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)

NCT Number: NCT04861259

Document Date: Statistical Analysis Plan Version 2: 04-Dec-2023

STATISTICAL ANALYSIS PLAN

STUDY 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)

STUDY NUMBER:	BO42353
STUDY NAME:	COMMUTE-a
VERSION NUMBER:	2
ROCHE COMPOUND(S):	Crovalimab (RO7112689)
EUDRACT NUMBER:	2020-002475-35
IND NUMBER:	151,511
NCT NUMBER	NCT04861259
EU CT NUMBER	2023-505089-27-00
PLAN PREPARED BY:	[redacted] M.Sc.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

SPONSORS:	F. Hoffmann-La Roche Ltd. Chugai Pharmaceutical Co. Ltd.
LEGAL REGISTERED ADDRESS:	Grenzacherstrasse 124 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp on the last page of this document.

CONFIDENTIAL

This is an F. Hoffmann-La Roche Ltd document that contains confidential information. Nothing herein is to be disclosed without written consent from F. Hoffmann-La Roche Ltd.

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 BO42353 (Version, Approval Date)
2	See electronic date stamp on the last page of this document.	Version 6, 16 May 2023
1	20 May 2021	Version 3, 6 April 2021

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The Statistical Analysis Plan (SAP) for Study BO42353 has been primarily amended [redacted] to implement the Sponsor's responses (from September 2021) to an U.S. Food and Drug Administration (FDA) information request (from August 2021) on Study BO42353 SAP Version 1. [redacted]

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.
	[redacted]	
	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 BO42353 Protocol Version 6.
	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 fractions and PK parameters of crovalimab.

Section	Description of Change	Rationale for Change
1.2, 2.2, and Figure 1	[redacted]	[redacted]
1.2 and 2.2	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.	Alignment with Study BO42353 Protocol Version 6.
1.2.2 and 4.7	Immunogenicity analyses have been added to the list of analyses that will be reviewed by the JMC.	Alignment with Study BO42353 Protocol Version 6.
2.2	[redacted]	[redacted]

Section	Description of Change	Rationale for Change
3	Analysis populations previously described in text are now presented in table format.	Alignment with latest SAP template.
	[redacted]	
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.
	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 based on 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.

Section	Description of Change	Rationale for Change
4.2.1	[redacted]	[redacted]
4.2.3		

Section	Description of Change	Rationale for Change
4.2.4	The language on subgroup analyses has been amended and streamlined.	[redacted]
4.3	Further clarifications with regards to the definitions of end of cTMAr and duration of cTMAr have been added in the definitions of the respective secondary efficacy endpoints.	To address feedback from the FDA on Study BO42353 SAP Version 1.
	The proposed exploratory efficacy analysis of the proportion of patients with at least a 3-point improvement from baseline in the FACIT-Fatigue was removed.	As it is exploratory and not tied to a study endpoint.
	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.
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.

Section	Description of Change	Rationale for Change
4.4 and 1.1 (cont.)	Week 13 for the following exploratory efficacy endpoint has been added in Section 1.1: • In adults (≥18 years), mean treatment satisfaction with crovalimab, as measured by the TSQM9 at Week 13 and Week 25. Accordingly, Week 13 has been added as an additional time point of analysis of this exploratory efficacy endpoint in Section 4.4.	As per the schedule of assessments in Study BO42353 Protocol.
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.
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 safety, PK, PD, and immunogenicity as part of JMC evaluations.	Alignment with Study BO42353 Protocol Version 6.

Section	Description of Change	Rationale for Change
Appendix 2	Schedule of activities has been removed.	As per latest SAP template and for consistency with the SAP Version 2 for Study BO42354 (COMMUTE-p).

ADA = anti-drug antibody; aHUS = atypical hemolytic uremic syndrome; cTMAr = complete thrombotic microangiopathy response; DTDC = drug-target-drug complex; eCRF = electronic Case Report Form; eGFR = estimated glomerular filtration rate; FACIT = Functional Assessment of Chronic Illness Therapy; 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; SNP = single nucleotide polymorphism; TSQM9 = ;Treatment Satisfaction Questionnaire for Medication-9.

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 15
   - 1.1 Objectives, Endpoints, and Estimands 16
   - 1.2 Study Design 22
   - 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 28
   - 4.2.1 Definition of Primary Efficacy Endpoint/Estimand 28
   - 4.2.2 Main Analytical Approach for Primary Efficacy Endpoint 28
   - 4.2.3 [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 36
   - 4.5.1 Extent of Exposure 36
   - 4.5.2 Adverse Events 36
   - 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 37
   - 4.6.3 Pharmacokinetic Analyses 37

4.6.4 Exploratory Biomarker Analyses 37
4.6.5 Immunogenicity Analyses 38
4.6.6 Pharmacodynamic / Biomarker Analyses 39
4.6.7 Health Status Utility 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 16
Table 2 Secondary/Exploratory Objectives and Corresponding Endpoints 17
[redacted] .. 25
.. 26
Table 5 Baseline Definitions 27

LIST OF FIGURES

Figure 1 Study Schema 23

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
eGFR	estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
FACIT	Functional Assessment of Chronic Illness Therapy
ICE	inter-current event
ICH	International Council on Harmonization
IV	intravenous
IxRS	interactive voice or web-based response system
JMC	Joint Monitoring Committee
KDQoL	Kidney Disease Quality of Life survey
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
QLQ-C30	Quality of Life Questionnaire Core 30
SAE	serious adverse event

SAP	Statistical Analysis Plan
SC	subcutaneous
SMART-Ig	Sequential Monoclonal Antibody Recycling Technology immunoglobulin
SNP	single nucleotide polymorphism
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 BO42353 (COMMUTE-a). The analyses described in this SAP will supersede those specified in the COMMUTE-a 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).

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 protein 5 (C5) 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] • [redacted] • [redacted] – [redacted] – [redacted] [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 9. • Proportion of patients with change from baseline to Week 25 (after 24 weeks on treatment) in chronic kidney disease (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.

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 C5 SNP Cohort	<u>For ALL (Naive, Switch, and C5 SNP) Cohorts:</u> • Change in serum creatinine from baseline to Week 25 (after 24 weeks on treatment). • 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.

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 C5 SNP Cohort (cont.)	• In adults (≥18 years), mean treatment satisfaction with crovalimab, as measured by the Treatment Satisfaction Questionnaire for Medication-9 (TSQM9) 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 having achieved cTMAr and remain in study follow-up (as per Protocol Section 4.7.2). • 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> • 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. <u>For C5 SNP Cohort only:</u> • Describe the clinical course of C5 SNP patients on crovalimab treatment.

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

Safety Objective	Corresponding Endpoints
• To evaluate the overall safety and tolerability of crovalimab	For All (Naive, Switch, and C5 SNP) Cohorts: • 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. For Switch Cohort only: • Incidence and severity of clinical manifestations of drug-target-drug complexes (DTDCs) in Switch Cohort patients who switched to crovalimab treatment from either eculizumab or ravulizumab treatment.
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the pharmacokinetics of crovalimab • 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 Objectives	**Corresponding Endpoints**
• To evaluate the immune response to crovalimab • The 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 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.
	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 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).
	Exploratory Health Status Utility Objective		**Corresponding Endpoint**
•	To evaluate health status utility scores of adolescent and adult patients treated with crovalimab	•	Change from baseline to Week 25 (after 24 weeks on treatment) in EuroQol 5Dimension 5-Level Questionnaire (5 level version; EQ-5D-5L) index-based and Visual Analog Scale (VAS) scores.

aHUS= atypical hemolytic uremic syndrome; 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 ≥12 years and with a body weight of ≥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.

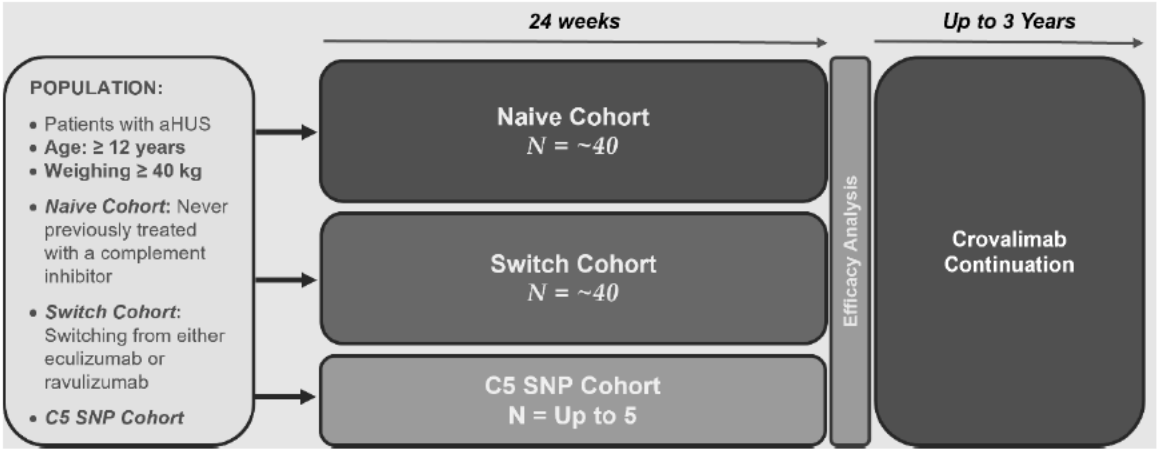
Efficacy endpoints will be analyzed separately for each cohort. Each cohort's role in the evaluation of efficacy is outlined below:

- Naive Cohort will enroll approximately 40 patients 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 primary, 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 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.
- C5 Single Nucleotide Polymorphism (SNP) Cohort will enroll patients with known C5 polymorphisms whose thrombotic microangiopathy (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.

Approximately 40 patients in the Naive Cohort and approximately 40 patients in the Switch Cohort will be enrolled in this study at approximately 80 sites globally (in approximately 20 countries). Recruitment to the Naive Cohort may be kept open to allow supplemental enrollment to replace patients whose complement-mediated aHUS diagnosis was ruled out post-enrollment, in order to have approximately 40 efficacy-evaluable patients for the primary efficacy analysis. No sample size is pre-specified for the C5 single nucleotide polymorphism (SNP) Cohort, and up to 5 patients are expected to be enrolled throughout the study.

The study schema is shown in Figure 1.

Figure 1 Study Schema



aHUS = atypical hemolytic uremic syndrome; N = number of patients; 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 Naive Cohort have reached the Week 25 visit (after 24 weeks on treatment) or discontinued from the crovalimab treatment, whichever occurs first.

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 BO42353, Section 3, for further details of the study design and to Study Protocol BO42353, Appendix 2, 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 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 (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.

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 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 as well as the strict inclusion/exclusion criteria of the study which were defined to enroll patients with primary complement-mediated aHUS, approximately 40 patients in the Naive Cohort and approximately 40 patients in the Switch Cohort are deemed sufficient to adequately characterize 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.

[redacted]

[redacted]

[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 complement mediated aHUS diagnosis being ruled out post-enrollment. 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 approximately 40 evaluable patients for the primary efficacy analysis.

3. ANALYSIS SETS

[redacted] 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.



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 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 C5 SNP 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 clinical 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.

[redacted]

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

[redacted]

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.

[redacted]

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

[redacted]

[redacted]

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 40 evaluable patients enrolled in the Naive Cohort have reached the Week 25 visit, or discontinued from crovalimab treatment, whichever is first.

[redacted].

[redacted]

[redacted]

[redacted]

[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 the 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 equations will be used to estimate eGFR:

Age at Screening	eGFR Equation	Formula
Adolescents (12-17 years)	Creatinine-based bedside Schwartz (Schwartz and Work 2009; Levey et al. 2009)	eGFR (mL/min/1.73 m^2) = 41.3 × (height in meters / sCr) if height is expressed in centimeters OR 41.3 × (ht / sCr), if height is expressed in meters
Adults (≥18 years)	2009 CKD-EPI creatinine equation (Levey et al. 2009)	eGFR (mL/min/1.73 m^2) = $141 \times \min(sCr / \kappa,1)^{\alpha} \times \max(sCr / \kappa,1)^{-1.209} \times 0.993^{AGE}$ [× 1.018 if female] [× 1.159 if black] κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of sCr/κ or 1, and max indicates the maximum of sCr/κ or 1.

CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration; eGFR= estimated glomerular filtration rate; sCr = standardized serum creatinine (mg/dL).

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 value 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 equations presented above. Due to different equations used to calculate eGFR for different age groups, sensitivity analyses regarding CKD stage may be also performed separately for the different age groups.

  – 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.

- 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.
  - Descriptive statistics for the total score, including mean, median, standard deviation, and range, will be used to summarize the patient-reported values and the changes from baseline to Week 25. Plots of mean total scores and 95% CIs at each time point up to Week 25 will be presented by cohort.

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 C5 SNP) Cohorts

- Change in serum creatinine from baseline to Week 25 (after 24 weeks on treatment).
- In adults ($\geq$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, 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.
- Change from baseline to Week 25 (after 24 weeks on treatment) in the number of missed days of school or work, as applicable.

- 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. It will be presented with other descriptive statistics for each time point, including standard deviation and 95% confidence interval.
- 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 to Week 25. 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

- 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 each of these cohorts, proportions will be reported with 2-sided 95% CIs will be computed using Wilson's score method, and are calculated with the number of evaluable patients in the respective cohort as the denominator.

For patients in the C5 SNP 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 by cohort (Naive Cohort, Switch Cohort, C5 SNP Cohort), for switch cohorts combined (Switch Cohort and Switching C5 SNP patients) and overall, as applicable.

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 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 crovalimab cohort.

4.6.2 Summaries of Demographics and Baseline Characteristics

Analyses will be performed by 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 C5 SNP 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 PK concentration–time data of crovalimab. Population and individual 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. 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 PK 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.

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

4.6.7 Health Status Utility Analyses

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

4.7 INTERIM ANALYSES

No interim efficacy analyses are planned. Interim analyses for safety, pharmacokinetics, pharmacodynamics, and immunogenicity may be performed as part of JMC evaluations, at specific time points, to monitor patient safety, 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 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, National Kidney Foundation® (Pediatric eGFR) calculator.

6. REFERENCES

Afshar-Kharghan V. Atypical hemolytic uremic syndrome. Hematology Am Soc Hematol Educ Program 2016(1);217–25.

Brocklebank V, Wood KM, Kavanagh D. Thrombotic microangiopathy and the kidney. Clin J Am Soc Nephrol 2018;13(2):300–17.

Fremeaux-Bacchi V, Fakhouri F, Garnier A, et al. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. Clin J Am Soc Nephrol 2013;8(4):554–62.

Fukuzawa T, Sampei Z, Haraya K, et al. Long lasting neutralization of C5 by SKY59, a novel recycling antibody, is a potential therapy for complement-mediated diseases. Sci Rep 2017;7(1):1080.

Goodship THJ, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int 2017;91(3):539–51.

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [resource on the Internet]. 2013 [cited 2020 Aug 07]. Available from: https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf.

Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med 2013;368(23):2169-81.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009;150(9):604-12.

Licht C, Ardissino G, Ariceta G, et al. The global aHUS Registry: methodology and initial patient characteristics. BMC Nephrol 2015a;16:207.

National Kidney Foundation® (Adult eGFR) Calculator. Available from: https://www.kidney.org/professionals/kdoqi/gfr_calculator.

National Kidney Foundation (Pediatric eGFR) Calculator. Available from: https://www.kidney.org/professionals/kdoqi/gfr_calculatorped.

Nester CM, Barbour T, de Cordoba SR, et al. Atypical aHUS: state of the art. Mol Immunol 2015;67(1):31-42.

Nester CM, Thomas CP. Atypical hemolytic uremic syndrome: what is it, how is it diagnosed, and how is it treated? Hematology Am Soc Hematol Educ Program 2012;2012:617–25.

Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17(8):857-72.

Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med 2009;361(17):1676-87.

Rondeau E, Scully M, Ariceta G, et al., and the 311 Study Group. The long-acting C5 inhibitor, ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naive to complement inhibitor treatment. Kidney Int 2020;97(6):1287–96.

Rubin DB. Multiple imputation after 18+ years. Journal of the American statistical Association. 1996;91(434):473-89.

Schwartz GJ and Work DF. Measurement and estimation of GFR in children and adolescents. J Am Soc Nephrol. 2009; 4(11): 1832-643.

Schwartz GJ, Schneider MF, Maier PS, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012;82(4):445-453.

Signature Page for Statistical Analysis Plan BO42353 Crovalimab (COMMUTE-a) Vers
System identifier: RIM-CLIN-513246

Approval Task	[redacted] Company Signatory 04-Dec-2023 11:10:45 GMT+0000