recommended that the Sponsor "{Modify the following items based on agreements in the iDMC Charter}":

- ☐ Continue the trial without modification
- ☐ Continue the trial with recommended modifications
- ☐ Stop the trial
- ☐ Put enrollment on hold pending further iDMC recommendation

Signed: _____ Date: _____

[redacted] M.D., iDMC [redacted]

Appendix 4 iDMC Recommendation Details

TO: [redacted], Ph.D.
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
USA
[redacted]
Mobile Phone No.: [redacted]

FROM: [redacted], M.D.

DATE: "{Date of communication}"

MOLECULE: Crovalimab

PROTOCOL: BO42162

SUBJECT: Recommendation following iDMC review of
"{e.g., first interim efficacy analysis, safety review, etc.}"

This communication should not include any data or quote any results of the trial. This form is optional and may be used to share additional information with the Sponsor's Data Review Board when the recommendation checked on the form "iDMC Recommendation" is anything other than "Continue the trial without modification."

The iDMC met by "{Teleconference/Face to Face}" on "{Date of meeting}" for protocol BO42162: A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN ADULT AND ADOLESCENT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS. Based on review of the data and the meeting discussion, the recommendation(s) and action item(s) are as follows:

1. Xxxxxxx
2. Xxxxxx
3. Xxxxx
4. . . . . .

Signed: _____ Date: _____

[redacted] M.D., iDMC [redacted]

Appendix 5
Conflict of Interest Guidance

The items below may guide the disclosure of potential conflicts of interest in the closed sessions as described in Section 4.2. Disclosures made by any iDMC member must be documented in the minutes of the closed session. Disclosures made by the iDMC Chair need to be communicated to the DRB Chair. At each meeting, only new possible conflicts of interest that have not been disclosed previously need to be disclosed.

1. Do you, your spouse, or dependent children (or any combination) have:
   - Any ownership interest, stock options, or other financial interest in any member of Roche Group or its affiliates whose value cannot be readily determined through reference to public prices?
   - Any equity interest in any member of Roche Group or its affiliates, such as bearer shares, non-voting equity security (NES or Genussscheine), or American Depository Receipts (ADR), that is equal to or exceeds U.S.$50,000? Note: If YES, this will require resignation from the iDMC.
   - A financial agreement with any member of Roche Group or its affiliates whereby the value of compensation could be influenced by the outcome of the above-listed study. This includes compensation that could be greater for favorable clinical results, compensation in the form of an equity interest in any member of Roche Group or its affiliates, or compensation tied to sales of the product tested in the above-listed study, such as a royalty interest?
   - Any propriety interest in the product tested in the above-listed study such as patents rights or rights under a patent, trademark, copyright or licensing agreement?
   - Received payments from any member of Roche Group or its affiliates which **in the aggregate** exceed U.S.$25,000? (For example, two payments to you, each for U.S.$10,000, and one payment to your spouse for U.S.$7,000 would be in excess of U.S.$25,000.) This includes fee-for-service activities such as retainers for consultation, speaking engagements, or participation in advisory boards on behalf of any member of Roche Group or its affiliates; also compensation in the form of equipment and payments to your institution attributable to you to support your activities.
2. Are you involved in any activities (e.g., iDMCs, clinical trials, consulting etc.) with any member of the Roche Group or any of its affiliates?
3. Are you involved in any activities (e.g., iDMCs, clinical trials, consulting etc.) with other sponsors that relate to products or molecules under investigation in the same disease area as the one investigated in the trial(s) covered under this Agreement?
4. Are you affiliated with or do you have financial interests in any contract research organizations (CROs) participating in the execution of the study/studies covered under this Agreement?

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