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

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: A PHASE III, MULTICENTER, SINGLE-ARM STUDY EVALUATING THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CROVALIMAB IN PEDIATRIC PATIENTS WITH ATYPICAL HEMOLYTIC UREMIC SYNDROME (aHUS)

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STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 2.0.

SAP Version	Approval Date	Based on Protocol BO42354 (Version, Approval Date)
2	See electronic date stamp on the last page of this document	Version 5, 18 May 2023
1	23 September 2021	Version 2, 27 May 2021

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The Statistical Analysis Plan (SAP) for Study BO42354 has been primarily amended to update the Switch Cohort sample size from approximately 10 patients to a minimum of 20 patients to allow for the enrollment of additional Switch Cohort patients to complete enrolment into Dose Confirmation Groups 1 and 2 as per the updates that have been made to these in Section 3.1.2 of Study BO42354 Protocol Version 5.

Key changes to the SAP, along with the rationale(s) for each change, are summarized below.

Section	Description of Change	Rationale for Change
1.1	Objectives, endpoints and estimands that were previously described in text are now presented in Table 1 (Primary Objective and Corresponding Estimand) and Table 2 (Secondary/Exploratory Objectives and Corresponding Endpoints).	Alignment with latest SAP template.
	The primary efficacy estimand population definition has been updated to clarify: • The inclusion of only those patients whose creatinine values have not normalized at baseline.	The language on the Primary Efficacy Estimand was revised to improve clarity on the population.
	Due to the re-classification of "PE/PI" as a "prohibited therapy" with Study BO42354 Protocol Version 5, apheresis has been removed from the list of inter-current events to avoid redundancy.	Alignment with Study BO42354 Protocol Version 5.
	The reporting periods for the secondary and exploratory efficacy endpoints have been clarified to state that changes are from baseline to Week 25 (after 24 weeks on treatment).	Alignment with Study BO42354 Protocol Version 5.
	The exploratory PK objective to evaluate the relationship between DTDC size and kinetics and PK parameters of crovalimab has been removed.	DTDC size determination is a semi-quantitative assay, and no correlation can be made between DTDC fraction and PK parameters of crovalimab.
1.2	A sentence stating the approximate number of sites and total number of patients globally has been added for additional clarity. Language has been added to clarify that only naive non-complement mediated aHUS patients who discontinue due to aHUS diagnosis being ruled out post-enrollment will be replaced. Language has been added to clarify that the primary analysis will be performed "when the first approximately 20 evaluable patients enrolled in the Naïve Cohort have reached the Week 25 visit (after 24 weeks on treatment), or discontinued from crovalimab treatment, whichever occurs first."	Alignment with Study BO42354 Protocol Version 5.

Section	Description of Change	Rationale for Change
1.2, 2.2, 4.6.3.1, Table 3 and Figure 1	The Switch Cohort sample size has been increased from approximately 10 patients to a minimum of 20 patients to allow for the enrollment of additional Switch patients to complete DCG1 and DCG2.	Alignment with Study BO42354 Protocol Version 5. Consequence of the updated dose confirmation group minimum sample size requirements.
1.2.2, 4.7	Immunogenicity has been added to the list of analyses that will be evaluated by the JMC	Alignment with Study BO42354 Protocol Version 5.
3	Analysis populations previously described in text are now presented in table format.	Alignment with latest SAP template.
	Primary analysis population has been updated to refer to eCRF data for Naive Cohort determination.	To clarify that cohort (Naive vs. Switch vs. Pretreated Cohort) assignment will be based on eCRF information (and not on IxRS data) as it is a single arm study.
	To include patients whose creatinine values have not normalized at baseline in primary analysis population and efficacy-evaluable population.	See the rationale for the respective change made in Section 1.1.
	The immunogenicity-evaluable population definition has been updated to require “at least one post-baseline ADA assessment” (instead of “at least one ADA assessment”).	The definition was updated 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.
	The Per Protocol Population has been removed.	To be consistent with removal of this population in Study BO42353 (COMMUTE-a) SAP. This population has not been included in Study BO42354 Protocol.

Section	Description of Change	Rationale for Change
4.1	Details have been added with respect to who will not review aggregated data.	Update made to align with JMC Agreement in order to maximize the integrity of the study.
	It has been clarified that the statistical considerations related to the dose confirmation analyses, being performed to support JMC reviews only, will have no impact on the statistical analyses planned to be conducted for this study.	For better clarity on statistical analyses for JMC reviews vs CSR.
	Baseline definition has been clarified for patients on dialysis and patients not on dialysis.	For better clarity on baseline definition.
	Language has been added to provide better clarity on whether central or local lab data will be used for analysis.	To ensure that baseline values used for analysis are central lab samples. If central lab assessments are not available, then local lab values converted to SI units will be used. In order to assess response, it is important that on-treatment samples originate from the same lab as the baseline samples.
4.2.1	The following further clarifying language with regards to definition of the primary efficacy endpoint has been added: "If a patient meets all the criteria at Week 21 and 4 weeks later (at Week 25) (including at any measurements taken between) the criteria are confirmed and the patient has reached a response. This response is considered to have started at the time when the patient first met the response criteria (i.e., at Week 21). A patient that withdraws from the study any time after cTMAr is confirmed, is still regarded being a responder."	Per the Sponsor's responses to FDA's comments received on COMMUTE-a SAP Version 1.

Section	Description of Change	Rationale for Change
4.2.3	The following sensitivity analyses of the primary efficacy endpoint have been added: • Using multiple imputation. • Including all patients in the Naive Cohort, whose complement mediated aHUS diagnosis was not ruled out post enrollment and who have received at least one confirmed dose of crovalimab (regardless of whether the patient had at least one post-baseline efficacy assessment). The following sensitivity analyses of the primary efficacy endpoint have been removed: • A sensitivity analysis modifying the ICE criterion regarding apheresis treatment to remove the requirement of repeated treatments. In this case, a single apheresis treatment during crovalimab treatment will be counted as ICE. • Sensitivity analysis for the primary efficacy endpoint based on per protocol population.	Per the Sponsor's responses to FDA's comments received on COMMUTE-a SAP Version 1 Per Study BO42354 Protocol Version 5 that makes PE/PI a prohibited therapy. For consistency with COMMUTE-a SAP. Per protocol population was removed in Section 3.
4.2.4	The language on subgroup analyses has been amended and streamlined.	For consistency with COMMUTE-a SAP. For COMMUTE-a SAP, this change was made due to the reduction of sample size of the Naive Cohort (from approximately 60 to approximately 40 patients). In COMMUTE-p SAP, the sample size of the Naive Cohort is even lower with approximately 20 patients.
4.3	Four censoring rules have been added. These will be applied in the secondary endpoint analyses of all three components of the cTMAr definition.	The ICE definitions and handling strategies for the primary efficacy endpoint of cTMAr are applicable also for the analyses of the three components of the cTMAr definition.

Section	Description of Change	Rationale for Change
4.4 and 1.1	The following new exploratory efficacy endpoint has been added in Section 1.1: • Change from baseline to Week 25 (after 24 weeks on treatment) in eGFR, using different eGFR equations. Respective analysis details have been added in Section 4.4.	To explore the impact of different eGFR equations on the eGFR results.
4.6.3.1	It has been clarified that, for the purpose of the JMC reviews only, a patient with ADA presence associated with complete loss of exposure will be replaced in all dose confirmation groups.	To avoid any bias in the dose confirmation step. As with other monoclonal antibody therapeutic agents, patients may develop ADA against crovalimab that can lead to loss of exposure and efficacy.
	It has been clarified that, for the purpose of the JMC reviews only, patients that discontinued study treatment prematurely (before Week 9) will be replaced in all dose confirmation groups.	Amount of PK data will not sufficient if a patient discontinues study treatment before Week 9.
	Language related to the dose confirmation analyses was updated.	To align with Study BO42354 Protocol Version 5.
4.6.5	The definition of persistent/transient ADAs was updated.	To align this definition with other crovalimab studies.
4.6.5 and 1.1	The following new immunogenicity endpoint has been added in Section 1.1: • For ADA-positive patients, the percentage of patients with loss of PK and PD. Respective analysis details have been added in Section 4.6.5.	Added this new immunogenicity endpoint based on the loss of PK and PD.

Section	Description of Change	Rationale for Change
4.6.6 and 1.1	The following two endpoints have been moved in Section 1.1 from exploratory efficacy endpoints to pharmacodynamic / biomarker endpoints: • Observed value and change over time in PD biomarkers, including complement activity (CH50) measured by a LIA. • Observed value and change over time in free C5 and total C5 concentrations in crovalimab-treated patients. Respective analysis details have been added in Section 4.6.6.	For consistency with other crovalimab studies.
4.7	Language has been added to allow for interim analyses to occur for efficacy, safety, PK, PD, and immunogenicity as part of JMC evaluations.	To align with Study BO42354 Protocol Version 5.

ADA = anti-drug antibody; aHUS = atypical hemolytic uremic syndrome; CSR = Clinical Study Report; cTMAr = complete thrombotic microangiopathy response; DCG = Dose Confirmation Group; DTDC = drug-target-drug complex; eCRF = electronic Case Report Form; eGFR = estimated glomerular filtration rate; FDA = U.S. Food and Drug Administration; ICE = inter-current event; IxRS = interactive voice or web-based response system; JMC = Joint Monitoring Committee; LIA = liposome immunoassay; PE/PI = plasma exchange/plasma infusion; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; SAP = Statistical Analysis Plan; SI = Système International.

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

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE 3

1. INTRODUCTION 14

1.1 Objectives, Endpoints, and Estimands 15

1.2 Study Design 21

1.2.1 Treatment Assignment 23

1.2.2 Data Monitoring 23

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION 24

2.1 Statistical Hypotheses 24

2.2 Sample Size Determination 24

3. ANALYSIS SETS 25

4. STATISTICAL ANALYSES 26

4.1 General Considerations 26

4.2 Primary Efficacy Endpoint/Estimand Analysis 27

4.2.1 Definition of Primary Efficacy Endpoint/Estimand 28

4.2.2 Main Analytical Approach for Primary Efficacy Endpoint 28

[redacted] 29

4.2.4 Supplementary Analyses for Primary Efficacy Endpoint 30

4.2.4.1 Subgroup Analyses for Primary Efficacy Endpoint 30

4.3 Secondary Efficacy Endpoint Analyses 30

4.4 Exploratory Efficacy Endpoint Analyses 34

4.5 Safety Analyses 35

4.5.1 Extent of Exposure 35

4.5.2 Adverse Events 35

4.5.3 Laboratory Data 36

4.5.4 Vital Signs and ECG 36

4.6 Other Analyses 36

4.6.1 Summaries of Conduct of Study 36

4.6.2 Summaries of Demographics and Baseline Characteristics 36

4.6.3 Pharmacokinetic Analyses 36

4.6.3.1 Dose Confirmation Analyses 37
4.6.4 Exploratory Biomarker Analyses 38
4.6.5 Immunogenicity Analyses 38
4.6.6 Pharmacodynamic / Biomarker Analyses 39
4.7 Interim Analyses 39
5. SUPPORTING DOCUMENTATION 39
6. REFERENCES 41

LIST OF TABLES

Table 1 Primary Efficacy Objective and Corresponding Estimand 15
Table 2 Secondary/Exploratory Objectives and Corresponding Endpoints 16
Table 3 Expected Enrollment in Naive, Switch, and Pretreated Cohorts 22
[redacted] 25
Table 5 Baseline Definitions 27

LIST OF FIGURES

Figure 1 Study Schema 22

LIST OF APPENDICES

Appendix 1 Glomerular Filtration Rate Category/Stage in Chronic Kidney Disease 40

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
AKI	acute kidney injury
C_{max}	maximum concentration
C_{trough}	trough concentration
C5	complement
CCOD	clinical cut-off date
CKD	chronic kidney disease
cTMAr	complete thrombotic microangiopathy response
DCG	dose confirmation group
eGFR	estimated glomerular filtration rate
ICE	inter-current event
ICH	International Council on Harmonization
IV	intravenous
IxRS	interactive voice or web-based response system
JMC	Joint Monitoring Committee
LDH	lactate dehydrogenase
LIA	liposome immunoassay
LLN	lower limit of normal
MAC	membrane attack complex
MAHA	microangiopathic hemolytic anemia
MedDRA	Medical Dictionary for Regulatory Activities
mTMAc	maintained TMA control
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PedsQL™	Pediatric Quality of Life Inventory
PD	pharmacodynamic
PK	pharmacokinetic
Q4W	every 4 weeks
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous

SMART-Ig	Sequential Monoclonal Antibody Recycling Technology immunoglobulin
TMA	thrombotic microangiopathy
ULN	upper limit of normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods that will be used to evaluate the efficacy, safety, pharmacokinetic (PK) and pharmacodynamic (PD) data for Study BO42354 (COMMUTE-p). The analyses described in this SAP will supersede those specified in the COMMUTE-p protocol for the purposes of a regulatory filing.

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 (aHUS) 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). Without effective therapy, the prognosis of aHUS is poor, with a global mortality rate of 25%, and progression to chronic kidney disease is common (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 estimates show 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). In children and adolescents, males and females are equally affected. Although onset may occur at any age, 40% of patients develop aHUS by 18 years of age (Noris and Remuzzi 2009).

Crovalimab is a novel, humanized anti-complement 5 (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). Crovalimab is based on Sequential Monoclonal Antibody Recycling Technology-Immunoglobulin (SMART-Ig; Recycling Antibody®; Fukuzawa et al. 2017) with pH-dependent antigen binding allowing for efficient target disposal, and enhancement of neonatal fragment crystallizable receptor

binding to improve antibody recycling efficiency. These characteristics result in a prolonged half-life.

[redacted] Based on clinical data, nonclinical pharmacology, and PD data, crovalimab is expected to lead to consistent complement component 5 inhibition throughout the dosing interval, resulting in suppression of complement-mediated endothelial injury and MAHA at the targeted dosing regimens.

1.1 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The primary purpose of this study is estimation of the efficacy of crovalimab in treatment-naive patients as measured by the proportion of patients in the primary analysis population reaching complete thrombotic microangiopathy response (cTMAr) status within the first 24 weeks of treatment.

The primary efficacy objective and the corresponding estimand are presented in Table 1.

Table 1 Primary Efficacy Objective and Corresponding Estimand

Primary Efficacy Objective	Estimand Definition
• To evaluate the efficacy of crovalimab in patients in the Naive Cohort (Primary Analysis Cohort)	• [redacted] Patients weighing ≤40 kg treated at a suboptimal dose (i.e., patients in the Dose confirmation groups who are initially treated at a dose not subsequently confirmed) are excluded from the population. • [redacted] • [redacted] – [redacted]

Table 1 Primary Efficacy Objective and Corresponding Estimand (cont.)

Primary Efficacy Objective	Estimand Definition
• To evaluate the efficacy of crovalimab in patients in the Naive Cohort (Primary Analysis Cohort) (cont.)	– [redacted] • [redacted]

The secondary and exploratory objectives and the corresponding endpoints are presented in Table 2.

Table 2 Secondary/Exploratory Objectives and Corresponding Endpoints

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy 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 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 Protocol Appendix 10. • 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).

Table 2 Secondary/Exploratory Objectives and Corresponding Endpoints (cont.)

• To evaluate the efficacy of crovalimab in patients in the Naive (Primary Analysis Cohort) and Switch Cohorts (cont.)	<u>For Naive Cohort only:</u> • Proportion of patients with platelet count ≥ lower limit of normal (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 LDH ≤ upper limit of normal (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. • Proportion of patients with cTMAr ongoing at Week 25. <u>For Switch Cohort only:</u> • Proportion of patients with maintained TMA control (mTMAc) from baseline through Week 25 (after 24 weeks on treatment).
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of crovalimab in patients in the Naive Cohort (Primary Analysis Cohort), Switch Cohort, and Pretreated Cohort	<u>For ALL (Naive, Switch, and Pretreated) Cohorts:</u> • Change in serum creatinine from baseline to Week 25 (after 24 weeks on treatment). • Change from baseline in fatigue to Week 25 (after 24 weeks on treatment) as measured by the Pediatric Quality of Life Inventory (PedsQL™) Multidimensional Fatigue Scale (MFS), and physical functioning, as measured by the PedsQL-Core in pediatric patients aged 2 to ≤ 18 years old. • Change from baseline to Week 25 (after 24 weeks on treatment) in physical functioning and physical symptoms as measured by the PedsQL Infant Scale in pediatric patients under 2 years old. • Change from baseline to Week 25 (after 24 weeks on treatment) in the number of missed days of daycare or school.

Table 2 Secondary/Exploratory Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of crovalimab in patients in the Naive Cohort (Primary Analysis Cohort), Switch Cohort, and Pretreated Cohort (cont.)	• For patients who discontinue crovalimab (as per Protocol Section 4.7.2), describe the clinical course of patients who discontinue crovalimab after achieving cTMAr. • Change from baseline to Week 25 (after 24 weeks on treatment) in estimated glomerular filtration rate (eGFR), using different eGFR equations. <u>For Naive Cohort only:</u> • 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. <u>For Switch Cohort only:</u> • In adolescents (12−17 years), proportion of patients with preference for crovalimab at Week 17, after switching from eculizumab or ravulizumab, as assessed by a Patient Preference Questionnaire (PPQ) developed by the Sponsor. • In children younger than 12 years old, proportion of caregivers with preference for crovalimab at Week 17, after switching from eculizumab or ravulizumab, as assessed by the caregiver-reported version of the PPQ developed by the Sponsor. <u>For Pretreated Cohort only:</u> • The exploratory efficacy endpoints will also include primary and secondary endpoints, as applicable to the Naive Cohort

Table 2 Secondary/Exploratory Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the overall safety and tolerability of crovalimab	<u>For All (Naive, Switch, and Pretreated) Cohorts:</u> • Incidence and severity of adverse events, with severity determined according to the most recent version of the 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. <u>For Switch Cohort only:</u> • 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.
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize the pharmacokinetics of crovalimab and, for patients weighing ≤ 40 kg, to confirm the dosing strategy • The exploratory PK objective for this study is to evaluate potential relationships between drug exposure and the efficacy and safety of crovalimab	• Serum concentrations of crovalimab over time.
Immunogenicity Objective	**Corresponding Endpoints**
• To evaluate the immune response to crovalimab • To exploratory immunogenicity objective for this study is to evaluate the potential effects of ADAs on efficacy, safety, and PK endpoints	• Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study. • For ADA-positive patients, the percentage of patients with loss of PK and PD.

Table 2 Secondary/Exploratory Objectives and Corresponding Endpoints (cont.)

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 Pretreated 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.
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• To identify and/or evaluate biomarkers that can potentially provide evidence of crovalimab activity (i.e., exploratory, PD or efficacy biomarkers) or increase the knowledge and understanding of disease biology (e.g., prognostic biomarker) and drug safety (safety biomarker)	• 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 reflecting renal injury. • Presence of genetic aberrations in genes known to be related to aHUS disease. • Presence of anti-factor H autoantibodies. • Identification of emerging inherited or acquired genetic aberrations in genes of the complement/coagulation system that may be associated with the disease. • Observed value and change over time in soluble complement 5b9 (sC5b9), and parameters reflecting hemolysis (reticulocyte count, free hemoglobin, haptoglobin, schistocytes).

aHUS = atypical hemolytic uremic syndrome; C5=complement component 5; CKD=chronic kidney disease; LDH =lactate dehydrogenase; LIA=liposome immunoassay; PK=pharmacokinetic; PD=pharmacodynamic; TMA =thrombotic microangiopathy.

1.2 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 ≥28 days to <18 years, and weighing ≥5 kg.

Approximately 40 sites globally (in approximately 13 countries) will participate to enroll approximately 45 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 20 patients who have not been previously treated with a complement inhibitor therapy. The primary efficacy analysis will be based on this cohort. Naive patients will also contribute to evaluating the secondary and exploratory efficacy objectives.
- Switch Cohort will enroll a minimum of 20 patients who switch to crovalimab from eculizumab or ravulizumab, which they have been receiving for at least 90 days (and, if switching from intravenous [IV] ravulizumab, they must have received at least two maintenance doses) as of Day 1 of study treatment, and whose thrombotic microangiopathy (TMA) was adequately controlled on the labeled dose. This cohort will contribute to evaluating the secondary and exploratory efficacy objectives.
- Pretreated Cohort will enroll patients who received treatment with either eculizumab or ravulizumab, and subsequently discontinued it. These patients must have received their last dose of eculizumab or ravulizumab at least 5.5 drug half-lives prior to Day 1 of crovalimab treatment (i.e., 10 weeks for eculizumab and 41 weeks for ravulizumab). Patients with known C5 polymorphisms (C5 SNPs) whose TMA responded poorly to treatment with either eculizumab or ravulizumab, per investigator's assessment may also be enrolled to this Cohort. C5 SNP patients who recently received either eculizumab or ravulizumab (i.e., less than 5.5 drug half-lives) will be monitored similar to the Switch Cohort patients. Given the anticipated heterogeneity of patients in the Pretreated Cohort, the efficacy will be evaluated separately for C5 SNP and non-C5 SNP patients, and in an exploratory fashion. Sample size will be based on operational feasibility, with patients being enrolled throughout the study, with no minimum pre-specified sample size. This cohort may enroll up to 10 patients.

Table 3 presents the expected enrollment in the Naive, Switch, and Pretreated Cohorts, by body weight category. Recruitment to the Naive Cohort may be kept open to allow supplemental enrollment to offset withdrawal from primary analysis of patients whose complement-mediated aHUS diagnosis was subsequently ruled out post-enrollment or of patients weighing <40 kg who received suboptimal dosing in the study (as per

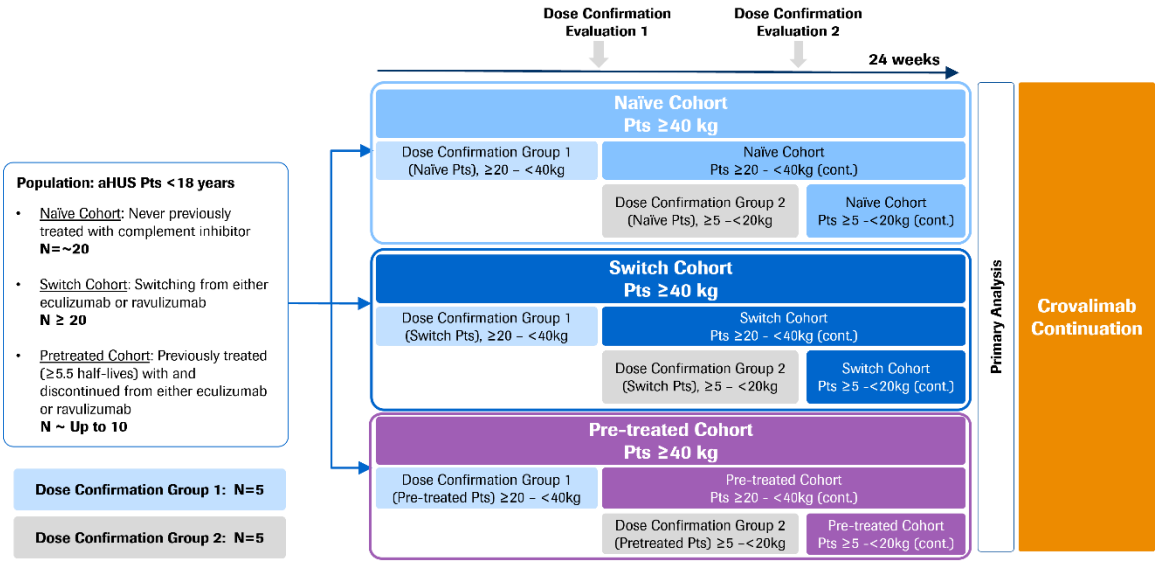
Protocol BO42354, Section 3.1.2), in order to have approximately 20 efficacy-evaluable patients for the primary efficacy analysis.

Table 3 Expected Enrollment in Naive, Switch, and Pretreated Cohorts

Body Weight Range	Patient Numbers in Naive, Switch, and Pretreated Cohorts
≥40 kg	≥6 patients (regardless of cohort)
≥20 kg to <40 kg	≥7 patients across all cohorts, including • ≥1 patient weighing ≥20 kg to<30 kg, and • ≥1 Switch patient
≥5 kg to <20 kg	≥7 patients across all cohorts, including • ≥2 patients weighing ≥5 kg to<12 kg, • ≥2 treatment-naive/pretreated patients, and • ≥1 Switch patient
Enrollment in each cohort	Approximately 20 treatment-naive patients A minimum of 20 Switch patients Pretreated Cohort may include up to 10 pretreated patients

The study schema is shown in Figure 1.

Figure 1 Study Schema



aHUS=atypical hemolytic uremic syndrome; cont.=continuation; N=number of patients; Pts=patients.

Notes: The total number of patients in each arm includes the evaluable patients from the dose confirmation groups. 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 20 evaluable patients enrolled in the Naive Cohort have reached the Week 25 visit (after 24 weeks on treatment), or discontinued from crovalimab treatment, whichever occurs first.

At the time of initiation of this study, no patients weighing ≤40 kg will have been treated with crovalimab. The current recommended dosing strategy for these patients has been derived from adults weighing ≥40 kg (as per Protocol BO42354, Section 4.3.2.1). Therefore, enrollment of patients weighing ≤40 kg will be staggered using two weight-based dose confirmation groups (DCGs). Initially, a group of patients weighing ≥20 kg to <40 kg will be enrolled, followed by a group of patients weighing ≥5 kg to <20 kg (Figure 1). Each DCG will enroll a minimum of 5 patients. After confirmation of the dosing strategy and the safety data for the relevant weight group by a Joint Monitoring Committee (JMC; see Section 1.2.2), further pediatric patients with body weights within the range of the confirmed dose will be enrolled. Refer to Protocol BO42354, Section 3.1.2, for details of the dose confirmation strategy for patients weighing <40 kg.

To collect long-term safety data, after completing 24 weeks of treatment with crovalimab (i.e., 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.

Refer to Study Protocol BO42354, Section 3 for further details of the study design and to Study Protocol BO42354, Appendices 1 to 4 for the Schedule of Activities.

1.2.1 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).

1.2.2 Data Monitoring

A 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 (including but not limited to adverse events [AEs], serious adverse events [SAEs], relevant laboratory data, and other specified safety parameters), PK, PD, and immunogenicity data.

The JMC will also review all aggregate available safety, PK, PD, and immunogenicity data to determine the appropriateness of the dose and dosing regimen in patients weighing ≤ 40 kg, at pre-specified times during the study. Details of the dose confirmation strategy in these patients and the timing of the JMC reviews are presented in Study Protocol BO42354, Section 3.1.2, and further detailed in the JMC Agreement.

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.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

This is a non-randomized, single-arm study. No formal statistical hypotheses are set.

2.2 SAMPLE SIZE DETERMINATION

The primary purpose of this study is estimation of the efficacy of crovalimab as measured by the proportion of patients in the Naive Cohort reaching cTMAr status anytime from baseline to Week 25 (within the first 24 weeks of 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, approximately 20 patients in the Naive Cohort and a minimum of 20 patients in the Switch Cohort are deemed sufficient to adequately characterize efficacy and safety of crovalimab in aHUS. Up to 10 patients may be enrolled in the Pretreated Cohort. If necessary, replacement of up to 5 patients per DCG is allowed in the event that the dose is not being confirmed and a new DCG is being required.

The primary efficacy analysis will be performed once the first approximately 20 evaluable patients enrolled in the Naive Cohort have reached the Week 25 visit, or discontinued from crovalimab treatment, whichever occurs first. However, the study will remain open to enrollment of a minimum of 6 patients with aHUS weighing ≥ 40 kg, a minimum of 7 patients with aHUS weighing ≥ 20 kg to < 40 kg (including at least 1 patient weighing ≥ 20 kg to < 30 kg and at least 1 patient from the Switch Cohort), and a minimum of 7 patients with aHUS weighing ≥ 5 kg to < 20 kg (including 2 patients weighing ≥ 5 kg to < 12 kg). These target sample sizes will allow the generation of adequate clinical evidence in pediatric patients weighing 5 kg and above.

[redacted]

The drop-out rate for this study is 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. Recruitment to the Naive Cohort may 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 approximately 20 evaluable patients for the primary efficacy analysis.

3. ANALYSIS SETS

The Analysis populations of the study are defined in Table 4. The primary efficacy analysis will be performed on the primary analysis population. All other efficacy analyses will be performed on the efficacy-evaluable population, unless otherwise specified. All safety analyses will be performed on the safety-evaluable population, unless otherwise specified.

Table 4 Analysis Populations

Population	Description
[redacted]	
Pharmacokinetic-Evaluable Population	The pharmacokinetic (PK) analyses will be performed based on the PK-evaluable population, defined as all patients who received at least one dose of crovalimab and have at least one post-dose concentration result.

Table 4 Analysis Populations (cont.)

Population	Description
Immunogenicity-Evaluable Population	The immunogenicity-evaluable population will consist of all patients who have received at least one dose of crovalimab and have at least one post-baseline ADA assessment.
Safety-Evaluable Population	Safety analyses will be performed based on the safety-evaluable population, defined as all patients who received at least one dose of crovalimab.

ADA = anti-drug antibody; [redacted]

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

The study is a non-randomized, single-arm open-label study. In order to maximize the integrity of the study, all key decision makers from the Sponsor (such as Clinical Scientist, Medical Monitor, Safety Strategy Leader [SSL], Study Safety Scientist, Project Lead Statistical Programmer, Project Lead Statistician) will not view aggregated data summaries by cohort until the time of the primary analysis.

The statistical considerations related to the dose confirmation analyses (see Section 4.6.3.1), being performed to support JMC reviews only, will have no impact on the statistical analyses planned to be conducted for this study as described in all other subsections of Section 4; i.e., all enrolled patients will be included in these statistical analyses as long as they fulfill the definitions of the respective analysis populations (Section 3) regardless if they were included in the dose confirmation analyses or not.

The key baseline definitions of the study are summarized in Table 5.

Table 5 Baseline Definitions

Baseline	Definition
Patients on dialysis: All parameters except for creatinine Patients not on dialysis: All parameters	Baseline will be defined as last available central pretreatment value taken on or before the day of first study treatment dose and will be used in summaries of demographics and baseline characteristics as well as any change from baseline analyses of efficacy and safety data. If a central pretreatment value is not available, the last available local lab pretreatment value taken on or before the day of first study treatment dose will be used as baseline.
Creatinine for patients on dialysis only	When a patient was on dialysis at baseline (i.e., dialysis occurred within 5 days prior to the first crovalimab administration), then the first creatinine assessment $\geq$ 6 days post dialysis will be used as baseline. All serum creatinine values obtained while a patient was on dialysis will be excluded from analyses. If a patient is on dialysis during the entire primary treatment period of the first 24 weeks, then baseline creatinine will not be calculated and this patient will be regarded as a cTMAr non-responder. If a central pretreatment value is not available, the last available local lab pretreatment value taken on or before the day of first study treatment dose will be used as baseline.

cTMAr = complete thrombotic microangiopathy response.

Unless specified otherwise, all continuous variables will be summarized with descriptive statistics (e.g., number of non-missing values, mean, standard deviation, median, minimum, and maximum). All categorical variables will be summarized with frequency counts and percentages. Data will be presented by cohort. If the number of patients is fewer than 10 in a cohort (e.g., in the Pretreated Cohort), then production of listings only, rather than summary tables, may be considered.
The importance of providing detailed reasons for study treatment discontinuation, as well as for discontinuations from the study, will be emphasized to the investigators.

All clinical laboratory data will be stored in the database in the units in which they were reported. Summary statistics at each assessment time will be presented by using the International System of Units (Système International d'Unités [SI]). Laboratory data not reported in SI units will be converted to SI units before processing. For analysis purposes, should results from central lab assessments not be available for a certain visit, then local laboratory values converted to SI units will be used.

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

4.2 PRIMARY EFFICACY ENDPOINT/ESTIMAND ANALYSIS

The primary efficacy analysis will be performed on the primary analysis population as defined in Section 3.

4.2.1 Definition of Primary Efficacy Endpoint/Estimand

The primary efficacy estimand, in accordance to International Council on Harmonization (ICH E9 [R1]) addendum, has been defined in Section 1.1 (see Table 1).

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

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

[redacted]

The latest time point at which a patient could first meet the cTMAr criteria will be at the Week 21 assessment. If a patient meets all the criteria at Week 21 and 4 weeks later (at Week 25) (including at any measurements taken between) the criteria are confirmed and the patient has reached a response. This response is considered to have started at the time when the patient first met the response criteria (i.e., at Week 21). A patient that withdraws from the study any time after cTMAr is confirmed, is still regarded being a responder.

4.2.2 Main Analytical Approach for Primary Efficacy Endpoint

The primary efficacy endpoint analysis will apply the primary efficacy estimand approach defined in Section 1.1.

The point estimate of the cTMAr proportion will be calculated, and the 95% CI will be computed using Wilson's score method as described in Newcombe (1998).

The primary efficacy analysis will be performed when the first approximately 20 evaluable patients enrolled in the Naive Cohort have reached the Week 25 visit, or discontinued from crovalimab treatment, whichever is first.

[redacted]

[redacted]

[redacted] Sensitivity analyses will be conducted, to assess the robustness of the primary efficacy endpoint analysis results and the impact of missing data on the estimated proportion of patients with cTMAr (see Section 4.2.3).

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

4.2.4 Supplementary Analyses for Primary Efficacy Endpoint

4.2.4.1 Subgroup Analyses for Primary Efficacy Endpoint

Subgroup analyses may be performed to descriptively compare the primary efficacy endpoint results across clinically important subgroups. Subgroup analysis results may be highly sensitive to variability caused by individual patients for subgroups with limited sample size.

4.3 SECONDARY EFFICACY ENDPOINT ANALYSES

The secondary efficacy endpoint analyses will be performed on the efficacy-evaluable population, separately for the Naive and Switch Cohort and overall (when applicable).

For Naive and Switch Cohorts

- **Dialysis requirement status** (yes/no); change from baseline to Week 25 (after 24 weeks on treatment):
  - Difference in the proportion of patients requiring dialysis at baseline and at Week 25 will be calculated. Two-sided 95% CIs for proportions at baseline and at Week 25 and for the difference in proportions will be calculated using Wilson's score method.
  - Within patient change from baseline through Week 25 on dialysis status will be summarized descriptively using categories: "initiated dialysis", "discontinued dialysis", "remained on dialysis", and "remained dialysis-free".

- Estimated value and change from baseline to Week 25 (after 24 weeks on treatment) in **estimated glomerular filtration rate (eGFR)**. The following equation will be used to estimate eGFR:

eGFR Equation	Formula
Creatinine-based bedside Schwartz equation* (Schwartz and Work 2009; Levey et al. 2009)	eGFR (mL/min/1.73 m^2) = 0.413 × (height/sCr), if height is expressed in centimeters OR 41.3 × (ht/sCr), if height is expressed in meters

eGFR= estimated glomerular filtration rate; ht = height (m); sCr = standardized serum creatinine (mg/dL).

*Validated for ages ≥ 1 year of age; used clinically starting from birth.

Serum creatinine measurements are not reliable with concurrent dialysis. Therefore, all serum creatinine values obtained while a patient is on dialysis will be excluded from all analyses. In these cases, eGFR will be imputed with a value of

10 mL/min/1.73 m^2 (Rubin 1996). Patients will be considered on dialysis from the first day of dialysis through 5 days after the end of dialysis.

  - Descriptive statistics, including mean, median, standard deviation, and range, will be used to summarize the continuous estimated eGFR by time point as well as the changes from baseline to Week 25.

- **Proportion of patients with change from baseline** to Week 25 (after 24 weeks on treatment) **in chronic kidney disease (CKD) stage**, based on the National Kidney Foundation Chronic Kidney Disease Stage presented in Appendix 1.

CKD stage will be defined using the calculated eGFR from the equation presented above.

  - CKD stage will be categorized and summarized descriptively by time point using patient counts and proportions. Change from baseline will be summarized using shift tables.
  - The CKD stage change from baseline will be summarized at Week 25 in addition by number and proportion of patients that improved (excluding those with Stage 1 at baseline), worsened (excluding those with Stage 5 at baseline), and were stable (no change from baseline). The 2-sided 95% CIs for proportions for each time point and for the difference in proportions between baseline and Week 25 will be calculated using Wilson's score method.

- Observed value and change from baseline to Week 25 (after 24 weeks on treatment) in **hematologic parameters** (platelet count, LDH, hemoglobin)
  - Platelet and hemoglobin measurements are not reliable with concurrent blood products transfusions. Therefore, platelet values obtained after transfusion initiation from the day of a transfusion of platelets through 3 days after the transfusion will be excluded from all analyses. Hemoglobin values obtained after transfusion initiation from the day of a blood transfusion of either whole blood or packed red blood cells through 7 days after the transfusion will be excluded from all analyses. If a patients' baseline measurement would be regarded as missing due to transfusion, the last valid value before transfusion initiation will be used as the baseline value.
  - Descriptive statistics, including mean, median, standard deviation, and range, will be used to summarize the continuous observed values and changes from baseline to Week 25.

For Naive Cohort only:

- The three **components of the cTMAr** definition will be analyzed separately applying the same analysis approach as described for the primary endpoint.
  - The below listed proportions will be calculated. Two-sided 95% CIs for these proportions will be calculated using Wilson's score method.
    - 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 LDH ≤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).
  - The following four censoring rules will be applied in the analysis of each of the three components of cTMAr:
    - Data from patients that have not reached the endpoint (see Table 2 for endpoint definitions) at time of the clinical cut-off date (CCOD) for the analysis will be censored at the date of the last visit when the endpoint was assessed prior to the CCOD.
    - Data from patients that have not reached the endpoint at time of treatment discontinuation will be censored at the date of the last visit when the endpoint was assessed prior to the treatment discontinuation.
    - Data from patients that have received a prohibited therapy at time of the CCOD for the analysis will be censored at the date of the last received prohibited therapy prior to the CCOD.
    - Data from patients that have received a prohibited therapy at time of treatment discontinuation will be censored at the date of the last received prohibited therapy prior to the treatment discontinuation.

- **Time to cTMAr**
  - Time to cTMAr will be analyzed using Kaplan-Meier methodology. Median time to cTMAr will be estimated along with the 2-sided 95% CI.
  - Data from patients that have not reached a cTMAr response at time of the CCOD for the analysis will be censored at the date of their last visit when cTMAr was assessed prior to the CCOD.
  - Data from patients that have not reached a cTMAr response at time of treatment discontinuation will be censored at the date of their last visit when cTMAr was assessed prior to the treatment discontinuation.

- The start of cTMAr will be considered to be the first time point at which all the criteria for cTMAr are met, that is, at the first of the 2 assessments required to be classified as a responder.
- Time to cTMAr will be calculated beginning from the first crovalimab administration.

- **Duration of cTMAr**, among patients who achieved cTMAr
  - Duration of cTMAr will be calculated as the time from start of cTMAr to end of cTMAr. The 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
    - $\geq$25% increase in serum creatinine from baseline.
  - Duration of cTMAr will be analyzed using Kaplan-Meier methodology. Median duration of cTMAr will be estimated along with the 2-sided 95% CI.
  - Once the end of cTMAr is confirmed, the end date of cTMAr is considered being the first visit at which all the criteria for end of cTMAr were met, that is, at the first of the 2 assessments (at least 4 weeks [a minimum of 26 days]) required to confirm the end of cTMAr.
  - Data from patients with no observed end of cTMAr at time of the CCOD for the analysis will be censored at their last visit when cTMAr was assessed prior to the CCOD.
  - Data from patients with no observed end of cTMAr at time of treatment discontinuation will be censored at their last visit when cTMAr was assessed prior to the treatment discontinuation.

- Proportion of patients with **cTMAr at Week 25**
  - The number and proportion of patients having all three cTMAr criteria confirmed at the Week 25 evaluation will be computed. A 2-sided 95% CI for the proportion will be calculated using Wilson's score method.

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
    - $\geq$25% increase in serum creatinine from baseline.

- The number and proportion of patients with mTMAc from baseline through Week 25 will be computed. A 2-sided 95% CI for the proportion will be calculated using Wilson's score method.

4.4 EXPLORATORY EFFICACY ENDPOINT ANALYSES

For ALL (Naive, Switch, and Pretreated) Cohorts:

- Change in serum creatinine from baseline to Week 25 (after 24 weeks on treatment).
- 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 pediatric patients aged 2 to <18 years old.
- Change from baseline to Week 25 (after 24 weeks on treatment) in physical functioning and physical symptoms as measured by the PedsQL Infant Scale in pediatric patients under 2 years old.
- Change from baseline to Week 25 (after 24 weeks on treatment) in the number of missed days of daycare or school.
- Observed value and change from baseline to Week 25 (after 24 weeks on treatment) in estimated glomerular filtration rate (eGFR), may be calculated using the following creatinine cystatin C-based CKID equation incorporating cystatin C and BUN to estimate eGFR:

eGFR Equation	**Formula**
Creatinine cystatin C-based CKID equation (Schwartz et al. 2012)	eGFR (mL/min/1.73 m^2) = $39.8 \times [ht/sCr]^{0.456} \times [1.8/cysC]^{0.418} \times [30/BUN]^{0.079} \times [1.076^{male}]\ [1.00^{female}] \times [ht/1.4]^{0.179}$

BUN = blood urea nitrogen (mg/dL); CKID= chronic kidney disease in children; cysC = cystatin C (mg/L); eGFR= estimated glomerular filtration rate; ht = height (m); sCr =standardized serum creatinine (mg/dL).

- Exploratory analysis will be performed using the creatinine cystatin C-based CKID equation for patients ≥2 years of age.
- Change from baseline is calculated at the patient level at each visit. Summary statistics will describe the values and mean change (95% CI) from baseline at each visit. Plots of mean values may be presented over time and by cohort.

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.
  - Increase in hemoglobin must be observed at 2 separate assessments obtained at least 4 weeks (a minimum of 26 days) apart, and any measurement in between.

For Switch Cohort only:

- In adolescents (12–17 years), 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.
- In children younger than 12 years old, proportion of caregivers with preference for crovalimab at Week 17, after switching from eculizumab or ravulizumab, as assessed by the caregiver-reported version of the PPQ developed by the Sponsor.

For each of these cohorts, proportions will be reported with 2-sided 95% CIs, and are calculated with the number of evaluable patients in the respective cohort as the denominator.

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

For patients who discontinue crovalimab and continue to be followed on study, data collected after discontinuation and/or restart of treatment will be analyzed in an exploratory fashion, separately from other exploratory endpoints. These exploratory analyses will be performed to describe the clinical course of TMA-relevant parameters (e.g., platelets, LDH, serum creatinine) over time.

4.5 SAFETY ANALYSES

Safety analyses will be performed based on the safety-evaluable population as defined in Section 3. Analyses will be performed overall and by cohort (i.e., Naive Cohort, Switch Cohort, and Pretreated Cohort).

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

4.5.1 Extent of Exposure

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

4.5.2 Adverse Events

All verbatim AE terms will be mapped to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms at the time of analysis, and AE severity will be graded according to the most recent version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) at the time of analysis. All AEs, SAEs, AEs leading to death, AEs of special interest, and AEs leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent AEs) 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.

4.5.3 Laboratory Data

Relevant laboratory data, including change from baseline, will be displayed by time, with grades identified where appropriate. Additionally, shift tables of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grades.

4.5.4 Vital Signs and ECG

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

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

Enrollment, study treatment discontinuation, and discontinuation from the study will be summarized by cohort. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by cohort. Compliance regarding different patient reported outcome questionnaires will also be summarized by cohort.

4.6.2 Summaries of Demographics and Baseline Characteristics

Analyses will be performed by treatment cohort and overall. Demographic and baseline characteristics will be summarized using number of records per variable, means, standard deviations, medians, and ranges (continuous variables) or absolute frequencies and proportions (categorical variables), as appropriate.

Demographic and baseline characteristics include: age, sex, race/ethnicity, weight, kidney transplant history, dialysis status at baseline, baseline LDH values, and history of LDH levels (for Switch Cohort), and other laboratory parameters of interest.

Disease history and patient treatment history will be summarized using descriptive statistics and/or listings.

4.6.3 Pharmacokinetic Analyses

Analyses will be performed by cohort and overall based on the PK population as defined in Section 3. Serum concentrations of crovalimab (e.g., maximum concentrations [C_{max}] and trough concentrations [C_{trough}]) will be presented descriptively, including arithmetic and geometric means, medians, ranges, standard deviations, and coefficients of variation, and in graphs (including concentrations versus time plots on linear and semi-logarithmic scales) as appropriate. For patients in the Switch Cohort (and for switching patients in the Pretreated Cohort), concentrations of ravulizumab and eculizumab at the time of crovalimab initiation will be presented descriptively including arithmetic and geometric means, medians, ranges, 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, race, sex, and body weight, on these parameters will be investigated graphically. Interpatient variability and drug accumulation will be evaluated. Details of the mixed effects modeling and results of these analyses will be reported in a document separate from the Clinical Study Report.

Additional exploratory PK analyses may be conducted as appropriate and will be detailed in a separate document. The relationship between drug exposure and efficacy, safety or PD endpoints and kinetics may also be explored. Data may be pooled with data from other studies evaluating crovalimab in aHUS or in other indications. These analyses will be reported in a dedicated report.

4.6.3.1 Dose Confirmation Analyses

Interim PK analyses will be conducted, as part of JMC evaluations, after at least 5 evaluable patients of each dose confirmation group (DCG; DCG 1: ≥20 kg to <40 kg, DCG 2: ≥5 kg to <20 kg) have completed 8 weeks of treatment and have reached the Week 9 evaluation (as per Protocol Section 3.1.2). DCG 1 or 2 patients that discontinued study treatment prematurely (before Week 9) will be replaced in the DCG. DCG 1 or 2 patients that have complete loss of crovalimab exposure (i.e., two consecutive concentrations <10 μg/mL during the first 8 weeks of treatment) associated with ADA positivity will be considered as "non-evaluable" and also will be replaced in the DCG.

Serum concentrations of crovalimab and PK parameters derived from the population PK model will be estimated and presented, as described above (see Section 4.6.3). The population PK model that was developed prior to the study will be used to perform empirical Bayesian analyses, and will be updated (if necessary), after all 5 patients of each DCG have reached at least 8 weeks of crovalimab treatment. If the predictive performance of the PK model (either unchanged or updated) is deemed acceptable, the model will be used to provide simulations to ensure that similar PK exposure metrics at steady state (i.e., $C_{trough,ss}$) and their dispersion (i.e., 90% prediction intervals) are achieved in pediatric patients, across the body weight continuum, and adolescent/adult patients (weighing at least 40 kg). Additionally, PK-PD relationship with PD parameters of interest (i.e., LIA, free C5 if available) will also be presented for each DCG, to ensure that crovalimab trough concentrations associated with complete terminal complement activity inhibition (i.e., approximately above 100 μg/mL) are achieved and maintained throughout the dosing interval. The dosing strategy for each DCG (weighing ≥20 kg to <40 kg or ≥5 kg to <20 kg) will be further adapted if the initial dosing regimen administered is determined to be inappropriate as assessed by the JMC review (i.e., if defined dose confirmation criteria are not met). In such situations, an additional cohort of 5 patients with the same body weight range (either weighing ≥20 kg to <40 kg or

≥5 kg to <20 kg) will be enrolled and will receive the updated dosing regimen. The same data review process (via JMC) will take place to confirm the adequacy of the updated dosing strategy in the new cohort of patients. If required, the protocol will be amended with a revised dosing schema for patients weighing <40 kg.

Further details about the dose confirmation analyses will be provided in a JMC Agreement.

4.6.4 Exploratory Biomarker Analyses

Exploratory biomarker analyses will be described in detail in a separate biomarker SAP.

4.6.5 Immunogenicity Analyses

Analyses will be performed by cohort and overall as applicable based on the immunogenicity-evaluable population as defined in Section 3. The numbers and proportions of anti-drug antibody (ADA)-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized. When determining post-baseline incidence, patients are considered to be ADA positive, if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (i.e., treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater than the titer of the baseline sample (i.e., treatment-enhanced ADA response). Patients are considered to be ADA negative, if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (i.e., treatment unaffected ADA response).

ADA responses may be further classified as transient ADA response or persistent ADA response as follows and summarized using descriptive statistics:

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

samples (irrespective of any negative samples in between) were separated by a period of 16 weeks or longer, or

Treatment-induced ADA incidence only in the last sampling time point of the treatment study period.

For ADA-positive patients, the percentage of patients with loss of PK and PD will be calculated as exposure below 100 μg/ml and CH50 above 30 U/ml.

Exploratory analyses to assess the relationship between ADA status and safety, efficacy, pharmacokinetics, and biomarker endpoints may be performed and reported via descriptive statistics.

4.6.6 Pharmacodynamic / Biomarker Analyses

The change over time in PD/biomarker endpoints (Table 2) will be presented using summary statistics, including means, medians, ranges, standard deviations, and coefficients of variation.

4.7 INTERIM ANALYSES

Interim analyses for efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity may be performed as part of JMC evaluations, at specific time points, to monitor patient safety, and to confirm the dose to be administered or to support regulatory submissions.

5. SUPPORTING DOCUMENTATION

Refer to Appendix 1.

Appendix 1 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 any evidence of kidney damage, neither GFR category/stage G1 nor G2 fulfill the criteria for CKD.

[a] Relative to young adult level.

Sources: KDIGO 2012; National Kidney Foundation® (Adult eGFR) calculator; and National Kidney Foundation® (Pediatric eGFR) calculator.

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