Official Title: A Phase III, Multicenter, Single-Arm Study Evaluating the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Crovalimab in Adult and Adolescent Patients with Atypical Hemolytic Uremic Syndrome (aHUS)

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PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, SINGLE-ARM STUDY EVALUATING THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CROVALIMAB IN ADULT AND ADOLESCENT PATIENTS WITH ATYPICAL HEMOLYTIC UREMIC SYNDROME (aHUS)**
PROTOCOL NUMBER:	BO42353
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TEST PRODUCT:	Crovalimab (RO7112689)
SPONSORS:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL HISTORY

Protocol		**Associated Country and/or Region Specific Protocols**		
Version	**Date Final**	**Country and/or Region**	**Version**	**Date Final**
7	See electronic date stamp on the final page of this document	China	7	To be determined
6	16 May 2023.	China	6	25 August 2023
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PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol BO42353 has primarily been amended to align with the recent Statistical Analysis Plan (SAP) update, Version 2, finalized December 4, 2023. Significant changes were the following:

- The interval between the two separate assessments required to confirm cTMAr has been clarified to be a minimum of 26 days to align with the protocol allowed ±2 day dose administration window (Sections 2.1.1, 2.1.2, 6.5.1, 6.5.2, 6.5.3).
- Observed value and change from baseline to Week 25 in eGFR, using different eGFR equations has been added as an exploratory efficacy endpoint to explore the impact of different eGFR equations on the eGFR results (Section 2.1.3).
- A new exploratory immunogenicity endpoint has been added to explore the percentage of patients with loss of PK and PD in ADA-positive patients (Section 2.4).
- Normalization of serum creatinine values at baseline has been added as an exclusion criterion to improve clarity on the definition of the primary analysis population (Sections 4.1.2).

Additional key changes to the protocol, along with the rationale(s) for each change, are summarized below.

- Because rapid diagnosis and early initiation of C5 inhibition prevents poor outcomes and irreversible renal impairment in aHUS, the following exclusion criteria have been updated to ensure the prompt initiation of C5 inhibition and to prevent the exclusion of complement-mediated aHUS patients due to disease symptomatology:
  - The exclusion criterion for fever has been shortened from 7 days to 3 days to allow for patients to enroll if there is no presence of fever within 3 days before the first crovalimab administration. Three days are sufficient to perform evaluations (e.g. cultures, imaging, laboratory assessments) to clarify if the source of the fever is due to an active systemic infection. Patients found to have an active systemic infection within 14 days of crovalimab administration will still be excluded.
  - Additionally, as fevers can be a result of the underlying aHUS pathology a clarification had been added to allow enrollment if fevers are solely due to the underlying aHUS symptomatology and if there is no evidence or suspicion of a systemic infection (Section 4.1.2).
- The exclusion criteria surrounding the demonstration of cobalamin C deficiency have been updated to prevent the exclusion of patients with non-clinically significant hyperhomocysteinemia and methylmalonic aciduria at TMA presentation. Significantly raised hyperhomocysteinemia and methylmalonic aciduria may be indicative of a Cobalamin C defect, however, non-clinically significant (for the Cobalamin C diagnosis) raised levels of homocysteine and methylmalonic acid (MMA) levels in absence of evidence of MMACHC gene mutation may alternatively

be due to the acute renal impairment related to aHUS. Therefore, Cobalamin C defect exclusion criteria has been amended to rely on an increase of ≥3 x ULN in both homocysteine AND MMA levels. In case homocysteine or MMA levels are below 3 x ULN, the Cobalamin C defect would be excluded (Section 4.1.2, Appendix 1).

- Rituximab has been added as a prohibited therapy due to the potential inhibitory effect of crovalimab on complement-dependent cytotoxicity of rituximab, crovalimab may reduce the expected pharmacodynamic effects of rituximab (Section 4.4.3).

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

- The 'Clinical Experience with Crovalimab' section has been updated to include key primary analysis results from the Phase 3 COMMODORE studies and the latest data from the COMPOSER study (Section 1.2.2 and 1.3).
- Observed value and change over time in PD biomarkers and parameters reflecting hemolysis has been moved to a new dedicated section for Pharmacodynamic/Biomarker objectives (Section 2.5) and Exploratory Biomarker Objectives (Section 2.6) respectively. In addition, presence of anti-factor H autoantibodies has been added as an exploratory biomarker objective (Section 2.6).
- Duration of study participation has been updated to align with the total duration of the study (Section 3.2.1 and Section 3.3).
- The rationale for single-arm study design was updated to clarify that approximately 400 patients will be treated with crovalimab in the four PNH studies (Section 3.4.3).
- The subsection on Prohibited Therapy (Section 4.4.3) has been updated to clarify that the use of other immunosuppressive therapies after enrollment (such as steroids, mTORi [eg, sirolimus, everolimus], CNI [e.g., cyclosporine or tacrolimus]) during the study are allowable as part of a post-transplant antirejection regime or if the patient has confirmed anti-complement factor antibodies requiring immunosuppressive therapy or steroids are being used for a condition other than aHUS (e.g., asthma).
- To align with the exclusion criteria of known DGKE nephropathy, testing for the detection of homozygous or compound heterozygous loss of function mutations in DGKE is no longer required at screening. Language was added to clarify that known DGKE mutations should be recorded in the patient medical records (Section 4.6, Appendix 1, and Appendix 10).
- Language has been added to allow results from the Anti-factor H autoantibodies testing to be shared with investigators in addition to results from the genetic analysis. In addition, it has been clarified that the results of these tests may also be shared with investigators for patients who discontinue study treatment but remain in study follow up (Section 4.6.1.2).
- The requirement for blood smears for schistocytes central analysis has been removed as the sample collection, processing and testing will be discontinued due to technical difficulties related to the analysis method and to a low percentage of

patients with evaluable results (Section 4.6.1.2, Section 4.6.4.3, Appendices 1, 3, 6).

  - The exploratory efficacy objective of blood smears for schistocytes was removed from Section 2.1.3.

- Language has been added to clarify that patients who discontinue crovalimab and do not switch to another C5 inhibitor are eligible for potential restart after achieving and maintaining cTMAr if they are naïve and after maintaining TMAc if they are switch (Section 4.7.2).
- A new subsection has been added to provide clarity on the definitions of the analysis populations of this study (Section 6.2).
- Language was added to clarify that patients with normalized creatinine at baseline will be excluded from the analysis (Section 6.5.2).
- Additional details on the statistical analysis were added for consistency with the BO42354 protocol (Section 6.5.2).
- The exploratory PK objective to evaluate the relationship between DTDC size and kinetics of crovalimab has been removed from Section 6.6 to align with Section 2.3. The DTDC size assay being semi quantitative does not allow such correlation (Section 6.6).
- The definition of the immunogenicity-evaluable population was updated to require “at least one post-baseline ADA assessment” (instead of “at least one ADA assessment”) to clarify that ADA assessment is possible only after crovalimab administration and to align with the definition that was implemented for the primary analyses of the Commodore 1 and 2 studies in PNH and to ensure consistency across the crovalimab program (Section 6.8).
- Text has been added to remind that patients should be assessed for drug toxicity prior to each dose and that dosing will occur only if the clinical assessment and any available local laboratory test values are acceptable in order to align with Section 4.3.1.2 (Appendix 1).
- Language has been added to clarify that for genetic testing, collection of an additional sample has been allowed if the initial sample is unsuitable for analysis (Appendix 1).
- An additional column header was added to the table to distinguish the Safety Follow-up Monitoring after C5 Switch Period required visits from the visits that are required when switching from crovalimab to a different C5 inhibitor. Since assessments need to be performed 24 and 46 weeks from the last dose of crovalimab and not from the point of switching to the first dose of a different C5 inhibitor, this was now clarified (Appendix 2).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, SINGLE-ARM STUDY EVALUATING THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CROVALIMAB IN ADULT AND ADOLESCENT PATIENTS WITH ATYPICAL HEMOLYTIC UREMIC SYNDROME (aHUS)**
PROTOCOL NUMBER:	BO42353
VERSION NUMBER:	7
REGULATORY AGENCY IDENTIFIER NUMBERS	EudraCT Number: 2020-002475-35 IND Number: 151,511 EU CT Number: 2023-505089-27-00 NCT Number: NCT04861259
TEST PRODUCT:	Crovalimab (RO7112689)
SPONSORS:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, SINGLE-ARM STUDY EVALUATING THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CROVALIMAB IN ADULT AND ADOLESCENT PATIENTS WITH ATYPICAL HEMOLYTIC UREMIC SYNDROME (aHUS)**
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TEST PRODUCT:	Crovalimab (RO7112689)
PHASE:	Phase III
INDICATION:	Atypical Hemolytic Uremic Syndrome (aHUS)
SPONSORS:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd.

STUDY RATIONALE

This study will evaluate the efficacy, safety, immunogenicity, pharmacokinetics, and pharmacodynamics of crovalimab in adult and adolescent patients with atypical hemolytic uremic syndrome (aHUS). The study includes three cohorts: one for complement inhibitor-treatment-naive patients, one for patients who switch from eculizumab or ravulizumab to crovalimab, and one for patients with a known complement component 5 (C5) single nucleotide polymorphism (SNP) mutation who may have responded poorly to previous treatment with eculizumab or ravulizumab. Specific objectives and corresponding endpoints for the study are outlined below.

OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective	Corresponding Endpoints
• The primary efficacy objective for this study is to evaluate the effect of crovalimab in treatment-naive (Naive) patients (primary analysis *population*).	• Proportion of patients with complete thrombotic microangiopathy (cTMAr) anytime from baseline to Week 25 (after 24 weeks on treatment) cTMAr is defined by meeting all of the following criteria at two separate assessments, obtained at least 4 weeks (*minimum 26* days) apart, and any measurement in between: • Platelet count ≥ lower limit of normal (LLN), and • Lactate dehydrogenase (LDH) ≤ upper limit of normal ULN and • ≥ 25% decrease in serum creatinine from baseline

Secondary Efficacy Objective	Corresponding Endpoints
• The secondary efficacy objective for this study is to evaluate the effect of crovalimab in patients in the Naive (primary analysis cohort) and Switch cohorts.	For Naive and Switch Cohorts: • Dialysis requirement status (yes/no); change from baseline to Week 25 (after 24 weeks on treatment); patients were considered as being on dialysis at baseline if dialysis occurred within 5 days prior to the first crovalimab administration • Observed value and change from baseline *to Week 25 (after 24 weeks on treatment)* in estimated glomerular filtration rate (eGFR) *as per Appendix 9*. • Proportion of patients with change from baseline *to Week 25 (after 24 weeks on treatment)* in chronic kidney disease stage, classified as improved, stable (no change), or worsened based on the National Kidney Foundation Chronic Kidney Disease Stage • Observed value and change from baseline *to Week 25 (after 24 weeks on treatment)* in hematologic parameters (platelet count, LDH, hemoglobin) • In adults (≥ 18 years), change from baseline *to Week 25 (after 24 weeks on treatment)* in fatigue as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire

	For Naive Cohort only: • Proportion of patients with platelet count ≥ LLN at two separate assessments, obtained at least 4 weeks (*a minimum of 26* days) apart, by Week 25 (after 24 weeks on treatment) • Proportion of patients with normalization of LDH (i.e., ≤ ULN) at two separate assessments, obtained at least 4 weeks (*a minimum of 26* days) apart, by Week 25 (after 24 weeks on treatment) • Proportion of patients with ≥ 25% decrease in serum creatinine from baseline, confirmed at two separate assessments obtained at least 4 weeks (*a minimum of 26* days) apart, by Week 25 (after 24 weeks on treatment) • Time to cTMAr • Duration of cTMAr, among patients who achieved cTMAr ○ End of cTMAr is considered to occur when all of the following criteria are met during the same visit, and are confirmed at an assessment that takes place 4 weeks later: ○ Platelet count < LLN, and ○ LDH > ULN, and ○ ≥ 25% increase in serum creatinine from baseline, and > ULN • Proportion of patients with cTMAr *ongoing* at Week 25
Secondary Efficacy Objective (cont'd)	Corresponding Endpoints (cont'd)
• The secondary efficacy objective for this study is to evaluate the effect of crovalimab in patients in the Naive (primary analysis cohort) and Switch cohorts.	For Switch Cohort only: • Proportion of patients with maintained TMA control (mTMAc) from baseline through Week 25 (after 24 weeks on treatment) TMA control (TMAc) is considered not maintained if all the following criteria are met during one of the visits between baseline and Week 25, and are confirmed at an assessment that takes place 4 weeks later *(minimum 26 days):* • Platelet count < LLN, and • LDH > ULN, and • ≥ 25% increase in serum creatinine from baseline, and > ULN
Secondary Safety Objective	Corresponding Endpoints
• The secondary safety objective for this study is to evaluate the overall safety and tolerability of crovalimab.	• Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for adverse events, Version 5(CTCAE v5)

	• Change in targeted vital signs and clinical laboratory test results • Incidence and severity of injection-site reactions, infusion-related reactions, hypersensitivity, malignant hypertension (including malignant renal hypertension), and infections (including meningococcal meningitis) • Incidence of adverse events leading to study drug discontinuation For Switch Cohort only: • Incidence and severity of clinical manifestations of drug-target-drug complexes (DTDCs) in patients who switched to crovalimab treatment from either eculizumab or ravulizumab treatment
Secondary Pharmacokinetic Objective	Corresponding Endpoint
• The secondary pharmacokinetic (PK) objective for this study is to evaluate the pharmacokinetics of crovalimab.	• Serum concentrations of crovalimab over time
Secondary Immunogenicity Objective	Corresponding Endpoints
• The secondary immunogenicity objective for this study is to evaluate the immune response to crovalimab.	• Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study
Pharmacodynamic / Biomarker Objectives	*Corresponding Endpoints*
• *To identify and/or evaluate biomarkers that can potentially provide evidence of crovalimab activity (i.e., PD biomarkers) in patients in the Naive Cohort (Primary Analysis Cohort), Switch Cohort and C5 SNP Cohort*	• *Observed value and change over time in PD biomarkers, including complement activity (CH50) measured by a liposome immunoassay (LIA)* • *Observed value and change over time in free C5 and total C5 concentrations in crovalimab-treated patients*

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

OVERALL DESIGN AND STUDY POPULATION

This single-arm, uncontrolled, multicenter, global Phase III study is designed to evaluate the efficacy, safety, immunogenicity, pharmacokinetics (PK), and pharmacodynamics (PD) of crovalimab in patients with aHUS, aged ≥ 12 years, and weighing ≥ 40 kg.

Patients will be enrolled in three parallel cohorts, based on their previous exposure and response to complement inhibitor therapy. All cohorts will contribute to PK and safety evaluations of crovalimab.

Phase:	Phase III	**Population Type:**	Adult and adolescent patients
Control Method:	None	**Population Diagnosis or Condition:**	Atypical hemolytic uremic syndrome
Interventional Model:	Parallel group	**Population Age:**	$>$12 years old
Test Compound{s}:	Crovalimab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not Applicable	**Study Intervention Assignment Method:**	Single arm
Number of Arms:	1	**Number of Participants to Be Enrolled:**	Approximately 80 patients

STUDY TREATMENT

Crovalimab administration must be initiated within 4 weeks of the onset of the initial TMA episode in the treatment-naive patients. All patients will receive crovalimab according to a weight-based tiered dosing approach schedule. A loading series will include an initial IV crovalimab dose on Week 1 Day 1, followed by four once weekly subcutaneous (SC) crovalimab doses on Week 1 Day 2, then on Weeks 2, 3, and 4. Maintenance dosing will begin at Week 5 and will continue every 4 weeks (Q4W) thereafter, for a total of at least 24 weeks of crovalimab treatment.

For patients in the Switch Cohort or C5 SNP Switching patients who are switching without a treatment break from eculizumab or ravulizumab, Week 1 Day 1 of crovalimab treatment will be scheduled 2 weeks from the patient's last dose of eculizumab or 8 weeks from the patient's last dose of intravenous (IV) ravulizumab. The Week 1 Day 1 dose of crovalimab may be administered with a window of +2 days when switching from eculizumab and +7 days when switching from ravulizumab (as per eculizumab and ravuluzimab labels). Week 1 Day 1 of crovalimab dose should not be administered earlier than the scheduled visit (i.e. before 2 weeks from the patient's last dose of eculizumab or before 8 weeks from the patient's last dose of IV ravulizumab).

Dose modification (only allowed from Week 9) is only required if the patient's body weight changes by $\geq$10% (compared with screening or the visit when the latest dose modification occurred, whichever is later) to exceed or become equal to 100 kg or to fall below 100 kg during the course of therapy.

DURATION OF PARTICIPATION

After completing 24 weeks of treatment with crovalimab (i.e. at the Week 25 visit), patients who derive clinical benefit may continue treatment during the extension period of the study, which may be a maximum of 3 years after the last patient has completed the primary treatment period, and then, as per the Roche Global Policy on Continued Access to Investigational Medicinal Product. The total duration of study participation for each individual is expected to range from 1 day up to approximately *8* years.

COMMITTEES

Independent Committees:	Joint Monitoring Committee
Other Committees:	Not Applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
aHUS	atypical hemolytic uremic syndrome
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AKI	acute kidney injury
ALP	alkaline phosphatase
BTH	breakthrough hemolysis
C5	complement component 5
CCOD	clinical cutoff date
CI	confidence interval
CKD	chronic kidney disease
CTCAE	Common Terminology Criteria for Adverse Events
cTMAr	complete TMA response
DGKE	diacylglycerol kinase ε
DTDC	drug-target-drug complex
DTDCs	drug-target-drug complexes
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
FACIT	Functional Assessment of Chronic Illness Therapy
FcRn	neonatal fragment crystallizable receptor
FDA	U.S. Food and Drug Administration
HBsAg	hepatitis B surface antigen
HCP	healthcare provider
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
ICH	International Council for Harmonization
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
IVIg	intravenous immunoglobulin
IxRS	interactive voice or web-based response system
JMC	Joint Monitoring Committee
KDQoL	Kidney Disease Quality of Life
LIA	liposome immunoassay

Abbreviation	Definition
LLN	lower limit of normal
MAC	membrane attack complex
MAHA	microangiopathic hemolytic anemia
MFS	Multidimensional Fatigue Scale
MN	mobile nursing
MMA	methylmalonic acid
MMACHC	methylmalonic aciduria and homocystinuria type C protein
mTMAc	maintained TMA control
mTORi	mammalian target of rapamycin inhibitor
NCI	National Cancer Institute
OLE	open-label extension
PD	pharmacodynamics
PE/PI	plasma exchange/plasma infusions
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic
PNH	paroxysmal nocturnal hemoglobinuria
POC	point-of-care
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
Q16W	every 16 weeks
Q8W	every 8 weeks
QLQ-C30	Quality of Life Questionnaire-Core 30
QoL	quality of life
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
SAP	Statistical Analysis Plan
SC	subcutaneous
sC5b-9	soluble complement 5b-9
SNPs	single nucleotide polymorphisms
STEC-HUS	Shiga toxin–producing Escherichia coli hemolytic uremic syndrome
TA	transfusion avoidance
TIC	transient immune complex
TMA	thrombotic microangiopathy
TTP	thrombotic thrombocytopenic purpura
TMAc	TMA control
TSQM	Treatment Satisfaction Questionnaire for Medication
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
ULN	upper limit of normal

Abbreviation	Definition
VAS	Visual Analog Scale

1. BACKGROUND

1.1 BACKGROUND ON ATYPICAL HEMOLYTIC UREMIC SYNDROME

Atypical hemolytic uremic syndrome (aHUS) is an ultra-rare, multisystem disease characterized by severe and life-threatening acute kidney injury (AKI), thrombocytopenia, and microangiopathic hemolytic anemia (MAHA; Noris and Remuzzi 2009; Fremeaux-Bacchi et al. 2013; Licht et al. 2015a). Atypical hemolytic uremic syndrome is due to dysregulation of the alternative complement pathway, often by the loss of function of regulatory proteins, which increases assembly of the membrane attack complex (MAC), C5b-9, resulting in endothelial injury, platelet activation, and thrombosis (Nester and Thomas 2012). The prognosis of aHUS is poor, with a global mortality rate of 25% and frequent progression to chronic kidney disease (Afshar-Kharghan 2016).

At least 50% of patients with aHUS have an inherited and/or acquired complement abnormality leading to dysregulated activity (Goodship et al. 2017). In addition to the classic clinical presentation of AKI, thrombocytopenia, and MAHA (Nester et al. 2015), due to microangiopathic changes throughout the body, extra-renal manifestations are common, with neurologic involvement (e.g., seizures, altered consciousness, cerebral artery thrombosis, stenosis), gastrointestinal involvement (e.g., diarrhea, pancreatitis, hepatitis), cardiac involvement (e.g., hypertension, myocardial infarction), skin involvement (e.g., digital/skin gangrene), ocular involvement (including blindness), and pulmonary involvement (Brocklebank et al. 2018).

Data on incidence and prevalence are scarce, but it is estimated to have an incidence of 2 cases per million per year in the United States and a prevalence of 3.3 cases per million for patients $<$18 years old in Europe (Constantinescu et al. 2004; Zimmerhackl et al. 2006). Unlike in children, where males and females are equally affected, adult females are more often affected likely secondary to pregnancy as a triggering event. Historically, aHUS was managed with plasma exchange/plasma infusions (PE/PI) with children having a higher mortality than adults (Fremeaux-Bacchi et al. 2013).

Historically, hemolytic uremic syndrome (HUS) was divided into diarrhea-positive (typical) and diarrhea-negative (atypical) HUS. In this protocol, aHUS denotes complement mediated thrombotic microangiopathy (TMA), and excludes other genetic (e.g., diacylglycerol kinase ε [DGKE] mutation, cobalamin C defect) or acquired (including infectious-, malignancy-, or drug-related) conditions associated with a clinical picture of HUS.

The elucidation of the pathogenesis of aHUS led to the successful introduction of complement component 5 (C5) inhibition into clinical practice. Inhibiting C5 prevents its

cleavage and formation of C5a and C5b-9, thus, blocking the C5a pro-inflammatory and the C5b-9-mediated endothelial injury with its ensuing consequences (Zuber et al. 2012).

Eculizumab, an intravenously administered humanized anti-C5 antibody, has become standard of care in the United States and the European Union, since its approval for the paroxysmal nocturnal hemoglobinuria (PNH) indication in 2007 and for the aHUS indication in 2011. The efficacy and safety of eculizumab in aHUS was demonstrated in two prospective trials (Legendre et al. 2013). Eculizumab inhibited complement mediated TMA in patients with aHUS and was associated with significant time-dependent improvement in renal function and normalization of platelet count and lactate dehydrogenase (LDH) activity (Legendre et al. 2013). A complete TMA response (cTMAr) was achieved in 65% (11 of 17) of patients resistant to PE/PI and 25% (5 of 20) of patients sensitive to PE/PI. A 2-year follow-up analysis showed that the clinical benefits, including improvements in hematologic parameters and renal function were maintained with ongoing therapy with eculizumab (Licht et al. 2015b).

Ravulizumab (Ultomiris®) was approved by the U.S. Food and Drug Administration (FDA) in 2019 (Ultomiris USPI) and by the European Medicines Agency (EMA) in 2020 (Ultomiris SmPC) for the treatment of aHUS. The approval in aHUS was granted based on two open-label, single-arm studies in patients with aHUS naive to C5 inhibitor treatment: ALXN 1210-aHUS-311 in adult patients and ALXN1210-aHUS-312 in pediatric patients. Ravulizumab is administered as an intravenous (IV) infusion every 8 weeks (Q8W) or every 4 weeks (Q4W) depending on body weight. In the studies ALXN1210-aHUS-311 and ALXN1210-aHUS-312, the primary endpoint was cTMAr during the 26-week evaluation period, as defined by normalization of platelet count, normalization of LDH, and a $\geq$25% improvement of serum creatinine from baseline, if met at two separate assessments obtained at least 4 weeks apart and at any measurement in between (Rondeau et al. 2020).

A cTMAr was observed in 54% (30 of 56) of adult patients in ALXN1210-aHUS-311 and 78% (14 of 18) of pediatric patients in ALXN1210-aHUS-312. Most frequent adverse event reactions were urinary tract infections, diarrhea, nausea, vomiting, headache, hypertension, and pyrexia. Serious adverse events were reported in 57% of patients, with the most frequent being hypertension and pneumonia. A total of 4 patients experienced deaths considered not related to ravulizumab: 2 patients experienced septic shock, 1 patient had intracerebral hemorrhage, and 1 patient died due to pretreatment cerebral arterial thrombosis after having been diagnosed with Shiga toxin-producing Escherichia coli hemolytic uremic syndrome (STEC-HUS) (Ultomiris USPI).

Although clinical outcomes such as renal survival and quality of life (QoL) for patients with aHUS have improved following the introduction of C5 inhibition as standard of care, there remains a significant unmet need. In regions where eculizumab or ravulizumab

are unavailable, PE/PI is still used for the treatment of aHUS (Kaplan et al. 2014; Loirat et al. 2016).

Clinic or hospital visits every 2 weeks (Q2W) for eculizumab (or Q8W for ravulizumab) infusions require a significant time commitment for patients with aHUS over a lifetime, considering travel times in addition to the duration of administration: 35 minutes for adult patients and 1–4 hours for pediatric patients for eculizumab (NICE 2015) and 1.9–3.3 hours for ravulizumab (Ultomiris USPI). This may overall negatively affect QoL, including but not limited to work schedules for adults and educational attendance and performance in school-aged children, as well as the lives of their caregivers.

In addition to the lifelong burden of treatment, the IV route of administration also bears infectious and vascular risks. The protection of peripheral and central veins is of utmost importance in patients with aHUS (Loirat and Frémeaux-Bacchi 2011), who may need long-term vascular access preservation due to their CKD for future dialysis access and renal transplantation. Additionally, given that 40% of aHUS patients are children, a subcutaneous (SC) route of administration would offer significant benefits by improving compliance and increasing independence. Repeated IV access for laboratory evaluations, medication administration, and hemodialysis is particularly challenging and traumatic in children (Thies 1999).

Additionally, 3.5% of individuals of Asian descent carry polymorphisms in C5 affecting Arg885, which corresponds to the eculizumab- and ravulizumab-binding site. These individuals are unresponsive to available complement inhibitors, experiencing a very high, unmet medical need (Nishimura et al. 2014).

1.2 BACKGROUND ON CROVALIMAB

1.2.1 Molecule and Nonclinical Data

Crovalimab is a novel, humanized anti-C5 monoclonal antibody. Crovalimab binds to complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex, C5b-9 (MAC). It inhibits terminal complement-mediated intravascular hemolysis in patients with PNH. Crovalimab is based on Sequential Monoclonal Antibody Recycling Technology (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. These characteristics result in a prolonged half-life and prolonged complement inhibition.

[redacted]. Based on clinical data, nonclinical pharmacology and pharmacodynamic (PD) data, crovalimab is expected to lead to consistent complement protein C5 inhibition throughout the dosing interval resulting in

suppression of complement-mediated endothelial injury and MAHA at the targeted dosing regimens.

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

Refer to the crovalimab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.2 Clinical Experience with Crovalimab

No studies of crovalimab in patients with aHUS have previously been conducted.

Crovalimab is investigated in 9 ongoing crovalimab clinical studies enrolling patients in SCD (BO42451, BO42452), PNH (BO42162, BO42161, YO42311, BP39144), atypical hemolytic uremic syndrome (aHUS) (BO42353, BO42354), and Lupus Nephritis (LN) (CA43761).

Primary analysis results from the pivotal Phase III Study BO42162 (COMMODORE 2) in patients with PNH not previously treated with complement inhibitors are available. Supportive clinical data are available for both PNH patients not previously treated with complement inhibitors and those currently treated with other C5 inhibitors from Phase III Study YO42311 (COMMODORE 3), Phase III Study BO42161 (COMMODORE 1), and Phase I/II Study BP39144 (COMPOSER).

Across the three Phase III PNH trials, crovalimab was demonstrated to be an efficacious treatment that is safe and well tolerated. This is further supported by long-term efficacy and safety data from the open-label extension period of the Phase I/II Study BP39144, where crovalimab was shown to be tolerable and patients with PNH treated with crovalimab maintained disease control. No clinical data are currently available for the ongoing clinical studies evaluating crovalimab in patients with aHUS (BO42353 and BO42354), SCD (BO42451 and BO42452) or LN (CA43761). Patient-level safety monitoring of the ongoing crovalimab clinical studies in aHUS, SCD, and LN has not identified any new safety signals associated with crovalimab treatment.

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

1.2.2.1 Safety Data from Studies BO42162, YO42311, BO42161, and BP39144

The safety results from studies BO42162, YO42311, BO42161, and BP39144 up to the CCODs (31 May 2023, 10 August 2022, 31 May 2023, and 28 August 2023, respectively) indicate that crovalimab is well tolerated in patients with PNH who were either treatment-naive or switching to crovalimab from eculizumab (or ravulizumab), with key safety parameters being similar between crovalimab-naive and crovalimab switch populations.

The formation of DTDC (transient immune complexes [TIC]) was identified early in the clinical development program as a potential safety concern. *As Crovalimab and eculizumab (or ravulizumab) bind to different epitopes on C5, when both medications are present in the circulation, complexes comprised of the two antibodies, bridged by C5 are formed. Data from the BO42162, BO42161, and BP39144 studies have identified DTDC are transient, but may lead to the development of type III hypersensitivity reactions (transient immune complex reaction [TICR]) (Section 5.1.1.3).*

For full details surrounding the development of DTDC and T3HS and for the most recent clinical safety data, please refer to the crovalimab Investigator's Brochure.

1.2.2.2 Pharmacokinetic and Pharmacodynamic Data from Studies BO42162, YO42311, BO42161, and BP39144

The PK and PD data from the four PNH studies support the administration of crovalimab at the recommended dose and dosing regimen for the treatment for patients with PNH, for both treatment-naïve and switch patients. No dose adjustment is necessary to account for patients' age, ethnicity, ADA status, hepatic/renal impairment, or previous C5 inhibitor therapies.

The recommended dosing regimen for crovalimab in adults uses a BW two-tiered dosing approach. The recommended dose and dosing regimen were investigated in the pivotal and supporting studies. Data demonstrated that throughout the assessment period, the observed trough concentration (C_{trough}) remained above 100 □g/mL in the majority of patients across Studies BO42161, BO42162, and YO42311. In addition, markers of terminal complement activity demonstrated that complete terminal complement activity inhibition was sustained throughout the assessment period for most patients, confirming the validity of the threshold concentration.

1.2.2.3 Immunogenicity Results from Studies BO42162, YO42311, BO42161, and BP39144

A pooled immunogenicity analysis from Studies BO42162, YO42311, BO42161 (with CCODs 31 May 2023, 10 August 2022, 31 May 2023, respectively) did not result in a

clinical meaningful impact of immunogenicity on PK, PD, efficacy and safety; however, few ADA-positive patients had a transient or persistent loss of exposure associated with a full/partial loss of crovalimab exposure and pharmacological activity , with variable impact on clinical response.

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

1.2.2.4 Efficacy Results from Studies BO42162, YO42311, BO42161, and BP39144

Primary efficacy results of Study BO42162 up to the primary analysis CCOD (16 November 2022) demonstrated non-inferiority of crovalimab versus eculizumab for the co-primary endpoints of hemolysis control and transfusion avoidance (TA). The same co-primary endpoints were also met for crovalimab in the primary efficacy analysis of single-arm study YO42311 (CCOD 10 August 2022).

The clinical benefit of crovalimab was confirmed across the secondary endpoints of BTH, hemoglobin stabilization and FACIT-Fatigue in studies BO42162 and YO42311.

Results of the exploratory efficacy endpoints of the BO42161 study up to primary analysis CCOD (16 November 2022) showed that patients switching to crovalimab from eculizumab maintained disease control and had similar efficacy to that of continued eculizumab treatment in terms of hemolysis control, TA, BTH, hemoglobin stabilization and FACIT-Fatigue.

Efficacy results from the BP39144 study up to the primary analysis CCOD (29 January 2020) showed that treatment-naive patients had improved disease control, and switched patients maintained disease control, after treatment with crovalimab as indicated by LDH, TA rates, and hemoglobin stabilization rates. During the OLE period (updated CCOD 28 August 2023), patients with PNH treated with crovalimab maintained disease control (median treatment duration of 4.7 years) as indicated by efficacy endpoints related to hemolysis control, TA, hemoglobin stabilization, and BTH.

In addition, a total of 10 patients with PNH with a single missense C5 heterozygous mutation and whose hemolysis was not controlled by previous eculizumab treatment were enrolled in Study BP39144 and non-randomized Arm C of Study BO42161. Most of these patients achieved and maintained complement inhibition throughout the primary treatment period. Patients with C5 polymorphisms generally had rapid and sustained decrease in LDH, which was maintained up to the latest CCODs for both studies (28 August 2023 for Study BP39144 and 31 May 2023 for Study BO42161).

Refer to the crovalimab Investigator's Brochure for additional details on efficacy results from clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale and Benefit

The main objective of effective aHUS treatment is to provide immediate, complete, and sustained inhibition of terminal complement activity to block renal damage and prevent thrombotic events. The current standard of care for adult and pediatric patients with aHUS is chronic, continual C5-inhibitor therapy (Afshar-Kharghan 2016; Loirat et al. 2016).

Patients treated with eculizumab are required to receive maintenance IV infusions Q2W, and patients treated with ravulizumab are required to receive maintenance IV infusions Q8W. Crovalimab binds with high affinity to complement protein C5, preventing generation of the terminal complement complex C5b-9 (MAC) and preserving renal function in patients with aHUS. Its high SC bioavailability, prolonged half-life, and extended complement inhibition through reduced target (C5) accumulation, [redacted], allow for SC, low volume dosing Q4W, with the potential to substantially reduce treatment burden, offering a meaningful potential benefit to individuals with aHUS.

Additionally, crovalimab may be an effective complement inhibitor for patients with C5 R885 SNPs (and similar C5 variants) who are failed by either eculizumab or ravulizumab and have a very high unmet medical need (details in Section 1.2.1).

1.3.2 Risk

Treatment with crovalimab was safe and well tolerated *(Section 1.2.2.1). No study of crovalimab in patients with aHUS has been conducted.* As a class effect of terminal complement inhibitors, there is a risk of meningococcal infection. Accordingly, standard mitigation strategies used for other C5 inhibitor therapies (i.e., vaccination against encapsulated organisms, high clinical suspicion for infection with monitoring) have been applied to patients treated with crovalimab, with no observed cases of meningococcal infection as of the CCOD*s for studies BO42162, YO42311, BO42161, and BP39144 (16 November 2022, 10 August 2022, 16 November 2022, and 28 Aug 2021 respectively).*

Optimized dosing strategy and risk minimization strategy including patient selection, monitoring, and management of clinical manifestation of DTDC (Section 1.2.2.1) were implemented after the occurrence of 2 DTDC-related adverse events in Study BP39144 (Part 3).

In this study, the risk of DTDC is relevant only to patients who might switch to crovalimab from eculizumab or ravulizumab treatment at study enrollment, and to patients who discontinue crovalimab and switch to eculizumab or ravulizumab. The dosing and risk minimization strategies identified based on Study BP39144 *(and used in studies*

BO42162, YO42311, and BO42161) will be implemented for these patients (see Section 5.1.1).

1.3.3 Benefit and Risk

In the context of lifelong therapy with complement inhibition, the benefit of reduced treatment burden with optimal disease control could be substantial in many patients with aHUS who require lifelong complement inhibition.

In addition to the lifelong burden of treatment, the IV route of administration also bears infectious and vascular risks. As detailed in Section 1.1, an SC route of administration would offer significant benefits by improving compliance and increasing independence. Repeated IV access for laboratory evaluations, medication administration, and hemodialysis is particularly challenging and traumatic in this population.

Crovalimab has shown promising clinical efficacy with effective reduction in intravascular hemolysis and effective terminal complement inhibition across patients with PNH in both the Naive and the Switch Cohorts in *studies BO42162, YO42311, BO42161, and BP39144*. Moreover, crovalimab has shown promising *clinical* efficacy in patients with C5 R885 polymorphisms (and potential for other C5 variants) who do not benefit from treatment with eculizumab or ravulizumab.

The clinical symptomatology of DTDC manifestation, which in this study is only relevant to patients who might switch to crovalimab from eculizumab or ravulizumab treatment at study enrollment, and to patients who discontinue crovalimab and switch to a standard-of-care inhibitor, has been transient, predictable, and medically manageable such that the overall benefit–risk may be considered positive in patients with aHUS.

1.3.3.1 Benefit and Risk-Coronavirus Disease-2019

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

2. OBJECTIVES AND ENDPOINTS

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the effect of crovalimab in treatment-naive (Naive) patients (primary analysis *population*) based on the following endpoint:

- Proportion of patients with complete response (cTMAr) anytime from baseline to Week 25 (after 24 weeks on treatment)

cTMAr is defined by meeting all of the following criteria at two separate assessments, obtained at least 4 weeks (*a minimum of 26* days) apart, and any measurement in between:

- Platelet count ≥ lower limit of normal (LLN), and
- *Lactate dehydrogenase (LDH) ≤ upper limit of normal (ULN)*, and
- ≥ 25% decrease in serum creatinine from baseline

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the effect of crovalimab in patients in the Naive (primary analysis cohort) and Switch Cohorts based on the following endpoints:

For Naive and Switch Cohorts:

- Dialysis requirement status (yes/no); change from baseline to Week 25 (after 24 weeks on treatment); patients are considered as being on dialysis at baseline if dialysis occurred within 5 days prior to the first crovalimab administration
- Observed value and change from baseline to Week 25 (after 24 weeks on treatment); in estimated glomerular filtration rate (eGFR), as per Appendix 9
- Proportion of patients with change from baseline to Week 25 (after 24 weeks on treatment); in CKD stage, classified as improved, stable (no change), or worsened based on the National Kidney Foundation Chronic Kidney Disease Stage
- Observed value and change from baseline to Week 25 (after 24 weeks on treatment); in hematologic parameters (platelet count, LDH, hemoglobin)
- In adults (≥ 18 years), change from baseline to Week 25 (after 24 weeks on treatment); in fatigue as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire

For Naive Cohort only:

- Proportion of patients with platelet count ≥ LLN at two separate assessments, obtained at least 4 weeks (*a minimum of 26* days) apart, by Week 25 (after 24 weeks on treatment)
- Proportion of patients with normalization of LDH (i.e., ≤ ULN) at two separate assessments, obtained at least 4 weeks (*a minimum of 26* days) apart, by Week 25 (after 24 weeks on treatment)
- Proportion of patients with ≥ 25% decrease in serum creatinine from baseline, confirmed at two separate assessments obtained at least 4 weeks (*a minimum of 26* days) apart, by Week 25 (after 24 weeks on treatment)
- Time to cTMAr
- Duration of cTMAr, among patients who achieved cTMAr

  - End of cTMAr is considered to occur when all of the following criteria are met during the same visit, and are confirmed at an assessment that takes place *at least* 4 weeks *(a minimum of 26 days)* later:
    - Platelet count < LLN, and
    - LDH > ULN, and
    - ≥ 25% increase in serum creatinine from baseline, and > ULN
- Proportion of patients with cTMAr *ongoing* at Week 25

For Switch Cohort only:

- Proportion of patients with maintained TMA control (mTMAc) from baseline through Week 25 (after 24 weeks on treatment)

TMA control (TMAc) is considered not maintained if all of the following criteria are met during one of the visits between baseline and Week 25, and are confirmed at an assessment that takes place *at least* 4 weeks *(a minimum of 26 days)* later:

- Platelet count < LLN, and
- LDH > ULN, and
- ≥ 25% increase in serum creatinine from baseline

2.1.3 Exploratory Efficacy Objective

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

For ALL (Naive, Switch, and C5 SNP) Cohorts:

- Change in serum creatinine from baseline *to Week 25 (after 24 weeks on treatment)*
- *Observed value and change from baseline to Week 25 (after 24 weeks on treatment) in eGFR, using different eGFR equations*
- In adults (≥ 18 years), change from baseline *to Week 25 (after 24 weeks on treatment)* in kidney disease symptoms as measured by the Kidney Disease Quality of Life survey (KDQoL), and in Physical Functioning, Role Functioning, and Global Health Status/Quality of Life as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)
- In adolescents (12–17 years), change from baseline *to Week 25 (after 24 weeks on treatment)* in fatigue as measured by the Pediatric Quality of Life Inventory (PedsQL™) Multidimensional Fatigue Scale (MFS), and Physical Functioning as measured by the PedsQL-Core
- In adults (≥ 18 years), mean treatment satisfaction with crovalimab, as measured by the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) at *Week 13 and* Week 25

- Change from baseline to Week 25 (after 24 weeks on treatment) in the number of missed days of school or work
- Describe the clinical course of patients who discontinue crovalimab after achieving cTMAr and remain in study follow-up (as per Section 4.7.2).

For Naive Cohort only:

- Proportion of patients with increase in hemoglobin ≥20 g/L from baseline to Week 25 (after 24 weeks on treatment), in the absence of a transfusion

For Switch Cohort only:

- Proportion of patients with preference for crovalimab at Week 17, after switch from eculizumab or ravulizumab, as assessed by a Patient Preference Questionnaire developed by the Sponsor

For C5 SNP Cohort only:

- Describe the clinical course of C5 SNP patients on crovalimab treatment

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the overall safety and tolerability of crovalimab, based on the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5 (CTCAE v5)
- Change in targeted vital signs and clinical laboratory test results
- Incidence and severity of injection site reactions, infusion related reactions, hypersensitivity, malignant hypertension (including malignant renal hypertension), and infections (including meningococcal meningitis)
- Incidence of adverse events leading to study drug discontinuation

For Switch Cohort only:

- Incidence and severity of clinical manifestations of DTDCs in patients who switched to crovalimab treatment from either eculizumab or ravulizumab treatment

2.3 PHARMACOKINETIC OBJECTIVES

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

- Serum concentrations of crovalimab over time

The exploratory PK objective for this study is as follows:

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

2.4 IMMUNOGENICITY OBJECTIVES

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

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

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

- *For ADA-positive patients, the percentage of patients with loss of PK and PD.*

2.5 *PHARMACODYNAMIC/BIOMARKER OBJECTIVES*

- *To identify and/or evaluate biomarkers that can potentially provide evidence of crovalimab activity using observed value and change over time in PD biomarkers including total complement activity (CH50) measured by a LIA, free C5, total C5.*

2.6 EXPLORATORY BIOMARKER OBJECTIVES

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that can potentially provide evidence of crovalimab activity (i.e., PD or efficacy biomarkers) or increase the knowledge and understanding of disease biology (e.g., prognostic biomarker) and drug safety (safety biomarker) based on the following endpoints:

- Observed value and change over time in exploratory serum/plasma biomarkers, including markers from the complement system, markers of endothelial cell activation/damage, and markers from the coagulation system
- Observed value and change over time in urinary biomarkers (see Appendix 7) reflecting renal injury
- Presence of genetic aberrations in genes known to be related to aHUS disease (see Appendix 8)
- *Presence of anti-factor H autoantibodies*
- Identification of inherited or acquired genetic aberrations in genes of the complement/coagulation system that may be associated with the disease (see Appendix 8)
- *Observed value and change over time in soluble complement 5b-9 (sC5b-9), and parameters reflecting hemolysis (reticulocyte count, free hemoglobin, haptoglobin)*

2.7 HEALTH STATUS UTILITY OBJECTIVE

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

- Change from baseline to Week 25 *(after 24 weeks on treatment)* in EQ-5D-5L index-based and Visual Analog Scale (VAS) scores

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Joint Monitoring Committee

A Joint Monitoring Committee (JMC) will be convened to evaluate safety, PK, PD, and immunogenicity data during the study, and provide recommendations on study conduct to ensure enhanced patient safety monitoring. Members of the JMC will be composed of Sponsor representatives (at minimum including a clinical scientist, safety scientist, biostatistician, and clinical pharmacologist), and at least two external experts, and will follow the JMC agreement document, outlining their roles and responsibilities.

The JMC will periodically review cumulative patient safety data, including but not limited to: adverse events, serious adverse events, relevant laboratory data, and other specified safety parameters.

Additional data review by the JMC may be requested by the external JMC members or by the Sponsor. Further details regarding the rules and guidelines of data review will be outlined in the JMC Agreement.

3.2 END OF STUDY AND LENGTH OF STUDY

3.2.1 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 (see Section 3.2.2), whichever occurs last. The end of the study is expected to occur a maximum of 5 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 recruitment of the first patient to the end of the study, is expected to be approximately 8 years.

At study completion, strong consideration should be given to patient enrollment onto existing aHUS registries for long-term follow-up.

3.2.2 Overview of Study Design

This single-arm, uncontrolled, multicenter, global Phase III study is designed to evaluate the efficacy, safety, immunogenicity, pharmacokinetics, and pharmacodynamics of crovalimab in patients with aHUS, aged $\geq$12 years, and weighing $\geq$40 kg. Approximately $7$0 sites globally will participate to enroll approximately 80 patients. Patients will be enrolled in three parallel cohorts, based on their previous exposure and

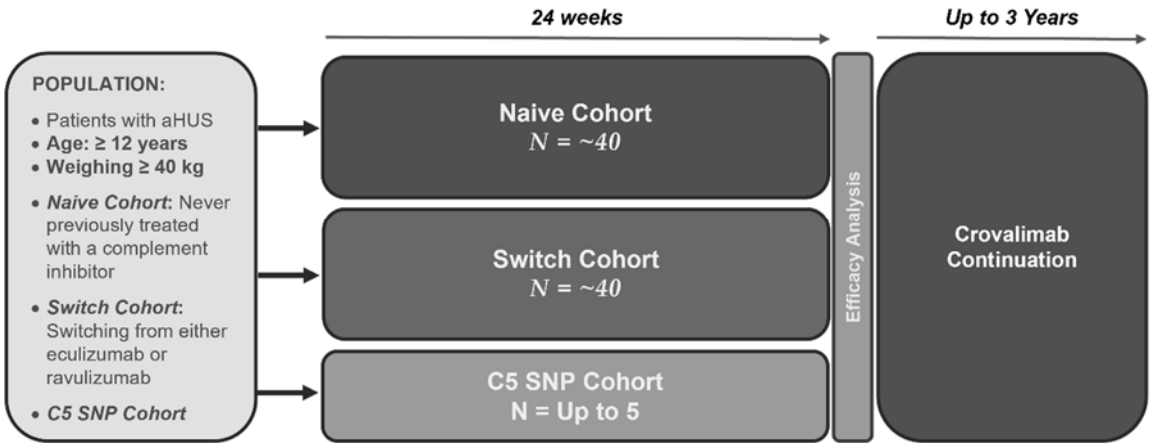
response to complement inhibitor therapy. All cohorts will contribute to PK and safety evaluations of crovalimab.

Efficacy endpoints will be analyzed separately for each cohort. Each cohort's role in the evaluation of efficacy is outlined below:

- Naive Cohort will enroll approximately 40 patients *in the primary analysis population (as defined in Section 6.1)* who have not been previously treated with a complement inhibitor therapy. The primary efficacy analysis will be based on this cohort (see details in Section 7.5). Treatment-naive patients will also contribute to evaluating the secondary and exploratory efficacy objectives.
- Switch Cohort will enroll approximately 40 patients who switch to crovalimab from eculizumab or ravulizumab, which they have been receiving for at least 90 days (and, if switching from IV ravulizumab, they must have received at least two maintenance doses) as of Week 1 Day 1 of crovalimab treatment, and whose TMA was adequately controlled on the labeled dose as of Day 1 of study treatment. This cohort will contribute to evaluating the secondary and exploratory efficacy objectives.
- C5 SNP Cohort will enroll up to 5 patients with known C5 polymorphisms, whose TMA responded poorly to treatment with either eculizumab or ravulizumab, per investigator's assessment. The efficacy in this cohort will be evaluated in an exploratory and descriptive fashion.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1. Approximately 40 patients in the Naive Cohort and approximately 40 patients in the Switch Cohort will be enrolled in this study at approximately 70 sites globally (in approximately 20 countries). Recruitment in the Naive Cohort may be kept open to allow supplemental enrollment to replace patients whose aHUS diagnosis was ruled out post enrollment, in order to have approximately 40 patients *(primary analysis population)* for the primary efficacy analysis. No sample size is pre-specified for the C5 SNP Cohort, and up to 5 patients are expected to be enrolled throughout the study.

Figure 1 Study Schema



aHUS = atypical hemolytic uremic syndrome; C5 = complement component 5; SNP = single nucleotide polymorphism. NOTE: There is a 46-week safety follow-up period following the last dose of study drug.

The study aims to evaluate the efficacy of crovalimab based on the primary endpoint of cTMAr for the Naive Cohort. The primary analysis will be performed when the first *approximately* 40 evaluable patients enrolled in the *primary analysis population of the* Naive Cohort have reached the Week 25 visit (after 24 weeks on treatment) or discontinued crovalimab treatment *(Section 6)*.

Crovalimab administration must be initiated within 4 weeks of the onset of the initial TMA episode in the treatment-naive patients. All patients will receive crovalimab according to a weight-based tiered dosing approach schedule (see Table 1).

A loading series will include an initial IV crovalimab dose on Week 1 Day 1, followed by four once weekly SC crovalimab doses on Week 1 Day 2, then on Weeks 2, 3, and 4. Maintenance dosing will begin at Week 5 and will continue Q4W thereafter, for a total of at least 24 weeks of crovalimab treatment.

For patients in the Switch Cohort or C5 SNP Switching patients who are switching without a treatment break from eculizumab or ravulizumab, Week 1 Day 1 of crovalimab treatment will be scheduled 2 weeks from the patient's last dose of eculizumab or 8 weeks from the patient's last dose of IV ravulizumab. The Week 1 Day 1 crovalimab dose may be administered with a window of +2 days when switching from eculizumab and +7 days when switching from ravulizumab (as per eculizumab and ravuluzimab labels). Week 1 Day 1 of crovalimab dose should not be administered earlier than the scheduled visit (i.e. before 2 weeks from the patient's last dose of eculizumab or before 8 weeks from the patient's last dose of IV ravulizumab).

Efficacy assessments will include platelet count, LDH levels, hemoglobin, assessments of renal function (including serum creatinine, cystatin C, BUN, and proteinuria/albuminuria/hemoglobinuria), dialysis status, as well as health-related quality of life (HRQoL) and health status utility outcome measures (see Appendix 1).

Safety assessments will include the incidence, nature, and severity of adverse events (including those of special interest), vital signs (with emphasis on blood pressure monitoring) and laboratory abnormalities graded per the NCI CTCAE v5, specifically blood sample analysis for hematologic and biochemical abnormalities and urinalysis.

To collect long-term safety and efficacy data, after completing 24 weeks of treatment with crovalimab (i.e., at the Week 25 visit), patients who derive clinical benefit may continue to receive crovalimab during the extension period of the study (which may last for a maximum of 3 years after the last patient has completed the primary treatment period [i.e., Week 25 visit]), and then, as per the Roche Global Policy on Continued Access to Investigational Medicinal Product (see Section 4.3.4).

Patients who are enrolled but whose aHUS diagnosis was subsequently ruled out will be excluded from the primary $analysis$ population, but they will be part of the safety analysis. These patients may continue treatment with crovalimab, if deemed appropriate by the investigator.

The screening period to ascertain study eligibility for the Naive Cohort and the C5 SNP Cohort may take up to 7 days, and for the Switch Cohort, may take up to 28 days. Patients who do not meet criteria for participation in this study (i.e., screening failure) may qualify for two re-screening opportunities (three screenings per participant) at the investigator's discretion. Any re-screening of treatment-naive patients for enrollment must be completed within 28 days of initial TMA presentation. Patients are not required to re-sign the Informed Consent Form, if they are re-screened within 30 days of previously signing the Informed Consent Form. The investigator will maintain a record of reasons for screening failure at each screening assessment (see Section 4.5.1).

Treatment-naive patients, who are screened and deemed ineligible for study enrollment, and who subsequently initiate off-study treatment with either eculizumab or ravulizumab, may be subsequently re-screened for study enrollment as a Switch patient (i.e., must remain on a stable dose of C5 inhibitor treatment for a minimum of 90 days [see Section 4.1.1] prior to the start of Week 1 Day 1 treatment with crovalimab). Patients who were previously screened and ineligible for enrollment in the Naive Cohort must be re-consented at the time of re-screen for Switch Cohort eligibility, and any prior Consent Form will be considered invalid.

The treatment discontinuation date is defined as the last day the patient receives a dose of crovalimab on the study. All patients who discontinue from crovalimab treatment 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. *Patients who continue crovalimab after discontinuation from the study treatment do not need to return for the safety follow up visit.* If these patients switch to a different C5 inhibitor, they should remain in safety follow-up and be monitored, as detailed in Section 5.1.1.5. For all patients who discontinue crovalimab and who are not eligible to resume crovalimab (as described in Section 4.7.2), the day of the safety telephone call at 46 weeks (approximately 10.5 months) after study treatment discontinuation represents the study discontinuation date. More details are provided in Section 4.7.1.

After approximately 40 patients in the Naive Cohort *(primary analysis population)* and approximately 40 patients in the Switch Cohort have been included in the study, enrollment at sites will be closed.

3.3 DURATION OF PARTICIPATION

After completing 24 weeks of treatment with crovalimab (i.e. at the Week 25 visit), patients who derive clinical benefit may continue treatment during the extension period of the study, which may be a maximum of 3 years after the last patient has completed the primary treatment period, and then, as per the Roche Global Policy on Continued Access to Investigational Medicinal Product. The total duration of study participation for each individual is expected to range from 1 day up to approximately *8* years.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Crovalimab Dose and Schedule

The goal of treatment with C5 inhibitor therapy is to achieve a rapid and complete suppression of C5 activity and to maintain this suppression throughout the dosing interval. Data from studies *BO42162, YO42311, BO42161, and BP39144* indicate that crovalimab concentrations of approximately 100 μg/mL achieve complete terminal complement activity inhibition. As shown by the evaluation of eculizumab/ravulizumab in patients with PNH and aHUS, the relationship between C5 inhibitor concentration and complement activity is disease-independent. Because crovalimab shares the same mechanism of action as eculizumab/ravulizumab, a disease-specific dose adaptation of crovalimab is not anticipated in patients with aHUS (Legendre et al. 2013; Howard et al. 2017; Pittock et al. 2019).

A population PK model was used to recommend a dose and regimen, achieving and maintaining crovalimab concentrations above a concentration of approximately 100 μg/mL associated with complement inhibition throughout the dosing interval. In the population PK model, body weight was identified as a covariate for crovalimab clearance and volume of distribution and was found to statistically influence these parameters when incorporated using allometric scaling with a coefficient fixed to 0.75 for the clearances and 1.0 for the volumes. Consequently, for a given dose, larger patients tend to be under-exposed as compared with smaller patients. To compensate for the

effect of body weight, a weight-based tiered dosing approach is proposed to ensure that all patients achieve a comparable crovalimab exposure.

This study will include two weight-based doses for crovalimab (see Table 1). Considerations for patients who switch from eculizumab or ravulizumab are presented in Section 3.4.1.1 and Section 3.4.1.2, respectively.

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

Crovalimab dose and dosing regimen in patients switching from eculizumab to crovalimab are presented in Table 1.

In patients switching from eculizumab to crovalimab, DTDCs form as eculizumab and crovalimab bind different C5 epitopes (Nishimura et al. 2020). Formation of DTDCs could result in a transiently lower crovalimab exposure that could lead to transient suboptimal complement inhibition.

The goal of crovalimab dose and dosing regimen are to maintain crovalimab above approximately 100 μg/mL, to ensure complement inhibition despite the transient formation of DTDCs.

A mechanistic model describing, simultaneously, the kinetics of total and free C5, the pharmacokinetics of crovalimab and eculizumab, and the kinetics of DTDCs was also used to recommend a dose and regimen minimizing the formation of large DTDCs in patients switching to crovalimab while maximizing the level of free crovalimab binding sites in all the patients.

The proposed dose and dosing regimen in this study has been first investigated in Study BP39144 Part 4. The PK data collected in patients in the Naive and Switch Cohorts indicate that the exposure of crovalimab was maintained over approximately 100 μg/mL and induced complement inhibition across all patients enrolled in Part 4. Additionally, the distribution of DTDC sizes at Day 29 (post-initiation of crovalimab) in patients in the Switch Cohort is comparable to that in patients in the Naive Cohort, suggesting that the DTDC impact will be minimal 4 weeks after the initial loading dose period (see Section 1.2.2).

3.4.1.2 Rationale for Crovalimab Dose and Schedule in Patients Switching from Ravulizumab

Ravulizumab and crovalimab bind different C5 epitopes. The mechanistic model developed based on patients switching from eculizumab to crovalimab was adapted and used to simulate the impact of switching from ravulizumab on crovalimab pharmacokinetics and the expected DTDC size distribution and profile.

Ravulizumab, as compared with eculizumab, has a prolonged half-life, which could have an effect on DTDC formation, and consequently on crovalimab pharmacokinetics and safety. However, in contrast to eculizumab, crovalimab and ravulizumab have similar recycling properties with pH-dependent target binding and disposal so that after endocytosis only the free antibody is recycled whereas C5 is degraded in lysosomes. This may favorably affect DTDC formation and elimination when switching patients from ravulizumab to crovalimab.

- After recycling, circulating antibodies (crovalimab or ravulizumab) are not expected to be bound to C5, thereby reducing the probability of forming complexes larger than the basic crovalimab-C5-ravulizumab motif. This is in contrast with eculizumab, which remains bound to its target through FcRn recycling, enabling generation of DTDCs constituted of more than a single crovalimab, C5, and eculizumab motif.
- pH-dependent target binding and increased target clearance leading to a decrease in the concentration of total C5, which is a critical element in DTDC formation and could therefore potentially reduce the formation of large DTDCs.

A shift in the DTDC size distribution towards their smallest form (crovalimab-C5-ravulizumab) is therefore expected in patients switching from ravulizumab to crovalimab. Larger DTDCs (i.e., DTDCs constituted of more than a single crovalimab, C5, and ravulizumab) are expected to be cleared or to dissociate within approximately 7–8 weeks, whereas smaller DTDCs (i.e., crovalimab-C5-ravulizumab) are expected to be cleared within hours. The combination of the recycling properties of ravulizumab minimizing the formation of large DTDCs and the rapid clearance of the smallest DTDCs is expected to result in only a moderate prolongation of DTDC presence in patients switching from ravulizumab, despite the significant longer half-life of ravulizumab compared with eculizumab.

Based on the modelling, in patients switching from ravulizumab to crovalimab, it is expected that all size DTDCs will persist for approximately 12 weeks. Consequently, the concentration sink triggered by the formation of DTDCs is expected to be less pronounced in patients switching from ravulizumab as compared with patients switching from eculizumab.

The dose and dosing regimen were optimized to compensate for the concentration sink triggered by the formation of DTDCs in patients with eculizumab. It is therefore expected, based on the model predictions that the dose and dosing regimen proposed for patients switching from eculizumab to crovalimab will also allow patients switching from ravulizumab to crovalimab to maintain crovalimab concentrations above 100 μg/mL.

3.4.2 Rationale for Patient Population

3.4.2.1 Primary *Analysis* Population

Patients with aHUS who were never treated with a C5-inhibitor therapy (treatment-naive) prior to study entry will comprise the primary *analysis* population for this Phase III study aiming to demonstrate efficacy and safety of crovalimab.

Treatment-naive aHUS patients are eligible for enrollment, if laboratory parameters confirm initial TMA presentation, as per Section 4.1.1. These requirements were specifically chosen to ensure inclusion of patients who have significant TMA, and therefore have the highest therapeutic need and chance to benefit from C5 inhibition treatment. The qualifying laboratory findings (including but not limited to HIV testing, direct Coombs, hepatic function levels), even if obtained prior to screening, can be used as screening values to enroll the patient, but only if documented in the medical records.

In addition, these requirements are consistent with the criteria used in a recent study demonstrating the benefit of the C5 inhibitor, ravulizumab, in patients with aHUS (Rondeau et al. 2020).

3.4.2.2 Inclusion of Switch Patients

Switch patients with aHUS will be included if they have a confirmed diagnosis of aHUS and have been treated at a stable dose of eculizumab or ravulizumab for at least 90 days as of Week 1 Day 1 of study treatment with crovalimab (including having received at least two maintenance doses, if switching from ravulizumab). The current standard-of-care for adult and pediatric patients with aHUS is chronic, continuous C5 inhibitor therapy. Given the significant risk of TMA reactivation, including potential harm to patients should there be a treatment-free washout period, a study that evaluates patients currently under treatment with C5 inhibitors should demonstrate that patients could be effectively switched from prior C5 inhibitor therapy to crovalimab without interruption of treatment or recurrence of symptoms. The role of the Switch Cohort will be to establish the PK profile and safety in these patients, and to support the efficacy demonstrated in the treatment-naive patient population.

3.4.2.3 Inclusion of C5 SNP Patients

Patients with known C5 SNPs and who, per investigator's assessment, have not adequately responded to eculizumab or ravulizumab will be eligible for enrollment. Crovalimab binds to a different C5 binding site than eculizumab and ravulizumab and has been shown in ex vivo experiments to block hemolysis in patients who have a single missense C5 heterozygous mutation that predicts an arginine at 885 (Arg885His missense mutation) (Fukuzawa et al. 2017). *Ten* patients with PNH, who have a single missense C5 heterozygous mutation and whose hemolysis was not controlled by previous eculizumab treatment, were enrolled in study BP39144 (Nishimura et al. 2020) *and the non-randomized Arm C of Study BO42161. Most of these patients achieved and maintained complement inhibition throughout the primary*

treatment period. Patients with C5 polymorphisms generally had rapid and sustained decrease in LDH, which was maintained up to the latest CCOD for each study.
Therefore, crovalimab may be an effective complement inhibitor for patients with R885 SNPs (and similar C5 variants) who are failed by either eculizumab or ravulizumab, and have a very high unmet medical need, regardless of indication.

3.4.2.4 Inclusion of Adolescents

Atypical hemolytic uremic syndrome in adolescents is indistinguishable from adults. Regardless of age of onset, aHUS is due to dysregulation of the alternative complement pathway, often by the loss of function of regulatory proteins, which increases assembly of the MAC, C5b-9, resulting in endothelial injury, platelet activation, and thrombosis. Therefore, the clinical manifestations and the response to treatment with C5 inhibitors are similar in patients with aHUS across the age continuum justifying inclusion of adolescents in this trial. Importantly, for these young individuals, the potential for reduced treatment burden offered by crovalimab may be particularly meaningful. Adolescents will be included in the primary efficacy population.

As per a systematic epidemiology review (Yan et al. 2020), in individuals less than 20 years of age, the prevalence of aHUS ranged between 2.21 and 9.4 per million people. Further reports demonstrated the highest prevalence to be in children between 0 and 4 years of age (3 per million children population). Between ages 5 and 9 years and 10 and 15 years, prevalence declined to 0.3 and 0 per million children population, respectively. Prevalence in adults was higher in Europe compared to Australia/New Zealand (5.75 and 2.4 per million people, respectively). The largest reference population was in Europe, with more than 16 million people and prevalence of aHUS was 4.96 per million total population. The United States/Canada were not included in the aforementioned analyses.

The Sponsor anticipates that, due to the rarity of disease, too few adolescents will be enrolled to allow for dedicated subgroup analyses. However, their data will be aggregated with the adult data given: 1) similar disease process, 2) similar response to intervention, and 3) anticipated similar crovalimab pharmacokinetics and pharmacodynamics in adolescents and adults. The inclusion of adolescent patients in the crovalimab Phase III studies will also provide an important age-specific safety experience.

3.4.3 Rationale for Single-Arm Study Design

Atypical hemolytic uremic syndrome is an ultra-rare disease with an incidence of 2 cases per million per year in the United States and a prevalence of 3.3 cases per million for patients $<$18 years old (Constantinescu et al. 2004; Zimmerhackl et al. 2006). In these settings, a randomized design comparing crovalimab against standard-of-care C5 inhibitor would have to include more patients than is operationally feasible in a reasonable timeframe.

The natural history of aHUS in the absence of complement inhibition is well described and patients experience chronic deterioration without spontaneous improvement. Thus, for patients naive to complement inhibitors, which comprise the primary efficacy population, one would not expect a spontaneous improvement and patients who will meet the proposed endpoint of cTMAr would likely achieve it due to treatment with crovalimab.

Four studies *have been conducted* in *patients with* PNH. In these studies, approximately 400 patients will be *treated with* crovalimab (Studies BO42162 and BO42161). Data collected from these studies will support interpretation of the aHUS data, with particular focus on the PK and PD parameters, as they are directly related to clinical efficacy, as well as providing a larger safety database.

Given these considerations, a single-arm study design is deemed sufficient to assess efficacy and safety of crovalimab in aHUS while maintaining operational feasibility of the study**.**

3.4.4 Rationale for Complete Thrombotic Microangiopathy Response as Primary Endpoint

The primary efficacy endpoint, which will be evaluated in the Naive Cohort, is the proportion of patients with cTMAr anytime from baseline to Week 25 (after 24 weeks on treatment). The composite measure simultaneously captures the effect of the drug on hematologic parameters, reflecting TMA activity, and on the renal function, as the most frequent clinical consequence. Therefore, it provides a comprehensive picture of the key components involved in TMA control. Furthermore, the response is required to be maintained for at least 4 weeks, ensuring that patients with a clinically inconsequential variation in laboratory values are not classified as responders. Accordingly, cTMAr became an established endpoint in the evaluation of clinical response to C5 inhibition treatment (Fakhouri et al. 2016; Greenbaum et al. 2016; Ito et al. 2019; Kato et al. 2019), and it was the primary endpoint in the recent study leading to approval of ravulizumab in the aHUS indication (Rondeau et al. 2020).

3.4.5 Rationale for Biomarker Assessments

Pharmacodynamic biomarkers will be assessed to monitor the biologic activity of crovalimab treatment. To monitor the total complement activity, the capacity of patients' serum to lyse marker enzyme-containing liposomes ex vivo will be determined using a LIA. The activity of the liberated marker enzyme is proportional to the complement activity in the sample (Jaskowski et al. 1999) and thus, a surrogate for the complement inhibitory activity of crovalimab.

Total C5 and free C5 concentrations will also be measured in patients' serum to assess the interaction of crovalimab against the drug target, C5. Soluble C5b-9 complex is considered a biomarker for complement activity and used to monitor activity of the

terminal pathway of complement downstream of C5 (Wehling et al. 2017). Additional factors of the complement system (e.g., C3, C4, and CFB) may be assessed, if needed.

A crosslink between the complement and coagulation system has been observed (Mollnes et al. 1988). Studies have demonstrated that active components of the coagulation cascade can trigger activation of the complement system and vice versa (Markiewski et al. 2007; Oikonomopoulou et al. 2012). For this reason, markers of endothelial activation and the coagulation system (e.g., P-selectin, D-dimer) may also be assessed, if indicated.

Further central laboratory assessments include the analysis of serum LDH and creatinine for determination of cTMAr or mTMAc as an efficacy endpoint, and the analysis of parameters reflecting hemolysis (i.e., free hemoglobin and Haptoglobin).

The absolute value and change over time in serum/plasma biomarkers will be assessed. The relationships between biomarkers and efficacy, safety, pharmacokinetics, and immunogenicity will also be investigated, as indicated.

Atypical hemolytic uremic syndrome is a heterogeneous disorder and excessive activation of the alternative pathway of the complement system has been shown to be triggered by underlying genetic aberrations in genes of the complement or coagulation cascade. Approximately 50% of patients harbor either loss of function mutations in regulators (i.e., *CFH*, *THBD*, *CFI*, *CD46*) or gain-of-activity mutations in complement activators (i.e., *CFB, C3*), or gene rearrangements in complement factor H-related genes (also linked to development of anti-factor H autoantibodies) (Giocoechea de Jorge and Pickering 2010). Studies have shown that some patients with aHUS carry defined risk haplotypes (mostly SNPs) of the genes encoding for FH, FHR1 or CD46, in addition to a complement mutation, causing increased susceptibility to development of aHUS (Rodríguez de Córdoba et al. 2014; Feitz et al. 2018).

The analysis of genes of the complement and coagulation pathway (including, but not limited to: *C5, CFH, CFI*, *CD46*, *CFB, C3, CFHR1-5, PLG, THBD*) will be performed using peripheral blood with the objective of better understanding the underlying mechanisms causing aHUS, as well as drug efficacy. The relationship between genetic biomarkers and efficacy as well as treatment duration will be explored. Further details on biomarkers measured and a list of genes are provided in Appendix 7 and Appendix 8.

Residual samples may be used for further exploratory research related to crovalimab or TMA, assay development, or assay validation, if allowed by country regulations.

Any analyses not specifically listed in the protocol as well as the analysis of polymorphisms in genes listed in Appendix 8 may be performed only if in line with country-specific regulations.

3.4.6 Rationale for Clinical Outcome Assessments

Patients with aHUS may experience many disease-related symptoms that affect HRQoL. In order to characterize the impact of treatment on the HRQoL of adult patients in this study, fatigue will be assessed using the FACIT-Fatigue Questionnaire whereas physical functioning, role functioning, and general health status/QoL will be assessed using selected scales of the EORTC QLQ-C30. Additional kidney disease-related symptoms will be assessed using a symptom-specific scale of the KDQoL.

To assess HRQoL in adolescents, the PedsQL MFS and Physical Functioning scale of the PedsQL Core will be used to assess fatigue and physical functioning, respectively, in children 12–17 years of age.

In addition, treatment satisfaction using the TSQM-9 (all adult patients), patient preference using the Patient Preference Questionnaire (Switch Cohort patients), and number of missed days of school or work (as applicable) will be assessed.
The EQ-5D-5L will be administered for producing health utility scores for economic modeling.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 40 patients in the Naive Cohort *(primary analysis population)* and approximately 40 patients in the Switch Cohort will be enrolled. Any eligible patients with a known C5 polymorphism may be enrolled in the C5 SNP Cohort (up to 5 patients are expected to be enrolled in this cohort).

4.1.1 Inclusion Criteria

For ALL Cohorts (Naive, Switch, and C5 SNP Cohorts), 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
- Age $\geq$ 12 years at time of signing Informed Consent Form or Assent Form
- Body weight $\geq$ 40 kg at screening
- Willingness and ability to comply with all study visits and procedures
- Vaccination against *Neisseria meningitidis* serotypes A, C, W, and Y $<$ 3 years prior to initiation of crovalimab treatment. Vaccination against serotype B should be administered in accordance with most current local guidelines or standard-of-care as applicable for patients with complement deficiency. If not previously administered, vaccination should be administered no later than 1 week after the first crovalimab administration. Vaccination currency with vaccination against serotypes A, C, W, Y and B should be maintained throughout the study, according to local

guidelines for patients with complement deficiency. In the absence of clear local guidelines for Neisseria meningitidis, the Advisory Committee on Immunization Practices 2020 Guidelines are recommended.

  - Patients who receive a vaccination <2 weeks before initiating crovalimab treatment or after start of crovalimab treatment must receive treatment with appropriate antibiotics from initiation of treatment until 2 weeks after the vaccination or according to local standards of care. Patients who refuse vaccination 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, the vaccinations should be administered no later than 1 week after the first crovalimab administration.

  - Patients who receive a vaccination <2 weeks before initiating crovalimab treatment or after start of crovalimab treatment must receive treatment with appropriate antibiotics from initiation of treatment until 2 weeks after the vaccination or according to local standards of care. Patients who refuse vaccination are not eligible for the study.

- Patients who have been vaccinated (partially or in full) against SARS-CoV-2 with a locally approved vaccine are eligible to be enrolled in the study, 3 days or longer after inoculation.

- For patients continuing to receive other therapies concomitantly with crovalimab (e.g., immunosuppressants, corticosteroids, mammalian target of rapamycin inhibitor [mTORi] [i.e., sirolimus, everolimus] or calcineurin inhibitors [i.e., cyclosporine or tacrolimus]): stable dose for ≥ 28 days prior to screening and up to the first crovalimab administration, AND ONLY if:

  - *The treatment is* part of an established post-transplant antirejection regimen, or

  - Patient had confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or

  - Steroids were being used for a condition other than aHUS (e.g., asthma).

- Adequate hepatic function, AST and ALT $\leq 3 \times$ ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis

- Female patients of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of crovalimab.

- For female patients of childbearing potential, an agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  - Female patients must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 46 weeks (approximately 10.5 months) after the final dose of crovalimab. A longer period of contraception after discontinuing crovalimab treatment may be needed based on exposure to other medicinal products (e.g., eculizumab and ravulizumab) according to their respective local labels.

- A female patient is considered to be of childbearing potential if she is postmenarchal, 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, sympto-thermal, 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.

- Patients with a prior kidney transplant are eligible if they have a known history of complement-mediated aHUS prior to the kidney transplant

<u>For Naive Cohort only:</u>

- Onset of initial TMA presentation, as defined by a patient with all of the following laboratory findings, within 28 days prior to the first dose of crovalimab (see Section 3.2.2 for further details regarding screening):
  - Platelet count < LLN, and
  - LDH ≥ 1.5 × ULN, and
  - Hemoglobin < LLN (adjusted for age and sex), and
  - Serum creatinine ≥ ULN in adults, or ≥ 97.5th percentile for age in adolescents (12–18 years). Patients who require dialysis for acute kidney injury (AKI) are also eligible.

  NOTE: If the patient has been receiving PE/PI, the patient's eligibility must be ascertained based on the above qualifying laboratory findings, obtained at onset of initial TMA presentation (prior to receiving any PE/PI) and must be within 28 days of the first crovalimab dose. The qualifying laboratory findings, even if obtained prior to screening, can be used as screening values to enroll the patient, but only if documented in the medical records.

<u>For Switch Cohort only:</u>

- Documented treatment with eculizumab or ravulizumab according to the local product label for aHUS. Eculizumab treatment received for at least 90 days as of Week 1 Day 1 of crovalimab treatment. Patients switching from IV ravulizumab

must have received at least two maintenance doses, as of Week 1 Day 1 of crovalimab.

- Clinical evidence of response to either eculizumab or ravulizumab, as documented by a platelet count ≥LLN, LDH ≤ULN, and stable (decrease or increase of ≤20%) or improving creatinine at two consecutive measurements at least 4 weeks apart prior to Week 1 Day 1 of crovalimab treatment

For C5 SNP Cohort only:

- Documented diagnosis of aHUS
- Known C5 polymorphism (e.g., Arg885)
- Documented treatment with either eculizumab or ravulizumab for aHUS, with poorly controlled TMA, per investigator's assessment

4.1.2 Exclusion Criteria

For ALL Cohorts (Naive, Switch, and C5 SNP Cohorts), patients who meet any of the following criteria, will be excluded from study entry:

- TMA associated with non-aHUS related renal disease
- Positive direct Coombs test
- Identified drug exposure–related TMA
- History of bone marrow transplant or organ transplant, other than kidney transplant
- Chronic dialysis (defined as dialysis for more than 4 weeks since TMA presentation) within 90 days prior to first crovalimab administration, and/or end stage renal disease (ESRD)
- History of a kidney disease, other than aHUS, affecting renal function, such as:
  - Known kidney biopsy finding suggestive of underlying disease other than aHUS
  - Known kidney ultrasound finding consistent with an alternative diagnosis to aHUS
  - Known family history and/or genetic diagnosis of noncomplement mediated genetic renal disease
- History of *N. meningitidis* infection within 6 months of study enrollment
- Known or suspected immune deficiency (e.g., history of frequent recurrent infections)
- Positive HIV test
- Life expectancy of <4 weeks
- Active systemic bacterial, viral, or fungal infection within 14 days before first crovalimab administration
- Presence of fever (≥38°C) within 3 days before the first crovalimab administration.

  If fevers are solely due to the underlying aHUS pathology, and there is no evidence or suspicion of a systemic infection, patients may enroll.

- Patient with active or evolving multi-system organ dysfunction or failure
- Immunized with a live attenuated vaccine within 1 month before first crovalimab administration
- Known systemic sclerosis (scleroderma), systemic lupus erythematosus, or anti phospholipid antibody positivity or syndrome
- Patients receiving chronic intravenous immunoglobulin (IVIg) within 8 weeks prior to start of screening, unless for unrelated medical condition (e.g., hypogammaglobinemia)
- History of malignancy within 5 years prior to screening and up to the first crovalimab 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 crovalimab 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 first crovalimab 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 the first crovalimab administration are eligible.
- History of hypersensitivity, allergic, or anaphylactic reactions to any ingredient contained in crovalimab, including hypersensitivity to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product
- Female patients who are pregnant, breastfeeding, or have the intention of becoming pregnant during the study or within 46 weeks (approximately 10.5 months) after the final dose of crovalimab treatment
- Participation in another interventional treatment study with an investigational agent or use of any experimental therapy within 28 days of screening or within five half-lives of that investigational product, whichever is greater. Patients enrolled in an eculizumab or ravulizumab interventional study are eligible for the Switch Cohort or the C5 SNP Cohort, provided they fulfill eligibility and stop their current trial.
- Substance abuse within 12 months prior to screening, in the investigator's judgment
- Splenectomy <6 months prior to screening
- Use of tranexamic acid within 7 days prior to screening
- 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

<u>For Naive Cohort only (additional exclusion criteria for treatment-naive patients):</u>

- First initiation of PE/PI more than 28 days prior to first crovalimab administration

- Last PE/PI completed less than 2 hours prior to first crovalimab administration
- *Normalization of serum creatinine values at baseline (<97.5th percentile for age)*
- Diagnosis of thrombotic thrombocytopenic purpura (TTP), as established by decreased ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) levels $\leq 10\%$
  - For patients who have received blood product transfusions, ADAMTS13 testing must be performed prior to transfusion. If this was not performed, ADAMTS13 testing must be performed as early as possible after the blood product transfusion, and again only once 14–21 days after the transfusion.
- Diagnosis of STEC-HUS, as demonstrated by a positive test result for Shiga toxin or detection of Shiga toxin–producing bacteria
- Clinical suspicion of Pneumococcal HUS, as suggested by a positive chest X-ray and/or positive culture of *S. pneumoniae*
- TMA secondary to cobalamin C defect (if not already known) as demonstrated by either increased total blood homocysteine levels *by* $\geq 3 \times ULN$ **and** increased blood or urine methylmalonic acid (MMA) levels *by* $\geq 3 \times ULN$, and/or MMACHC gene mutation. *In case one of the laboratory parameters (MMA or homocysteine) is normal, testing of the alternative laboratory parameter is not required.*
- TMA related to a known DGKE nephropathy caused by homozygous or compound heterozygous loss-of-function mutations in DGKE

If the evaluations for non-aHUS TMA testing (see Appendix 1 and Appendix 10) are performed but the results are not available by the end of screening, patients may be enrolled and dosed, based on the investigator's best clinical judgment. Patients who are enrolled but whose aHUS diagnosis is subsequently ruled out may continue treatment with crovalimab, if deemed appropriate by the investigator (see Section 3.2.2 and Section 5.4).

- Current or previous treatment with a complement inhibitor

For Switch Cohort and C5 SNP Cohort only (additional exclusion criteria for Switch patients and C5 SNP patients):

- Receiving PE/PI within 8 weeks of the first crovalimab administration (Switch Cohort only)
- Diagnosis of TTP at TMA onset, as established by decreased levels of ADAMTS13 $\leq 10\%$
- Diagnosis of STEC-HUS at TMA onset, as demonstrated by a positive test result for Shiga toxin or detection of Shiga toxin–producing bacteria
- Clinical suspicion of pneumococcal-related HUS at TMA onset, as suggested by a positive chest X-ray or positive culture of *S. pneumoniae*
- TMA secondary to cobalamin C defect, as demonstrated by either increased total blood homocysteine levels by *by* $\geq 3 \times ULN$ and increased blood or urine MMA

levels *by* $\geq 3 \times ULN$, and/or MMACHC gene mutation. *In case one of the laboratory parameters (MMA or homocysteine) is normal, testing of the alternative laboratory parameter is not required.*

- TMA related to a known DGKE nephropathy caused by homozygous or compound heterozygous loss-of-function mutations in DGKE

If the evaluations for non-aHUS TMA testing (see Appendix 1 and Appendix 10) are performed but the results are not available by the end of screening, patients may be enrolled and dosed, based on the investigator's best clinical judgment. Patients who are enrolled but whose aHUS diagnosis is subsequently ruled out may continue treatment with crovalimab, if deemed appropriate by the investigator (see Section 3.2.2 and Section 5.4).

For Switch Cohort and Switching C5 SNP patients only (switching C5 SNP patients are defined as those who received their last dose of eculizumab or ravulizumab less than 5.5 drug half-lives prior to Week 1 Day 1 of crovalimab administration [i.e., 10 weeks for eculizumab and 41 weeks for ravulizumab]):

- Positive for hepatitis B surface antigen (HBsAg) and/or hepatitis C virus (HCV) antibody at screening. Patients who are seropositive for HCV but without detectable HCV RNA are eligible.
- History of or ongoing cryoglobulinemia at screening

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a non-randomized, *single-arm study*. After initial written informed consent or assent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and drug dispensing code from an interactive voice or web-based response system (IxRS). For further screening details see Section 3.2.2.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is crovalimab. Appendix 11 identifies all investigational medicinal products for this study. Patients should receive their first dose of crovalimab treatment no later than 2 calendar days after enrollment. All visits and infusions may be administered with a window of ± 2 days, except the Week 1 Day 2 loading dose (Section 4.3.2.1), which should be administered on the scheduled day. If the timing of a protocol-mandated study visit coincides with a holiday or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date.

For patients in the Switch Cohort and C5 SNP patients switching without a treatment break from either eculizumab or ravulizumab, Week 1 Day 1 of crovalimab treatment will

be scheduled 2 weeks from the patient's last dose of eculizumab or 8 weeks from the patient's last dose of IV ravulizumab. The Week 1 Day 1 dose of crovalimab may be administered with a window of +2 days when switching from eculizumab and +7 days when switching from ravulizumab (as per eculizumab and ravuluzimab labels). Week 1 Day 1 of crovalimab dose should not be administered earlier than the scheduled visit (i.e. before 2 weeks from the patient's last dose of eculizumab or before 8 weeks from the patient's last dose of IV ravulizumab).

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Crovalimab

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

Crovalimab for IV Infusion and SC Administration

Crovalimab will be supplied by the Sponsor as a single-use vial formulation, containing a solution that can be used for infusion (IV) or for injection (SC). Each vial contains an extractable volume of 2 mL or 340 mg (nominal) crovalimab.

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

For SC administration, crovalimab solution for injection is used undiluted. In order to minimize the number of SC injections for patients, the administration per single injection of up to 2 mL drug product solution will be permitted.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The study treatment with crovalimab is summarized in Section 4.3.2.1. Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Crovalimab may be administered within ±2 days of the scheduled day, except the Week 1 Day 2 loading dose (Section 4.3.2.1), which should be administered on the scheduled day.

Guidelines for dosage modification and treatment interruption or discontinuations for patients who experience adverse events are provided in Section 5.

4.3.2.1 Crovalimab

Crovalimab will be administered as described in Table 1.

Table 1 Weight-Based Tiered Crovalimab Dosing Schedule

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

QW = weekly; Q4W = every 4 weeks; SC = subcutaneous.

All crovalimab formulation concentrations equal 170 mg per 1 mL.

Crovalimab may be administered within ±2 days of the scheduled day, except the Week 1 Day 2 loading dose, which should be administered on the scheduled day. *All the visits are calculated from W1D1.*

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

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

Height and weight will be recorded at screening for all patients. Height and weight will also be recorded at Weeks 5, 17, 25, 41, 49, and every 16 weeks (Q16W) thereafter.

Dose modification (only allowed from Week 9) is required if the patient's body weight changes by ≥10% (compared with screening or the visit when the latest dose

modification occurred, whichever is later) to exceed or become equal to 100 kg or to fall below 100 kg during the course of therapy.

4.3.2.2 Training for Self-Administration

For details on the requirements for administering initial subcutaneous doses in a monitored setting, see Section 4.3.2.1.

Over the course of the first five SC doses, patients and/or their caregivers will be trained in SC administration of crovalimab by a healthcare provider (HCP). The HCP will explain the process used for SC injection, facilitated by Instructions for Use written specifically for crovalimab. Through this process under supervision, the patient and/or caregiver will gain proficiency in the correct and safe self-administration of SC crovalimab. The HCP is to inform the patient/caregiver of the dose to be administered and dosing frequency. Note that during the course of the study, should the patient's body weight change to affect the dose, the new dose to be administered must be communicated to the patient/caregiver.

Hereafter, self-administration refers to self-injection by the patient or injection given by the caregiver, unsupervised by an HCP. "Patient" refers to either or both patient and/or caregiver, as appropriate.

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

Compliance with self-administration will be assessed throughout the study. Patients will be asked to record the administered doses in a patient diary and bring it along for each clinic visit.

Patients who choose to self-administer crovalimab will still be required to have a study visit every 4 weeks (Q4W) up to Week 25, then Q8W up to Week 49, and then Q16W thereafter. Crovalimab administration should occur after all assessments have been completed during the visit.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or mobile nurse]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site,

IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged or expired shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, by time monitoring (shipment arrival date and time) and temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study and/or their caregivers may receive and administer IMPs, and only authorized staff may supply or administer IMPs.

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

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the crovalimab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Crovalimab

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

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

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

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

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

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 28 days prior to enrollment until 46 weeks (approximately 10.5 months) after the final dose of crovalimab. All such medications should be reported to the investigator and recorded on the Concomitant Medication eCRF.

In the event of aHUS relapse, interventional (non-investigational) therapy should proceed at the discretion of the treating investigator after completing an unscheduled visit assessment (except when urgent treatment is required before the patient can undergo this assessment). If relapse interventions are initiated or crovalimab was interrupted, the Medical Monitor should be informed (as per Section 5.1.2.1 and Section 5.1.2.2), as soon as possible, ideally prior to next crovalimab dose.

4.4.1 Permitted Therapy

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

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1)
- Hormone-replacement therapy
- Immunosuppressant therapy as part of a post-renal transplantation regimen
- Anti-hypertensive medications
- Iron supplements
- Folic acid

Patients may receive other concomitant medications. All concomitant medications must be recorded in the Concomitant Medication eCRF.

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

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution Due to Effects Related to Cytochrome Enzymes

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

4.4.2.2 Herbal Therapies

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

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited *during the study*:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days (or 5.5 drug half-lives) prior to initiation of crovalimab treatment and during study treatment with crovalimab.
- Chemotherapy
- *Rituximab*
- Other complement inhibitor therapies (e.g., eculizumab, ravulizumab)
- PE/PI for the indication of aHUS at any time after the first dose of crovalimab. If PE/PI is performed, the patient will be immediately withdrawn from the trial. *The following concomitant medications and procedures are allowed under certain circumstances and with the following restrictions:*
  - *Use of other immunosuppressive therapies (such as steroids, mTORi [eg, sirolimus, everolimus], CNI [e.g., cyclosporine or tacrolimus]) during the study are not allowed unless part of an established post-transplant antirejection regime, or b) patient has confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or if steroids are being used for a condition other than aHUS (e.g., asthma).*

4.5 STUDY ASSESSMENTS

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

Additional (unscheduled) visits outside the specified visits are permitted at the discretion of the investigator. Procedures, tests, and assessments will be performed at the discretion of the investigator, but in case of aHUS symptomatology at a minimum the following tests should be performed for study purposes: LDH, platelet count, serum creatinine, BUN, cystatin C, haptoglobin, hematology panel, and urinalysis (see Section 4.6.1.1), as well as samples for pharmacokinetics, pharmacodynamics, and ADAs (see Appendix 1). Any procedures, tests, or assessments performed at the unscheduled visits must be recorded on the eCRFs. Any unscheduled LDH, serum creatinine, BUN, cystatin C, hematology, pharmacokinetics, pharmacodynamics, and ADA samples should be sent to the central laboratory per instructions in the laboratory manual. For other tests, local laboratory results may be used for unscheduled visit testing. Adverse events and vital signs must be recorded for each unscheduled visit.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and *any available* local laboratory test values are acceptable.

At applicable sites, certain study assessments and crovalimab administration may be performed by a mobile nursing (MN) professional at the patient's home or another suitable outpatient location to improve access and convenience for patients participating in the study. Patients who utilize MN can do so only for study visits on Weeks 13, 21, and 33. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days to allow relevant assessments to be performed by the MN professional.

4.5.1 Informed Consent Forms and Screen Failures

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms and Child's Informed Assent Forms (as applicable) for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. Adolescent patients aged 12–17 years will complete and sign an Informed Assent Form, and their parent(s) or legally authorized representative(s), per local regulations, will complete an Informed Consent Form.

All screening evaluations must be completed within a 7-day period for Naive and C5 SNP patients, and within a 28-day period for Switch patients, prior to the first dose and reviewed to confirm that patients meet all eligibility criteria before enrollment. If re-screening is required (see Section 4.2.1), then viral testing from the initial screening may be acceptable for screening assessment if performed ≤60 days prior to the first crovalimab administration. Testing related to non-aHUS TMA as described in Appendix 10 may be acceptable for screening assessment if previously documented in the medical records. The investigator will maintain a detailed record of all patients screened, and document eligibility or record reasons for screening failure, as applicable.

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

Medical history, including clinically significant diseases, surgeries, biopsies, cancer history (including prior cancer therapies and procedures), reproductive status (for female patients), smoking history, immunization history, and use of alcohol and drugs of abuse, will be recorded at screening. aHUS history, including results from genetic analysis, the dates of diagnosis, prior and ongoing treatments (including dialysis), as well as platelet count, packed red blood cells (pRBC), and plasma transfusions (i.e., simple infusion or via exchange) within the past 12 months should be recorded. The description of the major adverse vascular events (MAVEs) will also be collected as part of the patient's medical history prior to baseline as described in Appendix 5. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from 28 days prior to enrollment until 46 weeks (approximately 10.5 months) after the final dose of crovalimab will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and medical conditions should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity (where permitted by local regulations).

4.5.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems (see Appendix 1 for details). Height and weight will be recorded at screening, then at Weeks 5, 17, 25, 41, 49 and every 16 weeks thereafter until the end of the study. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Special focus should be on signs and symptoms of infections and signs of Type III hypersensitivity reactions, as detailed in the crovalimab Investigator's Brochure.

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

4.5.4 Vital Signs

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

4.5.5 Immunizations

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

4.5.5.1 *Neisseria meningitidis* vaccination, *Haemophilus influenzae* type B, and *Streptococcus pneumoniae* vaccinations

Vaccination against *N. meningitidis* serotypes A, C, W, and Y must be administered <3 years prior to initiation of crovalimab treatment. Vaccination against serotype B should be administered in accordance with the most current local guidelines or standard-of-care as applicable for patients with complement deficiency. If not previously administered, vaccination should be administered no later than 1 week after the first crovalimab administration. Vaccination currency with vaccination against serotypes A, C, W, Y, and B should be maintained throughout the study, according to local guidelines for patients with complement deficiency. In the absence of clear local guidelines for *N. meningitidis*, the Advisory Committee on Immunization Practices 2020 Guidelines are recommended.

H. influenzae type B *and S. pneumoniae* vaccinations should be administered, in accordance with the most current local guidelines or standard-of-care as applicable for patients with complement deficiency. These vaccinations must be administered no later than 1 week after the first crovalimab administration.

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

4.5.5.2 Other Vaccinations

Any other vaccines (with the exception of those discussed in Section 4.5.5.1) should not be administered on the same day as a crovalimab administration but, ideally, after

completion of the loading series at a time point between Day+3 after a maintenance dose and Day−3 before the next maintenance dose administration.

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

Live vaccinations should be discussed with the Medical Monitor.

4.6 LABORATORY, BIOMARKER, AND OTHER BIOLOGICAL SAMPLES

4.6.1 Laboratory Analyses

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

4.6.1.1 Local Laboratory Analyses

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

- Hematology: RBC count, hemoglobin, hematocrit, platelet count, WBC count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and reticulocyte counts. A manual differential may be performed.
- Chemistry panel (serum or plasma): sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard-of-care for the region), glucose, BUN or urea, serum creatinine, serum cystatin C, total protein, albumin, phosphate, magnesium, calcium, total and direct bilirubin, ALP (alkaline phosphatase), ALT, AST, uric acid, and LDH
  - Note for serum cystatin C: If available and analysis is routinely performed locally, then results from this analysis shall be entered into the eCRF.
  - LDH should also be analyzed, in case of unplanned events, such as signs and symptoms of anemia, increasing fatigue, hemoglobinuria/hematuria, respiratory distress, or other unforeseen events, as clinically appropriate.
- Coagulation: PTT/aPTT and PT/INR, fibrinogen, and D-dimers
- Haptoglobin and free hemoglobin (if available)
- Hepatitis B virus serology: HBsAg at screening (for Switch patients and for switching C5 SNP patients only)
- Hepatitis C virus (HCV) serology: HCV antibody and (if HCV antibody positive) HCV RNA at screening (for Switch patients and for switching C5 SNP patients only)
- HIV serology at screening

- Direct Coombs test at screening
- Pregnancy test
  - All female patients of childbearing potential will have a serum pregnancy test at screening. Either urine or serum pregnancy tests will be performed at specified subsequent visits. Serum pregnancy test may be necessary in patients with oliguria or anuria. Additionally, at the end of the study, a urine pregnancy test will be performed by the patient no more than 2 days before the 46-week (approximately 10.5 months) safety telephone call. The patient should report the result of the pregnancy test during the telephone call. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Urinalysis, including dipstick and point-of-care testing (pH, specific gravity, glucose, protein/albumin, ketones, RBCs, and hemoglobin)
  - If there is a clinically significant positive result (i.e., confirmed by a positive repeat sample), urine will be sent to the laboratory for urinalysis, microscopy and culture (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). If there is a known explanation for a positive dipstick result (e.g., menses), it should be recorded, and there is no need to perform laboratory for microscopy and culture.
  - For Switch patients and for switching C5 SNP patients only, during the first 10 weeks on crovalimab, a urine sample should be sent directly to the laboratory for urinalysis, microscopy, urine protein, urine hemoglobin, urine creatinine, and urine microalbumin. After the first 10 weeks, if there is a clinically significant positive result from dipstick or point-of-care (POC) testing, urine will be sent to the lab for urinalysis, microscopy and culture.
- Culture of *Streptococcus pneumoniae* bacteria at screening, if clinical suspicion of pneumococcal-related HUS

For the assessments listed below, if available as per locally defined regulation, central laboratory testing is acceptable as per Appendix 10:

- ADAMTS13 activity levels at screening
- Shiga toxin testing or detection of Shiga toxin-producing Escherichia coli bacteria at screening
- Cobalamin C defect testing at screening

4.6.1.2 Central Laboratory Analyses

Instruction manuals and supply kits will be provided for all central laboratory assessments. The following samples will be sent to one or several central laboratories, to the Sponsor, or to a designee for analysis (see Appendix 6):

- Serum/plasma samples for analysis of:
  - LDH, creatinine, cystatin C, and BUN

  - Immunogenicity (ADA), PK, total C5 and free C5
  - DTDCs (for Switch patients and for switching C5 SNP patients only)
  - Free hemoglobin and haptoglobin
  - Complement activity (CH50) by LIA
  - sC5b-9
  - Anti-factor H autoantibodies
- Whole blood for analysis of genes of the complement system/coagulation cascade or known to be associated with TMA (see Appendix 8) will be collected Week 1 Day 2 (see Appendix 1). If the sample is missed on Week 1 Day 2, it can be collected at any other scheduled visit. For countries who participate in Research Biosample Repository (RBR), the sample may also be used for genetic analysis for patients who consent to RBR (see Section 4.6.4); otherwise the remainder of the sample will be destroyed.
- Urine for the analysis of exploratory biomarkers for kidney functions (see Appendix 7)
- ADAMTS13 activity levels, Cobalamin C defect testing, if centrally available
- *Known DGKE mutations should be documented in the medical records of the patient.*

Samples will be used in line with the objectives (see Section 2) of this study. Excess or unused samples may be used for assay development and validation, and for exploratory research to aid in the understanding of disease, drug mechanism of action and safety if permitted by country specific regulations (see Section 4.6.4.1).

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.6.4), biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data. Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Results from genetic analyses *and/or anti-factor H autoantibodies testing* may be shared with investigators upon request after the patient has discontinued study *treatment* or completed Week 25. The report is generated for research purposes and is

not provided for guiding future treatment decisions. In case an investigator shares results with patients, sites must comply with local regulations related to data protection and sharing of genetic information with patients (e.g., offering of genetic counselling before sharing results).

4.6.2 Electrocardiograms

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

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

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

If at a particular timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.7.1. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.6.3 Clinical Outcome Assessments

Patient-reported outcome (PRO) instruments will be completed to assess the treatment benefit of crovalimab. In addition, PRO instruments (described in Section 4.6.3.2) will enable the capture of each patient's direct experience with crovalimab.

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

- For adult patients (aged ≥18 years): FACIT-Fatigue, EORTC QLQ-C30 (selected scales), KDQoL (selected scales), and TSQM-9
- For adolescent patients (aged 12–17 years): PedsQL-MFS and PedsQL Core (physical functioning scale only)
- For Switch Cohort patients: Self-report version of the Patient Preference Questionnaire
- For all patients: EQ-5D-5L and self-report of the number of missed school or work days.

4.6.3.1 Data Collection Methods for Clinical Outcome Assessments

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

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor via site-based tablets to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The tablet and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. Only in the event that the electronic data system and web back-up becomes unavailable will the Sponsor instruct sites to collect the PRO data on the approved paper versions of the screenshots. All information collected on approved paper versions will need to be submitted to the electronic device vendor and entered electronically.

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

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be no more than 15 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.

- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.6.3.2 Description of Clinical Outcome Instruments

Functional Assessment of Chronic Illness Therapy–Fatigue

The FACIT-Fatigue (v4) is a validated, reliable self-report measure for use in a variety of conditions including anemia (Cella et al. 2005; Lai et al. 2011; Acaster et al. 2015). It consists of 13 items that assess fatigue using a 7-day recall period. Items are scored on a 0 ("Not at all") to 4 ("Very much so") response scale. Relevant items are reverse scored and all items are summed to create total scores where higher scores are indicative of better functioning (i.e., less fatigue). This measure will be administered to adult patients only (see Appendix 1).

European Organisation for Research and Treatment of Cancer Quality of Life–Core 30

The EORTC QLQ-C30 (v3) is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health status (GHS)/QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptom items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS/QOL items are scored on a 7-point scale that ranges from "very poor" to "excellent." Scale scores are converted to a 0–100 response scale in which higher scores indicate higher response levels (i.e., higher HRQoL, higher symptom severity). This measure will only be administered to adult patients. Patients will complete a truncated version of the measure (EORTC IL17) that includes only the Physical Functioning (5 items), Role Functioning (2 items), and GHS/QoL (2 items) scales.

Kidney Disease Quality of Life Questionnaire–36 Symptoms and Problems Scale

The KDQoL 36 is a reduced version of a validated self-report measure of symptoms and HRQoL effects specific to patients with kidney disease receiving dialysis (Hays et al. 1994; Korevaar et al. 2002). It consists of the SF12 (v2) (Ware et al. 1996) and an additional 24 items that are scored into three scales: Burden of Kidney Disease (4 items), Symptoms and Problems (12 items), and Effects of Kidney Disease on Daily Life (8 items). Items in the three kidney disease–specific scales are converted to a 0–100 response scale and averaged into their respective domains. Higher scores indicate better outcomes (e.g., less burden, lower symptom severity). For this study, only the Symptoms and Problems scale will be used and will only be administered to adult patients.

Treatment Satisfaction Questionnaire for Medications-9

The TSQM-9 is an abbreviated, validated version of the TSQM (v1.4) that includes 9 items to assess perceived effectiveness (3 items), convenience of medication (3 items), and global satisfaction with medication (3 items) (Atkinson et al. 2004, Bharmal et al. 2009). Items are scored into three respective domains that range from 0 to 100, with higher scores representing higher satisfaction. This measure will be administered to adult patients at Weeks 13 and 25.

Pediatric Quality of Life Core

The PedsQL Core (v4) is a valid, reliable measure for assessing HRQoL in healthy children and adolescents, and those with acute or chronic health conditions (Varni et al. 2001, 2007). Self-report versions are available for children and adolescents that contain developmentally appropriate language for defined age groups (e.g., 5–7, 8–12, 13–17 years). This version contains 23 items that are scored into four respective domains: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). Physical and psychosocial health summary scores as well as an overall total score can be created by further combining domains. Domain and total scores are converted to a 0–100 scale, with higher scores indicative of better functioning. For this study, only the Physical Functioning scale of the adolescent self-report version with a 1-week recall period (i.e., acute adolescent version) will be used for patients 12–17 years old, as the wording is the same for this scale in the 8–12 and 13–17 self-report versions.

Pediatric Quality of Life Multidimensional Fatigue Scale

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

Patient Preference Questionnaire

The Patient Preference Questionnaire is a two-item measure of treatment preference developed by the Sponsor. Patients are asked to indicate their preference for IV eculizumab/ravulizumab or SC crovalimab and indicate the top three reasons for their choice. This instrument will be administered to both adolescent and adult switch cohort patients. It will be administered only once at Week 17.

Missed School or Work Days

Patients will be asked to indicate whether they missed days of school or work within the previous 4 weeks because of aHUS, the number of days missed, and the number of days they were expected to attend. Adolescents will be asked to report missed days of school, whereas adults will be asked to self-report missed days of school (if applicable, e.g., college, university) and/or work.

EQ-5D-5L

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

4.6.4 Optional Samples for Research Biosample Repository

4.6.4.1 Overview of the Research Biosample Repository

The Research Biosample Repository is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

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

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

4.6.4.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form

by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.6.4) will not be applicable at that site.

4.6.4.3 Sample Collection

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

- Leftover serum, plasma, whole blood, and urine from the samples sent to the central laboratories, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing, whole exome sequencing, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole genome sequencing and whole exome sequencing provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

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

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

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

4.6.4.4 Confidentiality

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

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

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

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

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

4.6.4.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

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

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

4.6.4.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data.

If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

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

4.6.4.7 Monitoring and Oversight

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

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

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

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

If a female patient of childbearing potential becomes pregnant while on crovalimab, continuation on study treatment may be permitted based on the investigator's clinical judgment, and in consultation with the Medical Monitor.

Study treatment will continue, only if it is in the best interest of the patient, after an assessment of the risks and benefits conducted by the investigator. For this decision, the investigator must consider the potential risks related to the study treatment, the risks related to discontinuing treatment, and the risks related to switching to another C5 inhibitor (e.g., DTDC-mediated Type III hypersensitivity reactions) in a pregnant female with aHUS. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. If the investigator decides to continue treatment, he or she must inform the Medical Monitor before proceeding.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. 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.

Patients who discontinue crovalimab and switch to treatment with another C5 inhibitor should remain in safety follow-up (see detailed monitoring guidance in Section 5.1.1.5).

Patients who discontinue crovalimab and meet criteria for discontinuation outlined in, Section 4.7.3 and want to remain eligible to restart crovalimab after a TMA recurrence should follow guidance outlined in Section 4.7.2 and Appendix 3.

4.7.2 Patients Who Discontinue Crovalimab and are Eligible to Remain in Long-term Follow-Up and Potentially Restart

Crovalimab is intended for life-long treatment. However, its discontinuation after achieving remission may be appropriate for selected patients. Patients who discontinue crovalimab after achieving cTMAr and do not switch to another C5 inhibitor will be encouraged to remain in the study if they fulfill all of the following criteria:

- Completed at least 24 weeks on treatment (i.e., after completing Week 25 visit)
- Achieved and maintained cTMAr *(if naïve patient) or maintained TMAc (if switch patient) while* on crovalimab for at least the 3 consecutive months immediately preceding crovalimab discontinuation
- Discontinuation of treatment was agreed upon between the investigator and the patient
- Patient must have a calculated creatinine clearance $\geq$30 mL/min
- Patient did not receive a renal transplant
- Patient does not have a history of prior aHUS relapse

Patients who do not fulfill these criteria may discontinue crovalimab at any time and will discontinue from the study after their safety telephone call 46 weeks (approximately 10.5 months) after treatment discontinuation.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Patients who discontinue treatment, meet all the criteria above and choose to remain enrolled in the study will continue to undergo regular follow-up evaluations for up to 2 years, as specified in Appendix 3.

If such a patient is subsequently diagnosed with TMA recurrence, they may have the option to resume crovalimab. If re-starting crovalimab treatment is considered to be in the best interest of the patient by the Investigator, the Medical Monitor should be informed, AND the following criteria are met:

- Patient has remained in follow-up and has continued to undergo study assessments (as scheduled)

- Patient did not receive another complement inhibitor at any point after crovalimab discontinuation
- Patient did not participate in another interventional clinical trial at any point after crovalimab discontinuation
- Patient should re-initiate treatment with crovalimab within 28 days of diagnosis of TMA recurrence
- Patient should meet the vaccination requirements, as per Section 4.1.1.
- For female patients of childbearing potential, an agreement to remain abstinent or use contraception, as per Section 4.1.1.
- Patient will restart treatment with crovalimab at the weight-appropriate regimen (Table 1, using weight at the time of restart), and will be followed, as per the Schedule of Activities, beginning on Study Day 1 (Appendix 1)
- Patients who re-start treatment with crovalimab following TMA recurrence should not attempt another discontinuation for at least 24 weeks.

Patients who restart crovalimab after discontinuation will do so according to the following dosing regimen considerations:

- Patients with interruptions in crovalimab treatment of ≥28 days and <3 months shall restart crovalimab treatment with the weight-based IV loading dose on Week 1 Day 1 and the Q4W maintenance dose starting on Week 1 Day 2, instead of Week 5.
- Patients with interruptions in crovalimab treatment of ≥3 months shall restart crovalimab treatment with the weight-based full loading dose series, followed by Q4W maintenance doses from Week 5 onwards, as per Section 4.3.2.
- If a patient restarts treatment with crovalimab, he or she must agree to remain in treatment for at least 24 weeks.

The Medical Monitor should be informed of the TMA event, prior to reinitiating crovalimab treatment.

Patients who respond to the resumption of crovalimab and then choose to discontinue crovalimab treatment a second time, will discontinue from the study after completing their safety follow up visits (see Appendix 1), and another re-initiation of treatment will not be allowed. Patients who do not respond to the resumption of crovalimab may discontinue crovalimab at the discretion of the investigator and will discontinue from the study after completing their safety follow-up site visit and safety telephone call. Any unscheduled visits to monitor response during the resumption of crovalimab should be entered into eCRFs, as per Appendix 1.

4.7.3 Patient Discontinuation from the Study

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

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

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

Before considering a patient lost to follow-up, at least three different documented attempts to contact them should be made. The attempts should include but not be limited to:

- A written contact (e.g., letter by certified mail or email with read receipt)
- Contact with the patient's primary care physician (where the patient has consented to this type of contact)

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the Investigator.

4.7.4 Study Discontinuation

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

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

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

4.7.5 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Crovalimab is *approved for the treatment of PNH in some countries and clinical trials in* aHUS *are* ongoing. The safety plan for patients in this study is based on clinical experience with crovalimab in the ongoing Study BP39144 as well as on the known class effects of available marketed C5 inhibitors. The anticipated important safety risks for crovalimab, as well as measures intended to avoid or minimize such toxicities, are outlined below. Refer to the Crovalimab Investigator's Brochure for a complete summary of safety information.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria (see Section 4.1.1 and Section 4.1.2, respectively) and close monitoring. Details regarding safety reporting for this study are provided in Section 5.4.

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

5.1.1 Risks Associated with Crovalimab

5.1.1.1 Meningococcal Infection

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

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

Patients in clinical studies of crovalimab will receive meningococcal vaccinations as described in Section 4.5.5.1.

All patients should be counseled about the risks and common signs and symptoms of meningococcal infections as well as antibiotics therapy. Patients should be closely monitored for early signs and symptoms of meningococcal infection, should be evaluated immediately if an infection is suspected and treated with antibiotics if necessary. Monitoring of patients for meningococcal infections should be continued for at least 46 weeks (approximately 10.5 months) after the last dose of crovalimab. The investigator should discuss continuation of crovalimab with the Medical Monitor for patients who are undergoing treatment for serious meningococcal infections.

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

5.1.1.2 Other Infections

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

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

5.1.1.3 Type III Hypersensitivity Reactions Related to Drug-Target-Drug Complex Formation

Type III hypersensitivity may occur due to the transient formation of DTDCs made of eculizumab or ravulizumab, crovalimab, and C5 in patients switching from eculizumab or ravulizumab to crovalimab. Such DTDCs could also form if patients transition from crovalimab to another C5 inhibitor that binds to a different epitope than crovalimab, upon discontinuation from or completion of a clinical study of crovalimab (see Section 1.2.2.1 for details). Characteristics of Type III hypersensitivity reactions associated with DTDC formation may include:

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

The renal manifestations of Type III hypersensitivity reactions are of particular concern in the aHUS patient population.

To minimize the risk for patients, monitoring guidelines are provided below for enhanced monitoring during study and for patients who discontinue crovalimab and switch to other C5 inhibitors. Guidelines for management of clinical manifestations of DTDCs are provided in Table 2.

5.1.1.4 Enhanced Monitoring during the Study for Patients Switching to Crovalimab upon Enrollment

Patients who switch to crovalimab from eculizumab or ravulizumab should be closely monitored during the first few weeks of switching to crovalimab, because of the potential risk of developing a DTDC–mediated Type III hypersensitivity reaction. This includes patients in the Switch Cohort, as well as switching C5 SNP patients, who received their

last dose eculizumab or ravulizumab less than 5.5 drug half-lives prior to Week 1 Day 1 of crovalimab treatment (i.e., 10 weeks for eculizumab and 41 weeks for ravulizumab).

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

Blood samples for monitoring will be collected after the first administration of crovalimab, then once weekly for the first 5 weeks (Weeks 1–5 of crovalimab administration), then Q2W through Week 9 (Weeks 7 and 9 of crovalimab administration), and Q4W through Week 25 of crovalimab administration (see Appendix 1).

The following laboratory assessments will be collected and assessed locally, as detailed in Section 4.6.1.1: safety laboratory assessments (chemistry and hematology), urinalysis, vital signs/limited physical exams, adverse event reporting, monitoring for hemolysis and transfusions, and LDH.

5.1.1.5 Monitoring for Patients Who Discontinue Crovalimab and Switch to Eculizumab or Ravulizumab after Study Discontinuation

Patients might discontinue study treatment with crovalimab and switch to treatment with eculizumab or ravulizumab, at the discretion of the treating physician. Such patients should remain in safety follow-up because of the potential risk of developing a DTDC–mediated Type III hypersensitivity reaction during the first few weeks of switching from one C5 inhibitor to another. Blood samples for monitoring will be collected after the first administration of eculizumab (or ravulizumab), then once weekly for the first 5 weeks (Weeks 1–5), and then at Week 7 and Week 9 after switching from crovalimab to eculizumab or ravulizumab (detailed in Appendix 2).

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

Due to the potential risk of DTDC-mediated Type III hypersensitivity reactions, it is recommended that patients who discontinue from study and choose not to remain in

safety follow-up while switching to eculizumab or ravulizumab also be monitored by the treating physician in the same manner.

5.1.1.6 Other Hypersensitivity Reactions and Infusion-Related Reactions

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

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

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

5.1.1.7 Injection-Site Reactions

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

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

5.1.1.8 Immunogenicity

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

5.1.2 Management of Patients Who Experience Adverse Events

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

5.1.2.1 Dose Modifications

Dose modification (only allowed from Week 9) is only required if the patient's body weight changes by ≥ 10% (compared with screening or the visit when the latest dose modification occurred, whichever is later) to exceed or become equal to 100 kg or to fall below 100 kg during the course of therapy.

5.1.2.2 Treatment Interruption

There are no planned treatment interruptions of crovalimab in this study.

If a dose of crovalimab is missed, the dose must be administered as soon as possible and then resume the regular dosing schedule *(i.e. following the delayed dose being administered, the next dose must be administered as per the original IXRS schedule)*. Two doses should not be administered on the same day to make up for missed doses. Resuming treatment after longer than 28 days of interruption for Q4W regimens should

be performed in consultation with the Medical Monitor (see Section 4.7.2 for guidance on resuming dosing regimen).

5.1.2.3 Management Guidelines

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

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

Table 2 Guidelines for Management of Patients Who Experience Adverse Events

Event	Action to Be Taken
Anaphylaxis	• If an anaphylactic reaction occurs, stop administration and permanently discontinue crovalimab. • Follow anaphylaxis treatment guidelines in Appendix 4.
Infusion-Related Reactions	
IRR: Grade 1, 2, or 3	• The crovalimab infusion should be temporarily held until resolution of symptoms to Grade 1 or better. • Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Crovalimab may be continued at the investigator's discretion.
IRR: Grade 4	• The crovalimab infusion should be stopped and not re-initiated. Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Discontinue crovalimab.
Injection-Site Reactions	
ISR Grade 1 or 2	• Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Crovalimab may be continued at the investigator's discretion.
ISR Grade 3 [b] or 4	• Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Crovalimab may be continued at the investigator's discretion and in discussion with the Medical Monitor. • Discontinue crovalimab if Grade 4 ISR occurs.
Type III Hypersensitivity Reactions (Serum Sickness [a])	
General Guideline	• Upon clinical presentation of a suspected Type III hypersensitivity reaction (initial manifestation of vasculitis, purpura, pruritus, arthralgia, etc.), treat according to severity. [a]

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

Event	Action to Be Taken
Grade 1 or 2 signs and symptoms	• For arthralgia, administer analgesics. NSAIDs should be avoided in patients with renal disease and/or thrombocytopenia. • For pruritus and rash, administer anti-histamines and topical corticosteroids. • Monitor kidney function and perform urinalysis. • Continue crovalimab.
Grade 3 signs and symptoms	• For high fever (e.g., temperature >38.5°C [>101.3°F]), more severe arthritis and arthralgias, or more extensive rashes, including extensive vasculitic eruptions, administer oral or IV methylprednisolone 1–2 mg/kg (or equivalent dose of other glucocorticoid).Glucocorticoids can frequently be rapidly tapered, with a total duration of therapy of less than 1 week. However, withdrawal will occasionally result in recurrence of the symptoms, in which case glucocorticoids should be restarted and tapered more slowly. • Monitor kidney function and perform urinalysis. • Continue crovalimab.
Grade 4 signs and symptoms	• Treat as Grade 3 reaction above. • Crovalimab may be continued at the investigator's discretion and in discussion with the Medical Monitor.
Infections	
Meningococcal meningitis	• Treat according to standard of care. • Discuss continuation of crovalimab with Medical Monitor.
Any other infection	• Treat according to standard-of-care on a case-by-case basis, depending on signs and symptoms. • Discuss continuation of crovalimab with Medical Monitor for Grade 3 infections that persist for >7 days, or for any Grade 4 infection.
Other Treatment-Related Toxicities Not Described Above	
Grade 1, 2, or 3	• Treat according to local practice. • Crovalimab may be continued at the investigator's discretion.
Grade 4	• Treat according to local practice. • Discontinue crovalimab.

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

Event	Action to Be Taken
Hy's Law	• Treat according to local practice. • Discontinue crovalimab

IRR = infusion-related reaction; ISR = injection-site reaction; NSAID = non-steroidal anti-inflammatory drug.

[a] Serum sickness and serum sickness-like reactions (Wener 2020).

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, Xray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
  - This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Type III hypersensitivity reactions (see Section 5.1.1.3).
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

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

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

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

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

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

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

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

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related and Injection-Site Reactions

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

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.

- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's

Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

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

If no other reason can be found to explain the combination of increased ALT/AST and total bilirubin, such as viral hepatitis A, B or C; preexisting or acute liver disease; or another drug capable of causing the observed injury, the presence of active hemolysis due to underlying disease should also be excluded as a contributing factor (FDA 2009). The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event); either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of aHUS.

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

If the death is attributed solely to progression of aHUS, "atypical hemolytic uremic syndrome progression" should be recorded on the Adverse Event eCRF.

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

5.3.5.9 Preexisting Medical Conditions

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

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events

on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Atypical Hemolytic Uremic Syndrome

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

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

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

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
  - In some cases, a medication error may be intercepted prior to administration of the drug.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse
  - In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For crovalimab, adverse events associated with special situations should be recorded as described below for each situation:

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

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

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.

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

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

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

5.3.5.13 Safety Biomarker Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours

after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

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

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

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

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

5.4.1 Medical Monitors and Emergency Medical Contacts

Medical Monitoring Contact Information for All Sites

To ensure the safety of study patients, access to Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service (if necessary), and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

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

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

Instructions for reporting serious adverse events that occur >46 weeks (approximately > 10.5 months) after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 46 weeks (approximately 10.5 months) after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF.

Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

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

5.4.3.2 Abortions

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

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

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

5.4.3.3 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the Crovalimab Investigator's Brochure.

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The primary purpose of this study is estimation of the efficacy of crovalimab as measured by the proportion of patients in the *primary analysis population (as defined in Table 4) of the* Naive Cohort reaching cTMAr status within the first 24 weeks on treatment.

The sample size for this study is based on clinical and operational considerations, taking into account the low incidence and prevalence of aHUS, and the low number of patients who are currently being treated with a complement inhibitor.

Given these limitations as well as the strict inclusion/exclusion criteria of the study which were defined to enroll patients with a primary complement-mediated aHUS, approximately 40 patients in the *primary analysis population of the* Naive Cohort and approximately 40 patients in the Switch Cohort are deemed sufficient to adequately characterize the efficacy and safety of crovalimab in aHUS. Additionally, patients in the C5 SNP cohort will be enrolled with no minimum sample size pre-specified. It is expected that up to 5 patients may be enrolled in the C5 SNP Cohort.



The drop-out levels for this study are expected to be low (Legendre et al. 2013). It is expected that some patients may not be included in the primary analysis *population* due to their aHUS diagnosis being ruled out post-enrollment (*Table 5*). Recruitment to the Naive Cohort may therefore be kept open to allow for additional enrollment allowing replacement of non-complement mediated aHUS patients whose diagnosis was subsequently ruled out post-enrollment, in order to achieve the target sample size of 40 patients for the primary efficacy analysis*, i.e., included in the primary analysis population*.

6.2 *ANALYSIS POPULATIONS*

The analysis populations of the study are defined in Table 5.

[redacted]



6.3 SUMMARIES OF CONDUCT OF STUDY

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

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized descriptively, including using number of records per variable, means, standard deviations, medians, and ranges (continuous variables) or proportions (categorical variables), as appropriate.

These characteristics may include age, sex, race/ethnicity, weight, body mass index, body temperature, baseline LDH values, history of LDH levels (for Switch Cohort), and other laboratory parameters of interest. Summaries will be presented overall and by treatment cohort.

6.5 EFFICACY ANALYSES

[redacted]

[redacted]

[redacted]

[redacted]

6.5.2 Primary Efficacy Endpoint

The primary efficacy objective for this study is to assess the effect of crovalimab therapy in treatment-naive (Naive) patients (primary analysis population) by calculating the proportion of patients reaching cTMAr at any time from baseline to Week 25 (after 24 weeks on treatment).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.5.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints are described in Section 2.1.2.

Categorical variables will be summarized using number of patients, and proportion of patients with corresponding 95% CI. Change from baseline will be summarized using shift tables where applicable.

Continuous variables including change from baseline will be summarized using descriptive statistics including mean, median, standard deviation and range. For eGFR, hematologic parameters (platelet count, LDH, hemoglobin) and FACIT, additional statistical modeling may be performed to evaluate changes over time.

Time-to-event endpoints will be analyzed using Kaplan-Meier methodology, and Kaplan-Meier curves will be produced. Median time-to-event, along with 95% CIs will be summarized if reached.

End of cTMAr is considered to occur when all of the following criteria are met during the same visit, and are confirmed at an assessment that takes place at least 4 weeks (a minimum of 26 days) later:

- *Platelet count < LLN, and*
- *LDH > ULN, and*
- *≥ 25% increase in serum creatinine from baseline, and > ULN*

TMA control (TMAc) is considered not maintained if all of above criteria are met during one of the visits between baseline and Week 25 and are confirmed at an assessment that takes place at least 4 weeks (a minimum of 26 days) later.

Further details about these analyses will be provided in the SAP.

6.5.4 Exploratory Efficacy Endpoints

All exploratory efficacy endpoints have been defined in Section 2.1.3. They will be described with summary statistics, tables, listings, and graphs as appropriate.

For patients in the C5 SNP Cohort, exploratory descriptive analyses will be performed to describe the clinical course of TMA-relevant parameters (e.g., platelets, LDH, serum creatinine) over time.

Separate exploratory descriptive analyses will be conducted to describe the clinical course of patients who discontinue crovalimab after achieving cTMAr and remain in study follow-up.

6.6 SAFETY ANALYSES

Safety analyses will be performed on the safety evaluable population, defined as all patients who received at least one dose of study drug. Summaries will be presented overall and by treatment cohort.

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

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

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

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

6.7 PHARMACOKINETIC ANALYSES

The PK analyses will be performed on the PK-evaluable population, defined as all patients who received at least one dose of study treatment, and have at least one post-dose concentration result. For all patients, serum concentrations of crovalimab will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation. Concentrations of ravulizumab and eculizumab at the time of crovalimab initiation will be presented descriptively including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Non-linear mixed effects modeling will be used to analyze the dose–concentration-time data of crovalimab. Population PK parameters, such as total exposure (area under the concentration–time curve), maximum serum concentration observed, clearance, and volume of distribution will be estimated. The influence of various covariates, such as age, sex, and body weight, on these parameters will be investigated graphically. Interpatient variability and drug accumulation will be evaluated.

Additional PK analyses may be conducted as appropriate. The relationship between PK and efficacy and safety endpoints may also be explored. Data may be pooled with data from other studies evaluating crovalimab. These analyses will be reported in a dedicated report.

6.8 IMMUNOGENICITY ANALYSES

The immunogenicity-evaluable population will consist of all patients who have received at least one dose of study treatment and have at least one *post-baseline* ADA assessment.

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

The relationship between ADA status and safety, efficacy, pharmacokinetics, and biomarker endpoints may be analyzed and reported via descriptive statistics. *Immunogenicity and loss of PK and PD analyses are described in more detail in the SAP.*

6.9 BIOMARKER ANALYSES

The absolute value and change over time in PD biomarkers will be presented using summary statistics, including means, median, range, standard deviations, and coefficients of variation. Genetic aberrations as well as serum/plasma/urine biomarker will be summarized and correlated with efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity endpoints and reported descriptively.

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

6.10 HEALTH STATUS UTILITY ANALYSES

Summary statistics will be calculated for the EQ-5D-5L health utility index−based and VAS scores, and changes in scores over the course of the study will be summarized descriptively. Additional economic modeling analyses will be conducted post hoc to support the integrated evidence plan and detailed in relevant analysis plans outside of the study SAP.

6.11 INTERIM ANALYSIS

No interim efficacy analyses are planned. Interim analyses for safety, PK, PD and immunogenicity may be performed as part of JMC evaluations, at specific timepoints, to monitor patient safety (see Section 3.1.1), or to support regulatory submissions.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

PRO data will be collected using an electronic device provided by a vendor (see Section 7.3 for details). In the event that the electronic device and web back-up is unavailable, only the approved paper versions of the screenshots provided to the investigators by the Sponsor should be completed. All information collected on approved paper versions will need to be submitted to the electronic device vendor and entered electronically.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC PATIENT REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server.
Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies

conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

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

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

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

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

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

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative(s), per local regulations. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

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

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

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

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

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

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1 Schedule of Activities

Study Week	Screening [a]	All Enrolled Patients															
															Extension Period		Study Discontinuation	
		Week 1 Day 1	*Week* 1 Day 2	2	3	4	5	7	9	13	17	21	25	29	Week 33 and Q8W Thereafter	Week 49 and Q16W Thereafter	Safety Follow-Up Site Visit [cc] (24 weeks after last dose)	Safety Telephone Call [cc] (46 weeks after last dose)
Informed consent/ assent [b]	x																	
Demographic data [c]	x																	
Medical history and baseline conditions [d]	x																	
Direct Coombs test	x																	
ADAMTS13 Activity, STEC-HUS test, *Streptococcus pneumoniae* test, cobalamin C defect, [e]	x																	

Appendix 1: Schedule of Activities

Study Week	Screening [a]	All Enrolled Patients															
															Extension Period		Study Discontinuation
		Week 1 Day 1	*Week* 1 Day 2	2	3	4	5	7	9	13	17	21	25	29	Week 33 and Q8W Thereafter	Week 49 and Q16W Thereafter	Safety Follow-Up Site Visit [cc] (24 weeks after last dose)	Safety Telephone Call [cc] (46 weeks after last dose)
Neisseria meningitidis, *Haemophilus influenzae* type B and *S. pneumoniae* vaccinations [f]	x																	
Viral serology (HIV, HBV and HCV) [g]	x																	
Physical examination [h]	x	x					x		x	x	x	x	x		x	x	x	
Weight and height [h]	x						x				x		x		Week 41 only	x	x	
Vital signs [i]	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	
Pregnancy test [j]	x	x					x		x	x	x	x	x		x	x	x	x
Concomitant medications [k]	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x

Appendix 1: Schedule of Activities

Study Week	Screening [a]	All Enrolled Patients																
															Extension Period		Study Discontinuation	
		Week 1 Day 1	*Week* 1 Day 2	2	3	4	5	7	9	13	17	21	25	29	Week 33 and Q8W Thereafter	Week 49 and Q16W Thereafter	Safety Follow-Up Site Visit [cc] (24 weeks after last dose)	Safety Telephone Call [cc] (46 weeks after last dose)
Hematology, including platelet count [l]	x	x		x	x	x	x	x	x	x	x	x	x		x	x	x	
Coagulation [m]	x	x									x		x		Q16W	x	x	
Local free hemoglobin and haptoglobin (if available) [n]	x	x		x	x	x	x	x	x	x	x	x	x		x	x	x	
Local chemistry, including LDH [o, p], BUN [o, p], serum cystatin C [n, o, p,] and serum creatinine [o, p]	x	x		x	x	x	x	x	x	x	x	x	x		x	x	x	
Urinalysis [q]	x	x		x	x	x	x	x	x	x	x	x	x		x	x	x	
12-Lead ECG [r]	x						x						x				x	
Adverse events [s]	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x

Appendix 1: Schedule of Activities

		All Enrolled Patients															
														Extension Period		Study Discontinuation	
Study Week	Screening [a]	*Week* 1 Day 1	*Week* 1 Day 2	2	3	4	5	7	9	13	17	21	25	29	Week 33 and Q8W Thereafter	Week 49 and Q16W Thereafter	Safety Follow-Up Site Visit [cc] (24 weeks after last dose)	Safety Telephone Call [cc] (46 weeks after last dose)
Serum ADA sample for crovalimab [t, u, v]		x		x	x	x	x		x	x	x	x	x		x	x	x	
Serum PK sample for crovalimab [t, u, v]		x	x	x	x	x	x		x	x	x	x	x		x	x	x	
Serum PK sample for eculizumab or ravulizumab (Switch and switching C5 SNP patients only) [t, u, v]		x																
Serum sample for central analysis of LDH, BUN, cystatin C, creatinine, and haptoglobin [v]	x	x		x	x	x	x	x	x	x	x	x	x		x	x	x	
Serum sample for free hemoglobin [v]	x	x		x	x	x	x	x	x	x	x	x	x		x	x	x	

Appendix 1: Schedule of Activities

		All Enrolled Patients															
														Extension Period		Study Discontinuation	
Study Week	Screening [a]	*Week* 1 Day 1	*Week* 1 Day 2	2	3	4	5	7	9	13	17	21	25	29	Week 33 and Q8W Thereafter	Week 49 and Q16W Thereafter	Safety Follow-Up Site Visit [cc] (24 weeks after last dose)	Safety Telephone Call [cc] (46 weeks after last dose)
Plasma and serum samples for PD biomarkers [t, u, v]		x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	
Blood samples for genetic testing and anti-FH-autoantibody [v, w]		x																
Serum sample for DTDC (Switch and selected C5 SNP Cohorts only) [u, v, x]		x	x	x	x	x	x	x	x	x	x	x	x					
Leftover urine for biomarker [y]		x		x	x	x	x	x	x	x	x	x	x		x	x	x	

Appendix 1: Schedule of Activities

Study Week	Screening [a]	All Enrolled Patients															
														Extension Period		Study Discontinuation	
		Week 1 Day 1	*Week* 1 Day 2	2	3	4	5	7	9	13	17	21	25	29	Week 33 and Q8W Thereafter	Week 49 and Q16W Thereafter	Safety Follow-Up Site Visit [cc] (24 weeks after last dose)	Safety Telephone Call [cc] (46 weeks after last dose)
FACIT-Fatigue, EORTC QLQ-C30 scales (adults only) [z]		x		x			x		x		x		x		Q16W [aa]	Q16W [aa]	x	
KDQoL (adults only) [z]		x					x		x		x		x		Q16W [aa]	Q16W [aa]	x	
PedsQL Core and PedsQL MFS (adolescents only) [z]		x		x			x		x		x		x		Q16W [aa]	Q16W [aa]	x	
TSQM-9 (adults only) [z]										x			x					
Missed School/Work Days and EQ-5D-5L [z]		x					x		x		x		x		Q16W [aa]	Q16W [aa]	x	

Appendix 1: Schedule of Activities

		All Enrolled Patients															
															Extension Period		Study Discontinuation	
Study Week	Screening [a]	*Week* 1 Day 1	*Week* 1 Day 2	2	3	4	5	7	9	13	17	21	25	29	Week 33 and Q8W Thereafter	Week 49 and Q16W Thereafter	Safety Follow-Up Site Visit [cc] (24 weeks after last dose)	Safety Telephone Call [cc] (46 weeks after last dose)
Patient Preference Questionnaire (Switch Cohort only) [z]											x							
Crovalimab administration [aa]		x	x	x	x	x	x		x [bb]	x [bb]	x [bb]	x [bb]	x [bb]	x	Q4W [bb]	Q4W [bb]		

ADA = anti-drug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 deficiency; aHUS = atypical hemolytic uremic syndrome; ALP = alkaline phosphatase; anti-FH = anti-factor H autoantibodies; epsilon; DTDC = drug-target-drug complexes; eCRF = electronic Case Report Form; EORTC = European Organisation for Research and Treatment of Cancer; EoT = End of Treatment; FACIT = Functional Assessment of Chronic Illness Therapy; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; IV = intravenous; KDQoL = Kidney Disease Quality of Life; LDH = lactate dehydrogenase; MFS = Multidimensional Fatigue Scale; PD = pharmacodynamic; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetic; POC = point of care; PRO = patient-reported outcomes; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; Q24W = every 24 weeks; QLQ-C30 = Quality of Life Questionnaire-Core 30; screen = screening; SC = subcutaneous; STEC-HUS = Shiga toxin-producing Escherichia coli hemolytic uremic syndrome; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9.

Notes:

Appendix 1: Schedule of Activities

All assessments should be performed within ±2 days of the scheduled visit. All assessments should be performed prior to dosing unless otherwise specified. *Patients should be assessed for drug toxicity prior to each dose; dosing will occur only if the clinical assessment and any available local laboratory test values are acceptable.* Crovalimab may be administered within ±2 days of the scheduled day, except the Week 1 Day 2 loading doses (Section 4.3.2.1), which should be administered on the scheduled day. For switch patients, the Week 1 Day 1 crovalimab dose may be administered with a window of +2 days when switching from eculizumab and +7 days when switching from ravulizumab (as per eculizumab and ravulizimab labels).

If the Screening Visit date and enrollment date occur on the same calendar day, it is not necessary to duplicate sample collection between the Screening Visit and the Week 1 Day 1 study visit.

Patients have the option to utilize mobile nursing only for study visits on Weeks 13, 21, and 33.

Additional (unscheduled) visits outside the specified visits are permitted at the discretion of the investigator. Procedures, tests, and assessments will be performed at the discretion of the investigator, but in case of aHUS symptomatology at a minimum the following tests should be performed for study purposes: LDH, platelet count, serum creatinine, BUN, hematology panel, urinalysis, as well as samples for PK, PD, ADA, (cystatin C and haptoglobin local values if available). Any procedures, tests, or assessments performed locally at the unscheduled visits must be recorded on the eCRFs. LDH, serum creatinine, BUN, cystatin C, haptoglobin, PK, PD, and ADA samples should also be sent to the central laboratory per instructions in the laboratory manual. For other tests, *any available* local laboratory results may be used for unscheduled visit testing. Adverse events and vital signs must be recorded for each unscheduled visit.

Switching C5 SNP patients are defined as patients with known C5 polymorphisms who received their last dose of eculizumab or ravulizumab less than 5.5 drug half-lives prior to Day 1 of crovalimab treatment (i.e., 10 weeks for eculizumab and 41 weeks for ravulizumab).

[a] Treatment-naive patients/C5 SNP patients: Screening = Day −7 to Day 1; Switch Patients: Screening = Day −28 to Day 1.

[b] Obtain written informed consent (or patient's assent and legal representative written informed consent if patient is <18 years of age and/or unable to give consent) before collection of any data. Patients will be enrolled after giving informed consent and/or assent (when appropriate).

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

[d] Medical history and baseline conditions, including clinically significant diseases, surgeries, biopsies, cancer history (including prior cancer therapies and procedures), aHUS history (including genetic factors causing aHUS, if available, dates of diagnosis and prior therapies, including dialysis), reproductive status (for female patients), 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.

[e] For Naive cohort only: If the results for these tests are not available prior to informed consent then the tests for STEC-HUS, ADAMTS13 activity, *S. pneumoniae* (positive chest X-ray or culture, only if suspicion) and Cobalamin-C defect (demonstrated by blood levels of total homocysteine [tHcy] $by \geq 3 \times ULN$ and blood or urine levels of methylmalonic acid [MMA] $by \geq 3 \times ULN$, and/or MMACHC gene mutation) must be performed during screening. *In case one of the laboratory parameters (MMA or homocysteine) is normal, testing of the alternative laboratory parameter is not required.* For patients who have received blood product transfusions, ADAMTS13 testing must be performed prior to transfusion. If this was not performed, ADAMTS13 testing must be performed as early as possible after the blood product transfusion, and again only once 14–21 days after the transfusion. Results of MMACHC mutation tests performed at any time can be used for eligibility assessment, rather than repeating such tests. For Switch and C5 SNP cohorts only. The tests for Cobalamin-C defect should be performed as described above, only if not documented in the medical records of the patient. The tests for STEC-HUS, ADAMTS13, and *S. pneumoniae* should not be performed or repeated at screening for patients in the Switch and C5 SNP cohorts. If available, documentation of test results performed prior to study enrollment will be recorded in the eCRF.

[f] Vaccination against *N. meningitidis* serotypes A, C, W, and Y should be administered < 3 years prior to initiation of crovalimab treatment. Vaccination against serotype B must be administered in accordance with most current local guidelines or standard-of-care as applicable for patients with complement deficiency. If not previously administered, vaccination should be administered no later than 1 week after the first crovalimab administration. Vaccination currency with vaccination against serotypes A, C, W, Y, and B should be maintained throughout the study according to local guidelines for patients with complement deficiency. In the absence of clear local guidelines for Neisseria meningitidis, the Advisory Committee on Immunization Practices 2020 Guidelines are recommended.
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.

[g] HBsAg and HCV antibody for Switch patients and switching C5 SNP patients only. 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. HIV serology must be performed for all Switch, Naive and C5 SNP patients.

[h] 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 at the visits indicated in the table. Abnormalities observed at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Height and weight will be recorded at screening for all patients and height and weight will also be recorded at Weeks 5, 17, 25, 41, 49 and every 16 weeks thereafter. Each new or worsened clinically significant abnormality should be recorded on the Adverse Event eCRF. Each assessment should be performed before administration of the crovalimab dose.

[i] 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. Assessments should be performed prior to crovalimab dose administration.

[j] Pregnancy tests will be conducted for all 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 within 2 days prior to the final telephone call follow-up (i.e., 46 weeks 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.

[k] Report any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 28 days prior to enrollment until 46 weeks after the final dose of study drug *(for exceptions see Section 4.1.1)*.

[l] Hematology parameters will be measured by a local laboratory, and must include WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells) and reticulocyte counts. A manual differential may be performed. Samples should be collected prior to crovalimab dose administration. Platelet count and a hematology panel will also be collected at any unscheduled visit due to aHUS symptomatology.

[m] Coagulation parameters include locally assessed PTT/aPTT and PT/INR, fibrinogen, and D-dimers. Samples should be collected prior to crovalimab dose administration.

[n] If available and analysis is routinely performed locally, then results from this analysis shall be entered into the eCRF.

[o] Chemistry panel includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, serum creatinine, total protein, albumin, phosphate, magnesium, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, and LDH. Samples should be collected prior to crovalimab dose administration. In countries where serum bicarbonate is not considered a standard chemistry measurement (e.g., Japan), serum bicarbonate is not required as a laboratory study in the screening or on-study serum measurements. LDH, BUN, cystatin C, and creatinine should be measured at any unscheduled visit due to aHUS symptomatology.

[p] Any tests performed locally must be recorded on the corresponding eCRFs.

[q] Urinalysis includes dipstick or POC (e.g., pH, specific gravity, glucose, protein/albumin, ketones, RBCs, and hemoglobin). If there is a clinically significant positive result (i.e., confirmed by a positive repeated sample), urine will be sent to the laboratory for urinalysis, microscopy and culture (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). If there is a known explanation for the positive dipstick or POC result (e.g., menses), it should be recorded and there is no need to perform laboratory for microscopy and culture. Samples should be collected prior to crovalimab dose administration. Switch Cohort patients and switching C5 SNP patients only: During the first 10 weeks on crovalimab, a urine sample should be sent directly to the laboratory for urinalysis, microscopy, urine protein, urine hemoglobin, urine creatinine, and urine micro-albumin. After the first 10 weeks, if there is a clinically significant positive result from dipstick or POC testing, urine will be sent to the lab for urinalyis, microscopy and culture.

[r] Performed locally. If screening ECG is abnormal, repeat at Week 1 Day 1 prior to the first dose of crovalimab. If screening and Week 1 Day 1 occur on the same day, do not repeat. After Week 25 assessment, ECGs should be performed only if clinically indicated. Assessment should then be performed prior to crovalimab dose administration. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[s] After informed consent has been obtained but prior to initiation of crovalimab, only serious adverse events caused by a protocol-mandated intervention should be reported. Subsequently, all adverse events will be reported until 46 weeks after the last dose of crovalimab. After this period, all deaths, regardless of cause, should be reported. 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 treatment.

[t] PK, PD (free/total C5, CH50, sC5b9), and ADA samples will be analyzed centrally. PK, PD, and ADA samples should be collected prior to the start of the crovalimab dose administration. In addition, at Week 1 Day 1, the PK samples should also be collected within 30 minutes after the end of the crovalimab infusion. For Switch Cohort patients and switching C5 SNP patients, a PK sample for eculizumab or ravulizumab should be collected on Day 1 before crovalimab administration. Serum ADA samples for crovalimab will be collected at the same time as PK samples, except at Week 1 Day 2. Only ADA samples from the following visits will be analyzed initially: Weeks 1, 9, 17, 25, 33, Q8W until Week 49, Q16W thereafter (remaining samples will be available for further analysis, if necessary). Additional PK, PD, and ADA samples should be collected in patients showing aHUS symptomatology or if clinically indicated. Whenever possible, crovalimab PK and ADA samples should be collected at the same time.

[u] In case of an adverse event of Type III hypersensitivity reaction, PK, PD, ADA, and exploratory safety (DTDC) samples are to be taken.

[v] Samples will be sent to a central laboratory for analysis (refer to the laboratory manual for further details). Samples should be collected prior to crovalimab dose administration. Serum samples for LDH, BUN, cystatin C, creatinine, hemoglobin, haptoglobin should be collected at any unscheduled visit due to aHUS symptomatology.

[w] Whole blood for genetic testing (see Appendix 8) and plasma for anti-FH autoantibodies. Samples can be taken at any time during the *first 25 weeks of the* study. For patients who receive blood product transfusion, anti-FH autoantibodies should be tested on samples collected prior to or at least 14 days after blood product transfusion. *Should the initial sample be unsuitable for analysis, an additional sample can be collected anytime during the study if within the limit of the recommended maximum allowable blood draw volumes.*

[x] On Week 1 Day 1, DTDC sample is to be collected before and after the end of infusion of the first dose of crovalimab (Switch Cohort patients and switching C5 SNP patients only). Subsequent DTDC samples are to be collected before the crovalimab dose. DTDC samples will be analyzed centrally.

[y] Leftover urine from urinalysis should be collected at each visit when local urinalysis is planned (except at screening) and sent to the central laboratory for exploratory biomarker.

[z] Completion of PRO questionnaires should occur prior to the performance of non-PRO assessments whenever possible.
The PRO questionnaires will be self-administered before a patient receives any information on disease status and prior to the administration of crovalimab.

[aa] Initial IV crovalimab loading dose on Week 1 Day 1, followed by SC doses thereafter.

[bb] These doses may be self-administered (training for self-administration is described in Section 4.3.2.2).

[cc] *FU safety assessment should be performed 24 weeks (site visit) and 46 weeks (safety telephone call) after the last dose of crovalimab. Note that patients who continue crovalimab after discontinuation from the study treatment do not need to return for the safety follow up visit.*

Appendix 2
Schedule of Activities for Patients Who Discontinue Crovalimab and Switch to Eculizumab or Ravulizumab After Study Discontinuation

	From treatment *start* with Other C5 Inhibitor							*From Last Crovalimab Dose*	
Week	1	2	3	4	5	7	9	24	46
Physical examination [a, b]	x	x	x	x	x	x	x	x	
Vital signs [b, c]	x	x	x	x	x	x	x	x	
Safety laboratory assessments [b, d]	x	x	x	x	x	x	x	x	
Urinalysis [b, e]	x	x	x	x	x	x	x	x	
Adverse events [f]	x	x	x	x	x	x	x	x	x

C5 = complement 5; eCRF = electronic Case Report Form; POC = point-of-care.

Note: W1D1 is from start of treatment with Other C5 Inhibitor. W24 and W46 are calculated from last crovalimab dose.

[a] Only a limited physical examination is required. Each new or worsened clinically significant abnormality should be recorded on the Adverse Event eCRF.

[b] On Week 1, blood samples should be collected after administration of eculizumab or ravulizumab. Thereafter, assessments and sampling should be performed prior to each eculizumab or ravulizumab dose administration.

[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 judgment in order to monitor the safety of a patient.

[e] Urinalysis includes dipstick or POC testing (pH, specific gravity, glucose, protein, ketones, RBCs, and hemoglobin). If there is a clinically significant positive result (i.e., confirmed by a positive repeat sample), urine will be sent to the laboratory for urinalysis, microscopy and culture (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). If there is a known explanation for the positive dipstick or POC testing 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 after the final dose of the study drug. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to crovalimab at any timepoint. See Section 5 for additional details and reporting requirements.

Appendix 3 Schedule of Activities for Patients Who Discontinue Crovalimab and Remain in Long-term Follow-up from Discontinuation Until Potential Restart

Crovalimab Discontinuation Week	Week 1 Day 1	Week 3 and Q2W Thereafter	Week 21 (Safety Follow-up)	Weeks 23 and 25	Week 27 and Q4W Thereafter	Unscheduled Visit
Limited physical examination [a]	x	x	x	x	x	x
Vital signs [b]	x	x	x	x	x	x
Concomitant medications [c]	x	x	x	x	x	x
Hematology, including platelet count [d]	x	x	x	x	x	x
Coagulation [e]	x	Q8W	x		Q8W	x
Local free hemoglobin and haptoglobin (if available) [f, g]	x	x	x	x	x	x
Local chemistry, including LDH [h, n], BUN [h, n], serum cystatin C [f, h, n], and serum creatinine [h, n]	x	x	x	x	x	x
Urinalysis [i]	x	x	x	x	x	x
Pregnancy test [j]	x		x			
12-lead ECG [g]	x		x			
Adverse events [k]	x	x	x	x	x	x
Serum sample for LDH, BUN, cystatin C, creatinine and haptoglobin [l]	x	x	x	x	x	x
Serum sample for free hemoglobin [l]	x	x	x	x	x	x
Plasma and serum samples for PD biomarkers [l, m]	x	Q8W	x		Q8W	x
Serum ADA sample for crovalimab [l, m]	x	Q8W	x		Q8W	x
Serum PK sample for crovalimab [l, m]	x	Q8W	x		Q8W (last PK sample at Week 43)	x

Appendix 3: Schedule of Activities for Patients Who Discontinue Crovalimab and Remain in Long-term Follow-up from Discontinuation Until Potential Restart

Note: Additional (unscheduled) visits outside the specified visits are permitted at the discretion of the investigator. Procedures, tests, and assessments will be performed at the discretion of the investigator, but in case of aHUS symptomatology at a minimum the following tests should be performed for study purposes: LDH, platelet count, hemoglobin, BUN, cystatin C, haptoglobin, serum creatinine, hematology panel, and urinalysis. Any procedures, tests, or assessments performed at the unscheduled visits must be recorded on the eCRFs. *Any available* local laboratory results may be used for unscheduled visit testing. The LDH and creatinine should also be tested centrally. Adverse events and vital signs must be recorded for each unscheduled visit.

[a] A limited physical examination will be required. Height and weight will be recorded at Week 1 for all patients and height and weight will also be recorded at Weeks 17, 31 and, Q16W thereafter. Each new or worsened clinically significant abnormality should be recorded on the Adverse Event eCRF.

[b] 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.

[c] Report any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient until the end of the study.

[d] Hematology parameters will be measured by a local laboratory, and must include WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells), and reticulocyte counts. A manual differential can be performed, platelet count and a hematology panel should be collected at any unscheduled visit due to aHUS symptomatology.

[e] Coagulation parameters include locally assessed PTT/aPTT and PT/INR, fibrinogen, and D-dimers.

[f] If available and analysis is routinely performed locally, then results from this analysis shall be entered into the eCRF.

[g] Performed locally.

[h] Chemistry panel includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, serum creatinine, total protein, albumin, phosphate, magnesium, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, and LDH. Samples should be collected prior to crovalimab dose administration. In countries where serum bicarbonate is not considered a standard chemistry measurement (e.g., Japan), serum bicarbonate is not required as a laboratory study in the screening or on-study serum measurements. LDH, BUN, cystatin C, haptoglobin, and creatinine should be measured at any unscheduled visit due to aHUS symptomatology.

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

[j] Pregnancy tests will be conducted for all female patients of childbearing potential. Pregnancy tests will be urine or serum tests performed locally. A urine pregnancy test will also be performed within 2 days prior to the final safety telephone call (i.e., 46 weeks after the final dose of crovalimab). The patient should report the result of the pregnancy test during the safety telephone call. The patient should report the result of the pregnancy test during the safety telephone call. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[k] All adverse events will be reported until 46 weeks after the last dose of crovalimab. After this period, all deaths, regardless of cause, should be reported. 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 treatment.

[l] Samples will be analyzed centrally (see laboratory manual for details). Serum samples for LDH, BUN, cystatin C, creatinine, hemoglobin, and haptoglobin should be collected at any unscheduled visit due to aHUS symptomatology.

[m] Last PK sample will be collected at Week 43. Additional PK, PD, and ADA samples should be collected in patients showing aHUS symptomatology or if clinically indicated. Whenever possible and applicable, crovalimab PK, PD, and ADA samples should be collected at the same time.

[n] Results from this analysis shall be entered into the eCRF.

Appendix 4 Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Anti-histamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer anti-histamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 5 Major Adverse Vascular Events (MAVEs)

The description of the major adverse vascular events (MAVEs) including the method of diagnosis (e.g., magnetic resonance imaging, ultrasound, angiogram), date of diagnosis, and the date resolved (or ongoing) will be collected on the electronic Case Report Form as part of the patient's medical history (prior to baseline). A MAVE is defined as any of the following events:

- Thrombophlebitis/deep vein thrombosis
- Pulmonary embolus
- Myocardial infarction
- Transient ischemic attack
- Unstable angina
- Renal vein thrombosis
- Acute peripheral vascular occlusion
- Mesenteric/visceral vein thrombosis or infarction
- Mesenteric/visceral arterial thrombosis or infarction
- Hepatic/portal vein thrombosis (Budd-Chiari syndrome)
- Cerebral arterial occlusion/cerebrovascular accident
- Cerebral venous occlusion
- Renal arterial thrombosis
- Gangrene (non-traumatic, non-diabetic)
- Amputation (non-traumatic, non-diabetic)
- Dermal thrombosis
- Other, specify

Appendix 6 Summary of Planned Central Laboratory Analyses

Objective	Sample	Assessment
PK/ADA	Serum	PK ADA DTDCs (only for patients who switch from eculizumab or ravulizumab to crovalimab, including switching C5 SNP patients)
PD Biomarker	Serum	Total C5 Free C5 CH50 (by LIA)
	Plasma	sC5b-9
Hemolysis and kidney function biomarker	Serum	Haptoglobin LDH Creatinine BUN Cystatin C
	Serum (plasma may be required depending on regional laboratory)	Free hemoglobin
Disease characterization	EDTA whole blood	Genetics (see Appendix 8)
	Plasma	Anti-factor H autoantibodies
Kidney function	Urine	sC5b-9 Kidney biomarkers (see Appendix 7)

ADA = anti-drug antibody; C5 = complement component 5; DTDC = drug-target-drug complex; EDTA = ethylenediaminetetraacetic acid; LIA = liposome immunoassay; PD = pharmacodynamic; PK = pharmacokinetic; sC5b-9 = soluble complement 5b-9.

Appendix 7 Urinary Kidney Biomarkers

Additional urinary biomarker for kidney function may be assessed in addition to soluble complement 5b-9 (sC5b-9). These biomarkers may include established, as well as research biomarkers:

Glomerular markers	Albumin (ALB), total protein (TP), cystatin-C (CST3), angiopoietin 2 (ANGPT2), p selectin (PSEL), vascular adhesion molecule 1 (VCAM1), caldesmon (CALD1), smoothelin B (SMTN), neutrophil gelatinase-associated lipocalin (NGAL), stromelysin 1 (MMP3), podocin (NPHS2), nephrin (NPHS1), synaptopodin (SYNPO)
Tubular markers	Liver-type fatty acid-binding protein (L-FABP), clusterin (CLU), cystatin-C (CST3), osteopontin (SPP-1), creatinine, albumin (ALB), total protein (TP), kidney injury molecule 1 (KIM-1), N acetyl β-D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL)
Inflammatory markers	Metalloproteinase inhibitor 1 (TIMP-1), monocyte chemoattractant protein-1 (MCP-1)
Complement markers	Soluble complement 5b-9 (sC5b-9)

Appendix 8 Listing of Genes Assessed to Characterize the Disease

8.1 Genes Known to be Altered in aHUS/TMA Disease	
C3	complement C3
C5	complement C5
CD46	CD46 molecule
CFB	complement factor B
CFH	complement factor H
CFHR1	complement factor H related 1
CFHR2	complement factor H related 2
CFHR3	complement factor H related 3
CFHR4	complement factor H related 4
CFHR5	complement factor H related 5
CFI	complement factor I
DGKE	Diacylglycerol kinase epsilon
MMACHC	methylmalonic aciduria and homocystinuria type C protein
THBD	thrombomodulin
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (a von Willebrand factor-cleaving protease)
8.2 Exploratory Genes of the Complement System or Coagulation Cascade	
C1QA	complement C1q A chain
C1QB	complement C1q B chain
C1QC	complement C1q C chain
C1R	complement C1r
C1S	complement C1s
C2	complement C2
C3AR1	complement C3a receptor 1
C4A	complement C4A (Rodgers blood group)
C4B	complement C4B (Chido blood group)
C4BPA	complement component 4 binding protein alpha
C4BPB	complement component 4 binding protein beta

8.2 Exploratory Genes of the Complement System or Coagulation Cascade (cont.)	
C5AR1	complement C5a receptor 1
C6	complement C6
C7	complement C7
C8A	complement C8 alpha chain
C8B	complement C8 beta chain
C8G	complement C8 gamma chain
C9	complement C9
CD55	CD55 molecule (Cromer blood group)
CD59	CD59 molecule (CD59 blood group)
CFD	complement factor D
CFP	complement factor P (properdin)
CLU	clusterin
CR1	complement C3b/C4b receptor 1 (Knops blood group)
CR1L	complement C3b/C4b receptor 1 like
CR2	complement C3d receptor 2
CR2	complement C3d receptor 2
FCN1	ficolin 1
FCN2	ficolin 2
FCN3	ficolin 3
ITGAM	integrin subunit alpha M
ITGAX	integrin subunit alpha X
ITGB2	integrin subunit beta 2
MASP1	mannan binding lectin serine peptidase 1
MASP2	mannan binding lectin serine peptidase 2
MBL2	mannose binding lectin 2
PIGA	phosphatidylinositol N-acetylglucosaminyltransferase subunit A
PLG	plasminogen
SERPING1	serpin family G member 1
VSIG4	V-set and immunoglobulin domain containing 4

8.2 Exploratory Genes of the Complement System or Coagulation Cascade (cont.)	
VTN	vitronectin
VWF	von Willebrand factor

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 deficiency; aHUS = atypical hemolytic uremic syndrome; TMA = thrombotic microangiopathy.
Notes: Exploratory genes (Appendix 8 Subsection 8.2) of the complement and coagulation cascade may be assessed if required as part of exploratory biomarker research.
In addition, analysis of proteins of the complement or coagulation cascade may be performed to confirm the biologic relevance of a newly identified mutation (e.g., to confirm the impact of a newly identified genetic aberration on the complement cascade).
The analysis includes somatic variants as well as polymorphisms in the genes listed above.
Methods include next-generation sequencing, multiplex-ligation dependent probe amplification and Sanger sequencing as needed.

Appendix 9 Glomerular Filtration Rate Category/Stage in Chronic Kidney Disease

GFR Category/Stage	GFR (mL/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased [a]
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

CKD = chronic kidney disease; GFR = glomerular filtration rate.

Note: In the absence of evidence of kidney damage, neither GFR category/stage G1 nor G2 fulfill the criteria for CKD.

[a] Relative to young adult level.

Source: KDIGO 2012

REFERENCES

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [resource on the Internet]. 2013 [cited 7 August 2020]. Available from: https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf.

Appendix 10 Exclusion Criteria Related to non-aHUS TMA

Diagnosis to be excluded	Test establishing diagnosis	Testing approach at screening	
		Naive Cohort	Switch and C5 SNP Cohorts
TTP	ADAMTS13 levels ≤ 10%[a]	Test at screening[b]	• Exclude patient if diagnosis was made at TMA onset • Document available test results in eCRF • Do not repeat test; do not perform new test at screening
STEC-HUS	Shiga toxin positive test or Shiga toxin−producing bacteria	Test at screening	
Pneumococcal HUS	Positive chest X-ray or positive culture of *Streptococcus pneumoniae*	Test at screening if clinical suspicion	
TMA secondary to cobalamin C defect	Increased total blood homocysteine levels *(≥3 × ULN)* and increased MMA *(≥3 × ULN)* levels and/or *MMACHC* gene mutation	• For MMACHC[b] mutation: Test at screening only if results were not documented in the medical records of the patient • For homocysteine and MMA levels: Test at screening	• Exclude patient if diagnosis was made at TMA onset • Document available test results in eCRF • Test at screening only if results were not documented in the medical records of the patient

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; C5 = complement component 5; eCRF = electronic Case Report Form; HUS = hemolytic uremic syndrome; MMA = methylmalonic acid; SNP = single nucleotide polymorphism; STEC-HUS = Shiga toxin–producing Escherichia coli hemolytic uremic syndrome; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.

NOTE: If the results of the tests performed during screening are not available, patients may be enrolled and dosed, based on the investigator's best clinical judgment.
Patients who are enrolled but whose aHUS diagnosis is subsequently ruled out may continue treatment with crovalimab, if deemed appropriate by the investigator.

[a] For patients who have received blood product transfusions, ADAMTS13 testing must be performed prior to transfusion. If this was not performed, ADAMTS13 testing must be performed as early as possible after the blood product transfusion, and again only once 14–21 days after the transfusion.

[b] If available as per locally defined regulation, central laboratory testing is acceptable.

Appendix 11
Investigational Medicinal Product Designations (for Use in European Economic Area)

Table 1 Investigational Product Designations for European Economic Area

Product Name	IMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Crovalimab (RO7112689)	IMP (test product) [a]	Unauthorized	Unauthorized

EEA = European Economic Area; IMP = investigational medicinal product

Signature Page for Protocol - BO42353 - PIASKY - v7 - Global/Core - Published
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Approval Task	[redacted] Company Signatory 01-Jul-2024 16:58:14 GMT+0000