Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ALXN1210-TMA-313

A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study of Ravulizumab in Adult and Adolescent Participants who have Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplant (HSCT)

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1. APPROVAL SIGNATURES

This document has been e-signed in ARISE (Veeva RIM). Please refer to the last page for signature details.

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2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

1. APPROVAL SIGNATURES 2
2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 3
TABLE OF CONTENTS 3
LIST OF TABLES 7
LIST OF FIGURES 7
3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 8
4. DESCRIPTION OF THE PROTOCOL 10
4.1. Study Design 10
4.2. Objectives and Endpoints 12
4.3. Planned Analyses 14
4.3.1. Dose Confirmation Analysis 14
4.3.2. Interim Analysis 14
4.3.3. Primary Analyses 14
4.3.4. Final Analysis 15
4.4. Data Monitoring Committee 15
4.5. Changes from Analyses Specified in the Protocol 15
4.6. Changes from Analyses Specified in the Previous Version of the SAP 15
5. DEFINITIONS 20
5.1. Efficacy 20
5.1.1. Primary Endpoint(s) 20
5.1.2. Secondary Endpoints 20
5.1.3. Exploratory Endpoints 26
5.2. PK and PD Endpoints 27
5.3. Safety 27
5.3.1. Adverse Events 27
5.3.2. Vital Signs 28
5.3.3. Laboratory Assessments 28
5.3.4. Electrocardiograms 28
5.3.5. Physical Examinations 28

5.3.6. Immunogenicity 28
6. DATA SETS ANALYZED (STUDY POPULATIONS) 29
6.1. All-Enrolled Set 29
6.2. ITT Set 29
6.3. Full Analysis Set 29
6.4. Safety Set 29
6.5. Per Protocol Set 29
6.6. PK and PD Analysis Set 30
7. STATISTICAL ANALYSIS 31
7.1. General 31
7.1.1. Handling of Dropouts or Missing Data 31
7.2. Study Participants 32
7.2.1. Disposition of Participants 32
7.2.2. Protocol Deviations 33
7.2.3. Demographics, Disease Characteristics, and History 33
7.2.3.1. Demographics and Baseline Characteristics 33
7.2.3.2. Disease and Transplant Characteristics 33
7.2.3.3. Medical/Surgical History and Baseline Physical Examination 35
7.2.4. Prior and Concomitant Medications/Therapies 35
7.3. Efficacy Analyses 36
7.3.1. Primary Efficacy Endpoint Analysis 36
7.3.1.1. Subgroup Analysis 37
7.3.1.2. Sensitivity Analyses 38
7.3.2. Analyses of Key Secondary Efficacy Endpoints 40
7.3.2.1. Overall Survival 40
7.3.2.2. Non-relapse Mortality 41
7.3.2.3. Number of TMA Response Criteria Met 42
7.3.2.4. Hematologic Response 42
7.3.2.5. Estimated Glomerular Filtration Rate 43
7.3.3. Analyses of Additional Secondary Endpoints 44
7.3.3.1. TMA Response 44
7.3.3.2. Time to TMA Response 44
7.3.3.3. TMA Response at and up to Specific Time Points 44

7.3.3.4. Other Response Endpoints....45
7.3.3.5. Hematologic Parameters....45
7.3.3.6. Modified TMA Response....45
7.3.3.7. Loss of Response....46
7.3.3.8. TMA Relapse....46
7.3.3.9. Duration of Response....46
7.3.3.10. Organ Dysfunction....46
7.3.3.11. Subgroup Analysis for Secondary Efficacy Analyses....47
7.3.4. Exploratory Analyses....48
7.3.4.1. Biomarkers and Genetic Markers....48
7.3.4.2. Clinical Outcomes Assessment....48
7.3.4.3. Health Resource Utilization....49
7.4. PK and PD Analyses....49
7.5. Safety Analyses....50
7.5.1. Study Duration, Treatment Compliance, and Exposure....50
7.5.2. Adverse Events....50
7.5.2.1. Overall Summary of AEs....51
7.5.2.2. AEs and SAEs by SOC and PT....52
7.5.2.3. AEs and SAEs by SOC, PT, and Relationship....52
7.5.2.4. AEs and SAEs by SOC, PT, and Severity....52
7.5.2.5. Deaths, Other SAEs, and Other Significant Adverse Events....52
7.5.2.6. TEAE by subgroup....52
7.5.3. Geographic region (Japan, rest of the world)Other Safety....52
7.5.3.1. Analyses for Laboratory Tests....52
7.5.3.2. Vital Signs....53
7.5.3.3. Electrocardiograms....53
7.5.3.4. GVHD Status....53
7.5.3.5. Immunogenicity....53
7.6. COVID-19 Related Analyses....53
8. REFERENCES....54
9. APPENDICES....55
9.1. Protocol Schedule of Events....55
9.2. Sample Size, Power, and Randomization....55

9.3. Technical Specifications for Derived Variables 55
9.3.1. Study Periods 56
9.3.2. Definition of Baseline Values 57
9.3.3. Change From Baseline 58
9.3.4. Percent Change from Baseline 58
9.3.5. Duration Calculation 58
9.3.6. Dates and Points of Reference 58
9.3.7. Analysis Visits 58
9.3.8. Analysis Value 59
9.3.9. Adverse Events 59
9.3.10. Concomitant Medications/Therapies 60
9.3.11. Death Dates 60
9.3.12. Serum Creatinine and eGFR 60
9.3.13. Platelets and Hemoglobin 61
9.3.14. EQ-5D-5L Scoring Algorithm for Health State Index 61
9.3.15. Scoring Algorithm for FACIT-Fatigue 62
9.4. Additional Subgroup Analysis 62
9.4.1. Japanese Subgroup analysis 62
9.4.2. East Asian Subgroup Analysis 63

LIST OF TABLES

Table 1: Abbreviations and Acronyms 8
Table 2: Objectives and Endpoints 12
Table 3: Criteria for Clinical Worsening 20
Table 4: Overview of TMA Response 21
Table 5: Censoring Rules for EFS 37
Table 6: Censoring Rules for OS 41
Table 7: Censoring Rules for Non-relapse Mortality 42
Table 8: Participants and Study Periods Included in Each Treatment Group for the Primary Analysis at 26 Weeks 56

LIST OF FIGURES

Figure 1: Study Design Schematic 11
Figure 2: F-S Scoring Algorithm 39

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this statistical analysis plan (SAP).

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
ADA	antidrug antibody
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AE	adverse event
AESI	adverse event of special interest
BSC	best supportive care
C5	complement component 5
CaGI-C	Caregiver Global Impression of Change
CaGI-S	Caregiver Global Impression of Severity
CEAC	Clinical Event Adjudication Committee
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	confidence interval
CIF	cumulative incidence function
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DMC	Data Monitoring Committee
EC	exclusion criteria
ECG	electrocardiogram
eCRF	electronic case report form
EFS	event-free survival
eGFR	estimated glomerular filtration rate
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level
F-S	Finkelstein-Schoenfeld
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
GI	gastrointestinal
GVHD	graft versus host disease
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
HSCT-TMA	hematopoietic stem cell transplant-associated thrombotic microangiopathy
IA	Interim analysis
IC	inclusion criteria
ITT	Intent-to-Treat
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
MNAR	missing not at random
NRI	nonresponder imputation
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PMM	pattern-mixture model
PPS	Per Protocol Set
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PT	Preferred Term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RMST	restricted mean survival time
SAE	serious adverse event
SAP	statistical analysis plan
SF-12	12-item Short Form Health Survey
SoA	Schedule of Activities
SOC	System Organ Class
ST-HUS	Shiga toxin-related hemolytic uremic syndrome
TE	Treatment-Emergent
TEAE	treatment-emergent adverse event
TMA	thrombotic microangiopathy
US TTO	Time Trade-Off value set for the United States
VAS	visual analog scale
WHO-DDE	World Health Organization Drug Dictionary Enhanced
WR	Win-Ratio

4. DESCRIPTION OF THE PROTOCOL

4.1. Study Design

ALXN1210-TMA-313 is a Phase 3, 2-stage, randomized, double-blind, placebo-controlled, multicenter study of ravulizumab in adolescent (≥ 12 to < 18 years of age) and adult (≥ 18 years of age) participants with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). The study will be conducted in 2 stages: a dose confirmation stage (Stage 1), followed by a randomized, double-blind, placebo-controlled treatment stage (Stage 2) once an adequate dosing regimen has been confirmed in Stage 1.

In Stage 1, the dosing regimen for HSCT-TMA participants will be confirmed in an open-label, single-arm period. In Stage 2, participants will be randomized to receive either blinded ravulizumab plus best supportive care (BSC) or a matching placebo plus BSC. Eligible participants include adults and adolescents who received hematopoietic stem cell transplant (HSCT) within 12 months prior to Screening and subsequently developed thrombotic microangiopathy (TMA) that does not resolve within 72 hours after withdrawal or adjustment of any TMA-associated medication and/or treatment of any associated underlying triggering condition.

For all participants enrolled (Stage 1 and Stage 2 participants), the study will consist of 3 periods: a Screening Period of up to 7 days, a 26-week Treatment Period (open-label for Stage 1, and randomized, double-blind, and placebo-controlled for Stage 2), and a 26-week Follow-up Period. All participants will receive BSC for the duration of the study or as long as deemed necessary by the Investigator.

For participants in Stage 1, the pharmacokinetic (PK) and free complement component 5 (C5) data collected over the first 21 days will be analyzed to confirm the adequacy of the initial dosing regimen to achieve complete inhibition of C5. This analysis may result in a modification to the dosing regimen, which will be used in Stage 2. If necessary, additional participants may be enrolled into Stage 1 either prior to or during the analysis (eg, if the distribution of the initial 10 is not optimal) or after the analysis if the dosing regimen cannot be confirmed.

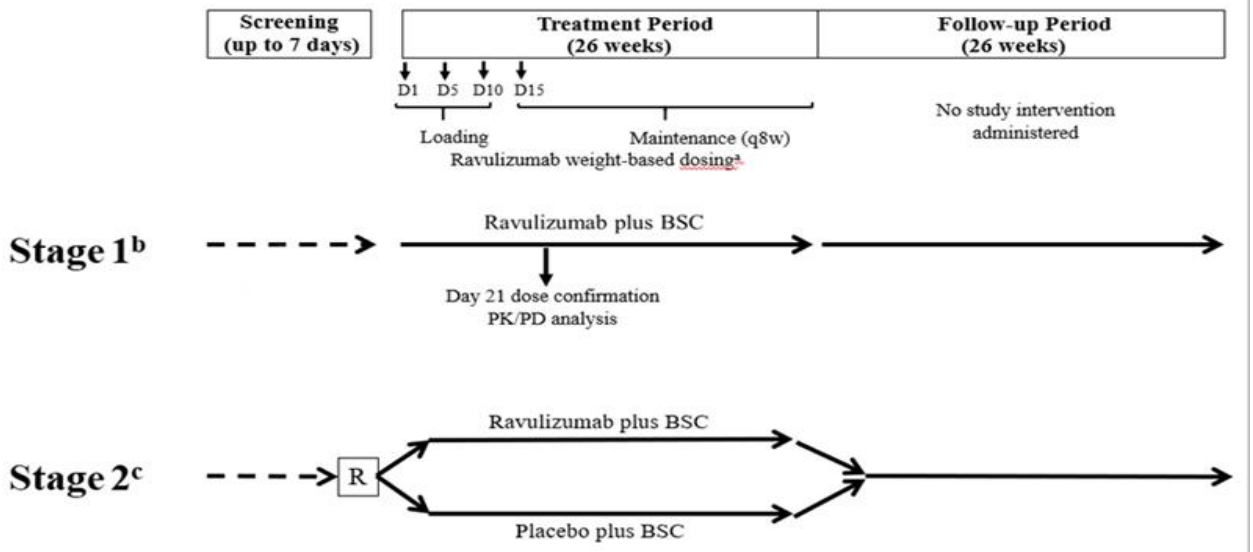
Following the dose confirmation assessment in Stage 1, approximately 124 participants will be enrolled in Stage 2 (a minimum of 10 adolescent participants ≥ 12 to < 18 years of age are planned to be enrolled). In Stage 2, participants will be randomized on Day 1 in a 1:1 ratio to receive either ravulizumab plus BSC or matching placebo plus BSC for 26 weeks (Figure 1). Randomization will be stratified based on geographic region (Japan and the rest of the world), and acute graft versus host disease (GVHD) status (no acute GVHD, Grade I-II acute GVHD, or Grade III-IV acute GVHD). Participants with an acute GVHD status of "acute GVHD present but cannot be graded" should be included in the "Grade I-II acute GVHD" stratification group in the IRT system. Participants with chronic GVHD rather than acute GVHD should be classified as "no acute GVHD".

Supplemental doses of ravulizumab will be CCI [redacted] for participants in Stage 1 and Stage 2 after Day 15 and within 4 weeks of maintenance dose according to protocol. In addition, participants in either treatment group who meet the pre-defined criteria for clinical worsening after Day 15 during the 26-week Treatment Period will be eligible for rescue treatment and may be unblinded for the Investigator to

determine appropriate rescue treatment. However, eculizumab is prohibited, and if ravulizumab is selected as rescue treatment, then concomitant administration of therapeutic plasma exchange is prohibited. Any participant in the placebo treatment group who receives ravulizumab as post-unblinding rescue treatment must enter a new 26-week Treatment Period followed by a 26-week Follow-up Period after the decision has been made to administer post-unblinding rescue treatment with ravulizumab.

After completion of the 26-week Treatment Period, all participants will enter the Follow-up Period and remain in the study for 26 weeks without further ravulizumab administration.

Figure 1: Study Design Schematic



Note: This study will include at least 10 participants in Stage 1 and 124 participants in Stage 2.

Note: Eligibility evaluation may be based on laboratory results obtained during the Screening Period or ≤ 14 days prior to the start of the Screening Period. Local or central laboratory results may be used to determine eligibility, with the exception of the ST-HUS screen, which must be confirmed by the central laboratory. Participants may be enrolled prior to availability of laboratory results from the ST-HUS screen and ADAMTS13 test, except in the UK, where all laboratory-based eligibility criteria must be met via local or central laboratory results prior to enrollment.

[a] Initial weight based dosing (Stage 1): 30 to < 40 kg D1 = 1200 mg, D5 = 300 mg, D10 = 300 mg, maintenance (D15 onward) = 2700 mg q8w; 40 to < 60 kg D1 = 2400 mg, D5 = 600 mg, D10 = 600 mg, maintenance (D15 onward) = 3000 mg q8w; 60 to < 100 kg D1 = 2700 mg, D5 = 900 mg, D10 = 900 mg, maintenance (D15 onward) = 3300 mg q8w; ≥ 100 kg D1 = 3000 mg, D5 = 900 mg, D10 = 900 mg, maintenance (D15 onward) = 3600 mg q8w.

[b] Open label.

[c] Double-blind Treatment Period followed by a Follow-up Period.

Abbreviations: ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; BSC = best supportive care; D = day; PD = pharmacodynamic; PK = pharmacokinetic; q8w = every 8 weeks; R = randomization; ST-HUS = Shiga toxin-related hemolytic uremic syndrome

4.2. Objectives and Endpoints

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of ravulizumab versus placebo in the treatment of adult and adolescent participants with HSCT-TMA	• Event free survival during the 26-week Treatment Period defined as the time from randomization until the first of the two following events: o Death o Clinical worsening[a]
Secondary	
Key Secondary Endpoints	
To assess overall survival	• Overall survival by Week 26 • Overall survival by Day 100
To assess non-relapse mortality	• Non-relapse mortality during the 26-week Treatment Period
To characterize TMA response after treatment with ravulizumab	• Number of TMA response criteria met during the 26-week Treatment Period • Hematologic response during the 26-week Treatment Period
To assess improvement in organ dysfunction	• Change from baseline in eGFR at Week 26
Other Secondary Endpoints	
To characterize TMA response after treatment with ravulizumab	• TMA response during the 26-week Treatment Period • Time to TMA response during the 26-week Treatment Period • TMA response and time to response for each individual component of TMA during the 26-week Treatment Period • Time to hematologic response during the 26-week Treatment Period • Hemoglobin response during the 26-week Treatment Period • Platelet response during the 26-week Treatment Period • Partial response during the 26-week Treatment Period • Loss of TMA response during the 26-week Treatment Period • Duration of TMA response during the 26-week Treatment Period and through 52 weeks • Changes from Baseline during the 26-week Treatment Period and through 52 weeks in the following: o Haptoglobin o Platelets o LDH o Hemoglobin • Modified TMA Response during the 26-week Treatment Period

Table 2: Objectives and Endpoints

Objectives	Endpoints
To assess improvement in organ dysfunction	• Change from Baseline in eGFR at Week 52 • Change from Baseline in TMA-associated organ dysfunction in renal system, cardiovascular system, pulmonary system, CNS, and GI system at 26 weeks and 52 weeks
To assess TMA relapse	• TMA relapse during the Follow-up Period
To assess overall survival	• Overall survival by Week 52
To assess non-relapse mortality	• Non-relapse mortality by Day 100, and through 52 weeks
Pharmacokinetic and Pharmacodynamic Endpoints	
To assess PK/PD of ravulizumab in adult and adolescent participants with HSCT-TMA	• Serum concentrations of ravulizumab over time • Changes in serum free C5 concentrations over time • Changes in serum total C5 concentrations over time
Safety	
To characterize the safety profile of ravulizumab in adult participants with HSCT-TMA	• Incidence of treatment-emergent AEs and treatment-emergent SAEs • Changes from Baseline in vital signs and laboratory parameters • Incidence of ADAs and assessment of immunogenicity
Exploratory	
To assess biomarkers, CCI [redacted], in adult and adolescent participants with HSCT-TMA	• Exploratory biomarker analyses will evaluate changes from Baseline in biomarkers, which may include, but are not limited to, CCI [redacted]
To assess complement pathway genetic mutations in adult and adolescent participants with HSCT-TMA	• Incidence of specific complement dysregulation-related mutations
To assess improvement in HRQoL and TMA symptoms in adult and adolescent participants with HSCT-TMA	• Change from Baseline in HRQoL outcomes as measured by EQ-5D-5L, EQ-5D-5L proxy (version 1), SF-12, and FACIT-Fatigue (in adult participants) and SF-12 (in adolescent participants) • Change from Baseline in TMA symptom severity as perceived by participant, caregiver, and clinician using PGI-S, CaGI-S, and CGI-S (in adult participants) • Change in TMA symptoms during the Treatment Period as perceived by participant, caregiver, and clinician using PGI-C, CaGI-C, and CGI-C (in adult participants)
To describe medical resource utilization in participants with HSCT-TMA	• Number, reason, and duration of hospitalizations including stays in intensive care unit (if applicable) • CCI [redacted] • Number of outpatient medical encounters (including physician or emergency room visits) and the underlying reason

Note: The criteria for clinical worsening must be confirmed by 2 independent samples collected at least 8 hours apart (ideally 24 hours apart).

[a] Clinical worsening is defined as meeting 2 or more of the following criteria:

- Doubling of serum creatinine from baseline or new requirement of dialysis
- Increase in LDH > 25% compared to baseline
- Reduction in platelets of > 25% compared to baseline
- Reduction in hemoglobin > 10% compared to baseline
- Increased requirement for platelets or RBCs at any time

Abbreviations: ADA = antidrug antibody; AE = adverse events; C5 = complement component 5; CCI [redacted]; CaGI-C = Caregiver Global Impression of Change; CaGI-S = Caregiver Global Impression of Severity; CGI-S = Clinician Global Impression of Severity; CGI-C = Clinician Global Impression of Change; CNS = central nervous system; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol 5-Dimension 5-Level; FACIT = Functional Assessment of Chronic Illness Therapy; GI = gastrointestinal; HSCT-TMA = hematopoietic stem cell transplant thrombotic microangiopathy; LDH = lactate dehydrogenase; PD = pharmacodynamic; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; HRQoL = health-related quality of life; RBC = red blood cell; SAE = serious adverse event; SF-12 = 12-Item Short Form Survey; TMA = thrombotic microangiopathy.

4.3. Planned Analyses

4.3.1. Dose Confirmation Analysis

An early analysis of the PK/pharmacodynamic (PD) data will be initiated when at least 10 participants complete Visit 5 on Day 21. All PK and free C5 data collected in all participants by that time will be analyzed to confirm the adequacy of the initial dosing regimen to achieve complete inhibition of C5.

Several analyses may be conducted prior to 10 participants completing Visit 5 on Day 21 as part of the dose confirmation analysis to support adjustments to the dosing regimen and/or the CCI [redacted] supplemental dosing for participants ongoing in Stage 1. If necessary, additional participants may be enrolled into Stage 1 either prior to or during analysis (eg, if the distribution of the initial 10 is not optimal) or after the analysis if the dosing regimen cannot be confirmed. If necessary, the dosing regimen will be adjusted. Details for the dose confirmation analysis will be included in a separate PK/PD analysis plan.

4.3.2. Interim Analysis

The sample size re-estimation (SSR) was removed in protocol amendment 6.0. Alexion decided not to conduct the optional early efficacy interim analysis described in protocol amendment 6.0. Therefore, no description of the optional early efficacy analysis is provided in this SAP.

4.3.3. Primary Analyses

The primary analysis will be conducted when

- 66 deaths or clinical worsening events occur within week 26, or
- all participants in Stage 2 have been followed for 26 weeks from randomization or withdraw from the initial 26 weeks of the study, and all participants in placebo treatment group who receive ravulizumab as post-unblinding rescue treatment have discontinued from the study or completed Day 29 of the Rescue Treatment Period (R5 Visit in the Schedule of Activities [SoA], Protocol Table 2),

whichever is earlier.

All analyses will be conducted using all data collected up to the data cut for the primary analysis.

4.3.4. Final Analysis

The final study analysis will be conducted at the end of the study, after all participants have completed or discontinued early from the 26-week Follow-up Period.

4.4. Data Monitoring Committee

An independent Data Monitoring Committee (DMC), comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion. The specific responsibilities of the DMC will be described in the DMC Charter, which is maintained as a separate document.

Final decisions regarding the conduct of the study will be made by Alexion after consultation with the DMC. All appropriate regulatory authorities and Ethics Committees will be notified of any significant action.

4.5. Changes from Analyses Specified in the Protocol

Not applicable.

4.6. Changes from Analyses Specified in the Previous Version of the SAP

SAP Version	Version Date	Change	Rationale
1.0	19 Nov 2020	Not applicable	Original version
2.0 DRAFT	Dec 2022	Revised definition of the primary endpoint components	To align with changes made in PA3, the primary endpoint components were updated. Rationale from PA3: “Expansion of platelet eligibility criteria in Section 5.1 requires adjustment to the platelet threshold for those who qualify with a platelet count of >50,000/mm3. To align the endpoint with change in LDH eligibility criteria.”
		Added additional secondary endpoints: Change from Baseline in haptoglobin, platelets, LDH, and hemoglobin	To assess temporal trends in hematologic and renal parameters.

		Added detailed descriptions of estimands related to the primary and key secondary efficacy endpoints/analyses	To bring primary and key secondary endpoints into the estimand framework.
		Removed 52-week, response-based endpoints from the analysis plan	52-week response-based endpoints removed due to lack of laboratory data collection during the follow-up period. Additionally, response-based endpoints at 52 weeks did not align with the previously updated definition of "loss of response", which can only occur in the initial 26-week treatment period. To align with this definition, it is assumed that any response or loss of response during the follow-up period could not be attributed to active drug (or BSC).
		Updated the overall sample size calculations based on updated assumptions and added sample size re-estimation procedure (Section 4.3.2)	Due to enrollment challenges and feasibility issues, the Sponsor reviewed the sample size assumptions in order to reduce the number of participants in Stage 2. Through these efforts, the TMA response treatment effect size is revised based on new information and further evaluation since the initiation of Study ALXN1210-TMA-313, along with expert and regulatory agency feedback. This change in treatment effect size results in a reduction of the sample size for Stage 2. Additionally, in order to mitigate a lower-than-expected TMA response treatment effect size, an SSR is incorporated to provide the opportunity to increase the sample size following an interim analysis performed by an unblinded independent statistical center that is not involved with study

			conduct or final analysis of study data.
		Updated the definition of All-Enrolled Set, FAS, and Per Protocol Set populations (Section 6).	Patients are allowed to be enrolled while results from STEC and/or ADAMTS13 screen are pending. Following the receipt of any positive aforementioned results will exclude patients from the FAS. This change adheres to the principles outlined in ICH E9.
2.0 FINAL	16 Dec 2024	Revised primary endpoint: "Event-free survival during the 26-week Treatment Period defined as time from randomization until the first of the two following events: death and clinical worsening."	To align with the changes in protocol amendment 6.0.
		Added key secondary endpoint: "Number of TMA response criteria met during the 26-week Treatment Period."	To align with the changes in protocol amendment 6.0.
		Time to TMA response during the 26-week Treatment Period and the original primary endpoint of TMA response were moved to other secondary endpoints.	To align with the changes in protocol amendment 6.0.
		Updated the overall sample size calculations based on updated primary endpoint and assumptions	To align with protocol amendment 6.0.
		Removed the sample size re-estimation procedure	To align with protocol amendment 6.0.
		Added the definition of ITT set	To align with protocol amendment 6.0.
		Modified TMA response (during 26-week treatment period) was added as a secondary endpoint and will be analyzed using the same methodology as for TMA response.	To align with protocol amendment 6.0.
		Overall survival by Day 100 was added as a key secondary endpoint and added in the hierarchal testing procedure.	To align with protocol amendment 6.0.
		Additional HSCT was added as an intercurrent event	To align with protocol amendment 6.0.

		Intercurrent events for primary analysis and sensitivity analysis of overall survival through 100 days, 26 weeks, and 52 weeks was updated.	Analysis details for overall survival were clarified to provide a more complete assessment of survival in this patient population.
		Simplified/removed some sensitivity analyses for the non-key secondary endpoints	To streamline some unnecessary sensitivity analyses.
3.0 FINAL	Feb 2025	Clarified that the clinical worsening component of the EFS endpoint will be positively adjudicated	To corroborate the clinical worsening component of the EFS endpoint and in line with the US FDA recommendation
		Added a sensitivity analysis using the win-ratio approach	To use a different approach to analyze the EFS composite endpoint and in line with the US FDA recommendation.
4.0 FINAL	July 2025	Added sensitivity analyses for the primary/key secondary endpoint by treating participants taking prohibited of Ecu or other complement pathway agents as events/non-responders.	To assess treatment effect when treating participants taking prohibited medication as failure/non-responder.
		Added subgroup analysis for Japanese subgroup and East Asian subgroup.	To support country-specific submission for PMDA and NMPA.
		Added the language of sensitivity analysis for primary endpoint/key secondary endpoints where the stratification factors are adjusted if the values stratification factors at baseline and used in randomization stratification factors are different in more than 10% of the participants.	To evaluate the impact of possible mis-stratification during randomization.
		Clarified the death after the informed consent withdrawal could be included in the analysis if the local law and regulation permits.	To align with the local law and regulation about the vital status reporting after the informed consent withdrawal.

		Removed ‘end of study’ in the TEAE definition	To not limit the end of TEAE to the end of study.
		Added subgroup analysis for AE tables	To align AE subgroup analysis with other Rav indications.
		Separated the TEAE reporting by treatment period and follow up period	To align with the AE reporting in other Rav indication

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoint(s)

The primary endpoint, event-free survival (EFS), is defined as the time from randomization until the first of the following two events: death and clinical worsening up to Day 183.

The component of the clinical worsening is described in Table 3 (Protocol Section 3.2).

Table 3: Criteria for Clinical Worsening

Clinical worsening is defined as meeting 2 or more of the following criteria (confirmed by 2-independent samples collected at least 8 hours apart): • Doubling of serum creatinine from baseline or new requirement of dialysis • Increase in LDH > 25% compared to baseline • Reduction in platelets of > 25% compared to baseline • Reduction in hemoglobin > 10% compared to baseline • Increased requirement for platelets or RBCs at any time

Once considered as meeting the protocol criteria for clinical worsening by the Investigator, the met criteria will be documented on the electronic case report form (eCRF). The participants are eligible for rescue treatment if clinical worsening criteria are met after Day 15 during the 26-week Treatment Period. The rescue treatment eligibility must be confirmed by 2 independent samples collected at least 8 hours apart (ideally 24 hours apart), with at least 1 of the 2 samples analyzed by the central laboratory.

For analysis purposes, clinical worsening events will be adjudicated by the Clinical Event Adjudication Committee (CEAC). Only positively adjudicated events will be used for the primary endpoint analysis.

5.1.2. Secondary Endpoints

The key secondary efficacy endpoints of the study are the following:

- Overall survival by Week 26.
  - Survival time will be assessed as the time in days from reference start day (Section 9.3.6) to an event of death within Day 183.
- Overall survival by Day 100
- Non-relapse mortality during the 26-week Treatment Period
  - Non-relapse mortality is defined as a participant's death due to any cause during the study, with the exception of death due to underlying disease progression or relapse (the reason for HSCT). Time to non-relapse mortality is assessed as the

time in days from reference start day (Section 9.3.6) to an event of non-relapse death in the period of analysis.

- Number of TMA response criteria met during the 26-week Treatment Period

The TMA response is defined in Table 4.

Table 4: Overview of TMA Response

		TMA Response Parameter
TMA response	Hematologic response	If baseline platelet count ≤ 50000/mm^3, the following criteria must be met: • Absolute platelet count > 50000/mm^3 without platelet transfusion support during the prior 7 days If baseline platelet count > 50000/mm^3, the following criteria must be met: • ≥ 50% increase in platelet count compared to baseline value without platelet transfusion support during the prior 7 days
		Normalization of LDH and absence of schistocytes [a]
	Renal response	At least 50% reduction of proteinuria[b] from Baseline

CCI or a result of CCI should be considered the CCI in alignment with the International Council for Standardization in Hematology recommendations for CCI (Zini 2021).

[b] Defined as the protein:creatinine ratio
Abbreviations: LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy

The TMA response components include platelet response, Lactate dehydrogenase (LDH) response (inclusive of LDH and schistocytes), and renal response (proteinuria). A participant could meet 0, 1, 2, or 3 TMA response criteria during the 26-week Treatment Period.

Participants must meet each individual TMA response component criterion at 2 separate assessments obtained at least 24 hours apart, and any measurement in between. The first laboratory value used to assess an individual TMA response component will be based on central laboratory results; the second (confirmatory) laboratory value will be assessed based on the earliest value obtained after the first value. For platelets and proteinuria, local laboratory results may be used for the second (confirmatory) value in the absence of a valid central result. The local urine protein and local urine creatinine are used to derive proteinuria. LDH must be assessed centrally for both measurements.

If the participants meet more than one TMA response criteria, those responses must overlap for at least 1 day.

In the presence of missing laboratory values at any scheduled visits, the following rules will be applied when deriving the response time interval for individual TMA response component:

– When there is only 1 scheduled visit with a missing value between 2 non-missing assessments (from either scheduled or unscheduled visits), the second non-missing assessment can be used to confirm the individual TMA response criterion met, or the loss of response at the first non-missing assessment for this criterion.

  - When there are 2 or more consecutive scheduled visits with missing values between 2 non-missing assessments, the second non-missing assessment cannot be used to confirm the individual TMA response criterion met during the time interval between 2 non-missing assessments. No response will be assigned to the 2 consecutive scheduled visits with missing values.

Missing values falling on unscheduled visits will not impact the assessment of individual TMA response.

The following intercurrent events will be considered as treatment failures:

  - Meeting clinical worsening criteria, as in Table 3 and recorded on the eCRF
  - Treatment discontinuation
  - Death at any time during the study
  - Additional HSCT

Under the composite endpoint strategy, non-responder imputation (NRI) will be employed if a participant meets the treatment failure rules as defined above (ie, assume no response from the event of treatment failure onward for all 3 TMA response components).

- Hematologic response as defined in Table 4 during the 26-week Treatment Period.
  - Participants must meet the platelet response and LDH response and those responses must overlap for at least 1 day.
  - NRI will be employed using the composite endpoint strategy, in the same way as defining TMA response criteria met.
- Change from Baseline in estimated glomerular filtration rate (eGFR) during the 26-week Treatment Period. This will be based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for participants ≥ 18 years of age and the Bedside Schwartz formula for participants < 18 years of age.

Additional secondary efficacy endpoints are as follows:

- TMA response during the 26-week Treatment Period

The derivation of TMA response follows the same rule as for the individual TMA response component and all intervals during which each individual criterion is met must overlap for at least 1 day to be classified as having met the TMA response. The time interval of a positive TMA response is defined as the duration when all 3 TMA response criteria are met simultaneously.

- Time to TMA response, defined as the days from reference start day (Section 9.3.6) to the first day that the participant satisfies the criteria for TMA response, during the 26-week Treatment Period. The start date of TMA response is the initial date where all individual criteria are met, simultaneously.
- TMA response at each post-baseline visit during the 26-week Treatment Period.
- Response for each individual component of TMA response during the 26-week Treatment Period.

- Time to response for each individual component of TMA response, defined as time in days from the reference start day (Section 9.3.6) to first date of meeting individual response criterion following during the 26-week Treatment Period. The initial response for each individual criterion needs to be confirmed by a second assessment at least 24 hours apart, and any measurement in between. Once confirmed, the start of the time interval will be set as the date of initial response for this criterion. Time to hematologic response, defined as time in days from reference start day (Section 9.3.6) to first date of hematologic response during the 26-week Treatment Period.
- Hemoglobin response is defined as the ability to maintain hemoglobin ≥ 10 g/dL without CCI support during the prior 7 days. The criterion must be met at 2 separate assessments obtained at least 24 hours apart, and any measurement in between. Hemoglobin response will be assessed during the 26-week Treatment Period.
- Platelet response is defined as follows:
  - If baseline platelet count ≤ 50000/mm^3, the following criteria must be met:
    - Absolute platelet count > 50000/mm^3 without platelet transfusion support during the prior 7 days
  - If baseline platelet count > 50000/mm^3, the following criteria must be met:
    - ≥ 50% increase in platelet count compared to baseline value without platelet transfusion support during the prior 7 days

  The criteria must be met at 2 separate assessments obtained at least 24 hours apart, and any measurement in between. Platelet response will be assessed during the 26-week Treatment Period.
- Partial TMA response is defined as meeting ≥ 1, but not all, criteria for TMA response as defined in Table 4 Participants with partial TMA response are mutually exclusive to participants with complete TMA response. Partial response will be assessed during the 26-week Treatment Period.

- Modified TMA Response is defined by the criteria in the table below:

		TMA Response Parameter
Modified TMA response	Modified Hematologic response	If baseline platelet count ≤ 50000/mm^3, the following criteria must be met: • Absolute platelet count > 50000/mm^3 without platelet transfusion support during the prior 7 days If baseline platelet count > 50000/mm^3, the following criteria must be met: • ≥ 50% increase in platelet count compared to baseline value without platelet transfusion support during the prior 7 days
		At least 50% reduction of LDH from baseline and absence of schistocytes[a] Or Normalization of LDH and absence of schistocytes[a]
	Renal response	At least 50% reduction of proteinuria from baseline

CCI [redacted] or a result of CCI [redacted] should be considered the CCI [redacted] in alignment with the International Council for Standardization in Hematology recommendations for CCI [redacted] (Zini 2021).

Abbreviations: LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

The definition of modified TMA response is the same as the TMA response as in Section 5.1.2, except for the criteria for LDH responder, which allows a at least 50% reduction of LDH from baseline and absent of schistocytes.

- Loss of TMA response at participant level is defined only for participants who have achieved TMA response during the 26-week Treatment Period, as the event of failing to meet 1 or more TMA response criteria at a subsequent visit during the 26-week Treatment Period. At least 1 parameter must fail to meet the response criteria at 2 separate assessments obtained at least 24 hours apart, and any measurement in between. Similar to the confirmation of TMA response, the loss of individual component response must be confirmed by a second laboratory result at least 24 hours apart. The occurrence of treatment failure events defined in Section 5.1.2 will also be treated as loss of TMA response.
- TMA relapse is defined only for participants who have achieved TMA response (Section 5.1.2) during the 26-week Treatment Period, as evidence of worsening hematologic and renal dysfunction due to TMA during the post-treatment 26-week Follow-up Period and requires treatment intervention, as determined by the Investigator.
- Duration of TMA response is defined only for participants who have achieved TMA response under composite endpoint strategy and will be assessed as the time in days from the initial TMA response in the 26-week Treatment Period to the first occurrence of loss of response in the 26-week Treatment Period or TMA relapse in

the 26-week Follow-up Period. Duration of response will be assessed after all participants have discontinued or completed the 26-week Treatment Period. Additionally, the analysis of duration of response will be repeated after all participants have discontinued or completed the 26-week Follow-up Period. Loss of response can only occur during the 26-week Treatment Period; relapse can only occur during the 26-week Follow-up Period.

- Changes from Baseline during the 26-week Treatment Period and through 52 weeks in the following:
  - Haptoglobin
  - Platelets
  - LDH
  - Hemoglobin
- Change from Baseline in TMA-associated organ dysfunction in renal system, cardiovascular system, pulmonary system, central nervous system (CNS), and gastrointestinal (GI) system through 26 and 52 weeks.
  - Renal dysfunction:
    - Kidney function status will be assessed by urine protein:creatinine ratio, serum creatinine, and eGFR based on creatinine using the CKD-EPI formula in participants ≥ 18 years of age and Bedside Schwartz formula in participants < 18 years of age (Section 9.3.12).
    - Renal dysfunction will be defined as doubling of serum creatinine from Baseline or requirement of dialysis. A participant will be considered as requiring dialysis:

      Baseline Visit: if there is any dialysis within 5 days prior to the first dose of study treatment

      Post-Baseline Visit: if there is any dialysis within 5 days prior to the visit.
  - Cardiopulmonary dysfunction will be defined as the presence of cardiopulmonary symptoms (excluding hypertension) or use of any mechanical ventilation. Cardiopulmonary symptoms include, but are not limited to, pulmonary hypertension, pleural effusion, pulmonary edema, pericardial effusion, and serositis.
    - The presence of cardiopulmonary symptoms at Baseline and post-Baseline Visits will be assessed and recorded on the eCRF.
    - Use of any ventilatory or respiratory support, including mechanical ventilation, will be reported on the participant's Nonpharmacologic Therapies and Procedures eCRF page.
    - The presence of hypertension will also be assessed and recorded on the eCRF.

  - CNS dysfunction will be defined as confirmed posterior reversible encephalopathy syndrome (PRES), or any signs of headache, confusion, visual loss, or seizures at Baseline and post-Baseline Visits, as recorded on the eCRF.
  - GI dysfunction will be defined as presence of signs and symptoms of GI involvement at Baseline and post-Baseline Visits, including diarrhea, vomiting, pain, and bleeding as recorded on the eCRF.
- Overall survival through 52 weeks.
- Non-relapse mortality by Day 100 and through 52 weeks.

5.1.3. Exploratory Endpoints

The exploratory endpoints of the study are as follows:

- Changes from Baseline in biomarkers, which may include, but are not limited to, CCI [redacted]
- Incidence of specific complement dysregulation-related mutations.
- Change from Baseline in clinical outcomes:
  - Change from Baseline in health-related quality of life (HRQoL) outcomes, as measured by European Quality of Life 5-Dimension 5-Level (EQ-5D-5L), EQ-5D-5L Proxy (version 1), 12-item Short Form Health Survey (SF-12), and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue (in adult participants) and SF-12 (in adolescent participants).
    - Based on responses to the EQ-5D-5L questionnaire or EQ-5D-5L Proxy version 1, visual analog scale (VAS), and the health state index score, a weighted summary of health states represented in 5 dimensions, will be used to assess the HRQoL for adults. The detailed description and scoring algorithm can be found in Section 9.3.14.
    - SF-12 survey will be scored in both adults and adolescents for the 8 domains addressing each specific area of functional health status, including physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health during the last 4 weeks. Raw domain scores are used to determine the physical and mental component summary scores on a scale of 0 to 100 with 100 representing the best health condition. The physical and mental component scores are scored using the PROCoRE validated software.
    - The sum score with equal weight for 13 items in the FACIT-Fatigue Scale (Version 4), with each item evaluated by a 5-point Likert-type scale from 0 to 4 (4 representing the highest level of fatigue), will be calculated. The detailed description and scoring algorithm can be found in Section 9.3.15. The scale will be assessed for adults only.

- The Global Impression scale comprises Global Impression of Severity (including single-item measures of Patient Global Impression of Severity [PGI-S], Caregiver Global Impression of Severity [CaGI-S], and Clinical Global Impression of Severity [CGI-S]), evaluating the severity of psychopathology on a Likert scale from 1 to 6 (6 representing the highest level of severity), and Global Impression of Change (including single-item measures of Patient Global Impression of Change [PGI-C], Caregiver Global Impression of Change [CaGI-C], and Clinical Global Impression of Change [CGI-C]), evaluating the change from the initiation of treatment on a similar 7-point scale. These scales will be assessed for adults only.

5.2. PK and PD Endpoints

The PK endpoints of the study are as follows:

- Serum concentrations of ravulizumab over time.
- Changes in serum free C5 concentrations over time.
- Changes in serum total C5 concentrations over time.

5.3. Safety

The safety and tolerability endpoints of the study are as follows:

- Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs).
- Changes from Baseline in vital signs and laboratory parameters.
- Incidence of antidrug antibodies (ADAs) and assessment of immunogenicity.

5.3.1. Adverse Events

An adverse event (AE) is defined as untoward medical occurrence in a participant administered a pharmaceutical product and does not necessarily have a causal relationship with study treatment. The definition of serious adverse event is described in Protocol Section 10.4. An AE can therefore be any unfavorable or unintended sign (eg, an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the study intervention. AE relationship to study treatment will be assessed as not related or related to study treatment.

AE severity is assigned to 1 of the following categories from the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (fatal). Each CTCAE term is a Lowest Level Term per Medical Dictionary for Regulatory Activities (MedDRA). Each Lowest Level Term will be coded to a MedDRA Preferred Term (PT).

Adverse events of special interest (AESI) will include meningococcal infections in this study.

5.3.2. Vital Signs

Vital signs will include systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), oral temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]), and pulse oximetry (%).

5.3.3. Laboratory Assessments

Laboratory assessments are defined in Protocol Section 10.3.

Samples collected at Screening may be tested at either a local or a central laboratory. If local laboratory tests are used for platelet count, hemoglobin, schistocytes, and proteinuria, duplicate samples will be collected for central laboratory testing to ensure results for Baseline and post-Baseline measurements for analyses are obtained from the central laboratory. In the event of duplicate samples from local and central laboratories (for any time point), central laboratory results will be used for analysis.

5.3.4. Electrocardiograms

Single 12-lead electrocardiograms (ECGs) will be conducted according to the SoAs in the protocol to obtain heart rate, PR, QRS, QT, and corrected QT intervals. The QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

5.3.5. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the following organs/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, musculoskeletal, and neurological state. An abbreviated physical examination will include, at a minimum, a body-system relevant examination based upon Investigator judgment and participant symptoms.

5.3.6. Immunogenicity

Blood samples will be collected to test for the presence of ADAs to ravulizumab in serum according to the SoA in the protocol. Samples with confirmed positive ADA will be further tested for ADA titer and the presence of neutralizing antibodies.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

Data from each stage will be analyzed and reported separately, except for selected safety analyses, which may combine results from both stages. The primary population for comparative assessment of the efficacy endpoints is the Full Analysis Set (FAS).

6.1. All-Enrolled Set

The All-Enrolled Set will include all participants who sign the informed consent and are randomized in Stage 2 or are enrolled in Stage 1. The All-Enrolled Set will primarily be used for disposition summaries and selected efficacy analyses for Stage 1 participants. Selected listings will also utilize the All-Enrolled Set.

6.2. ITT Set

The ITT set includes all participants who sign the informed consent and are randomized in Stage 2.

6.3. Full Analysis Set

The FAS will include all participants who sign the informed consent and randomized in Stage 2, excluding participants who enroll prior to availability of ST-HUS and/or ADAMTS13 laboratory results and are subsequently found to be ineligible after enrollment.

The primary population for comparative assessment of the efficacy endpoints is the FAS. For the main treatment comparisons of efficacy assessments, participants will be assessed according to the treatment they were randomized to receive, regardless of the treatment they actually received ("as randomized" approach).

Validity of participants to the FAS will be reviewed and determined prior to database lock and study unblinding.

Sensitivity analysis for primary endpoints and key secondary endpoints will be run using the ITT Set if the FAS and ITT Set are different.

6.4. Safety Set

The Safety Set will include all participants who sign the informed consent and receive at least 1 dose of study treatment (ravulizumab or placebo). Participants will be analyzed according to the study treatment they actually received. All safety analyses will be performed on the Safety Set.

6.5. Per Protocol Set

The Per Protocol Set (PPS) will only be applicable for specific Stage 2 data analyses. The PPS will consist of FAS participants who meet all of the following criteria:

- Treatment compliance, defined in Section 7.5.1, is ≥ 80%.
- Have not received any disallowed medications or undergone any disallowed therapeutic procedures (Protocol Section 6.5.3) during the 26-week Treatment Period.

- Did not violate the below inclusion criteria (IC) or exclusion criteria (EC) in the study:
  - Met IC:
    - IC No. 2: Participants received HSCT within the past 12 months prior to Screening.
    - IC No. 4: Confirmed HSCT-TMA diagnosis as required per protocol.
  - Did not meet EC:
    - EC No. 3: Positive direct Coombs test.
    - EC No. 4: Diagnosis or suspicion of disseminated intravascular coagulation.
    - EC No. 6: Diagnosis of veno-occlusive disease, regardless of severity.
    - EC No. 7: Known human immunodeficiency virus (HIV) infection by HIV-1/HIV-2 test at Screening.
- Not unblinded except for rescue treatment evaluation.

Validity of participants to the PPS will be reviewed and determined prior to database lock and study unblinding.

The primary analysis and key secondary efficacy analyses will be repeated on the PPS as sensitivity analyses. PPS will be analyzed according to the actual study treatment received. A participant whose actual treatment is placebo would have to receive placebo for all study drug exposure visits. The actual treatment of a participant in placebo group is ravulizumab if they receive any dose of ravulizumab prior to switching to ravulizumab for rescue treatment (if rescue ravulizumab is administered).

6.6. PK and PD Analysis Set

All participants who sign the informed consent and receive at least 1 dose of ravulizumab and who have evaluable PK or PD data. PK and PD analyses will be performed on the PK/PD Analysis Set.

7. STATISTICAL ANALYSIS

7.1. General

All analyses will be performed using SAS® Version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software.

Data from Stage 1 and Stage 2 of the study will be analyzed and reported separately, except for selected safety analyses, which may combine results from both stages. The main set of analyses will be focused on comparing results in the FAS between the 2 randomized Stage 2 treatment groups (ravulizumab treatment group and placebo treatment group), while selected descriptive statistics will be provided for Stage 1 efficacy data using the All-Enrolled Set for Stage 1 participants. The p-values from sensitivity analyses for efficacy endpoints are for descriptive purpose only and not adjusted for multiplicity. To evaluate the delayed treatment effect of ravulizumab, the efficacy data collected during the post-unblinding Rescue Treatment Period and Follow-up Period will be summarized separately for participants in the placebo group who receive ravulizumab as the rescue treatment. The participants and study periods included in each treatment group for the analyses performed in the primary endpoint analysis are summarized in Table 8 in Section 9.3.1.

Summary statistics will be computed and displayed by treatment group, by visit (where applicable), and by stratification factors (when relevant). Descriptive statistics for continuous variables will minimally include the number of participants (n), mean, SD, minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. The Kaplan-Meier (KM) method will be used for the time-to-event analyses (eg, EFS, overall survival) and competing risk analysis will be used for other time-to-event analyses (eg, time to TMA response, non-relapse mortality). Graphical displays will be provided as appropriate. The CI will be constructed as 2-sided with 95% CI. The significance level is 0.05 for 2-sided unless specified otherwise. Data listings will be provided for data collected or derived for analysis in the relevant analysis populations.

For analyses adjusted for stratification factors, the values of the stratification factors entered for randomization will be used. If the values of the stratification factors at randomization are different than the actual values at baseline in more than 10% of the participants, sensitivity analyses using values at baseline will be conducted for the primary efficacy endpoint and the key secondary endpoints.

7.1.1. Handling of Dropouts or Missing Data

Intercurrent events

The strategies for handling the intercurrent events will be described in the analysis section for each endpoint.

Missing data handling

The following missing data handling approaches will be used:

- For time-to-event endpoints (EFS, overall survival, time to TMA response), missing data will be handled by censoring. Censoring mechanisms for these endpoints will be described in Section 7.3.2.

- A confirmatory result for individual TMA response component (details in Section 5.1.2) cannot be from an assessment that has 2 or more preceding consecutive missing scheduled assessments between it and an earlier assessment when the TMA response criterion was met. This approach will also be applied to other response-type endpoints.
- The NRI method is applied in the main analysis of response endpoints under the composite endpoint strategy, where no response is conservatively assumed from the intercurrent events onward.
- For patient-reported outcomes (PROs), missing Baseline responses will not be imputed in the main analysis. Sensitivity analyses will impute the missing Baseline responses by leveraging the reasons for missing Baseline responses. Missing post-Baseline responses on PROs will not be imputed in either the main analysis or sensitivity analyses.
- For continuous endpoints with more than 1 post-Baseline time points, the comparative results will be based on the MMRM described above, under the assumption of missing at random (MAR), using data actually observed. Multiple imputation will be used in the sensitivity analysis to assess the robustness of comparative results, given the occurrence of missing data at post-Baseline time points. A pattern-mixture model (PMM) with control-based pattern imputation (Little, 1996; Ratitch, 2011) will be used under the "missing not at random" (MNAR) assumption.
- Incomplete or missing dates will be imputed as described in Section 9.3.9, Section 9.3.10, and Section 9.3.11.

7.2. Study Participants

7.2.1. Disposition of Participants

A summary of disposition will include the number and percentage of screened, screen failure, enrolled, randomized (Stage 2 only), and treated participants by treatment group (Stage 1 Ravulizumab, Stage 2 Placebo, or Stage 2 Ravulizumab) and overall. In addition, the number and percentage of participants who discontinue from study treatment and the primary reason for treatment discontinuation, as well as the number and percentage of participants who discontinue from the study and the primary reason for study discontinuation (including coronavirus disease 2019 [COVID-19]-related reasons), in the Treatment Period, Rescue Treatment Period, and Follow-up Period will be summarized by treatment group. The number and percentage of participants included and excluded and the reasons for exclusion from each analysis set defined in Section 6 will be summarized.

For Stage 2 randomized participants, the number and percentage of participants meeting the criteria for rescue treatment and the number and percentage of participants who receive rescue treatment will be summarized.

7.2.2. Protocol Deviations

Protocol deviations will be determined per the Protocol Deviation Management Plan. The number and percentage of participants with specific protocol deviations will be summarized for all enrolled participants by important and nonimportant deviations for each of the treatment groups (Stage 1 Ravulizumab, Stage 2 Placebo, or Stage 2 Ravulizumab) and overall.

Protocol deviations from monitoring reports and other relevant sources will also be reviewed, and any important deviations will be included in the list that is summarized and reported.

7.2.3. Demographics, Disease Characteristics, and History

All demographics, baseline characteristics, and disease characteristics will be summarized using the FAS, the PPS, and the Safety Set. Summary statistics will be presented by treatment group (Stage 1 Ravulizumab, Stage 2 Placebo, Stage 2 Rescue Ravulizumab, and Stage 2 Ravulizumab) and overall, where applicable.

7.2.3.1. Demographics and Baseline Characteristics

The following demographic variables will be summarized:

- Sex
- Race
- Ethnicity
- Age at Screening (years): descriptive statistics (n, mean, median, SD, minimum, maximum) and by frequency of participants in each age category: 12 to < 18, 18 to < 45, 45 to < 65, and ≥ 65 years
- Baseline weight (kg): descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants in the following categories: 30 to < 40, 40 to < 60, 60 to < 100, and ≥ 100 kg
- Baseline height (cm) by descriptive statistics for continuous variables
- Geographic region
- Acute GVHD status (no acute GVHD, Grade I-II, or Grade III-IV)

7.2.3.2. Disease and Transplant Characteristics

The following characteristics will be summarized by treatment group:

- History of prior HSCT
  - Number of prior HSCTs per participant
  - Transplant modality (type of donor): autologous, allogeneic
  - Reason for HSCT
- Current HSCT

  - Transplant modality (type of donor): autologous, allogeneic related, allogeneic unrelated, unknown
  - For allogeneic transplant recipients, the following will be described:
    a. Related donor type: syngeneic, human leukocyte antigen (HLA)-identical sibling, HLA-matched other relative, HLA-mismatched relative
    b. Degree of related donor mismatch: HLA-mismatched 1 allele, HLA-mismatched ≥ 2 alleles
    c. Unrelated donor: HLA matched unrelated, HLA mismatched unrelated
  - Hematopoietic stem cell origin (product origin): bone marrow, peripheral blood stem cell, single cord blood unit, other
  - Transplant indication: malignancy, hematologic malignancy, non-malignancy
  - Reason for HSCT
  - Use of conditioning regimen and regimen prescribed: myeloablative, non-myeloablative, reduced intensity
  - Use of radiation and radiation prescribed: total body, total body by intensity-modulated radiation therapy, total lymphoid or nodal regions, thoracoabdominal region
  - Engraftment achieved (neutrophil and platelet)
- Time from TMA diagnosis to randomization by descriptive statistics for continuous variables
- Baseline TMA laboratory values (platelets, hemoglobin, LDH, eGFR, proteinuria) by descriptive statistics for continuous variables
- Presence of schistocytes at Baseline (yes, no), schistocytes <=1% or a result of "none" should be considered the “no”.
- Transfusion history
  - RBC transfusions during the Screening Period
  - Platelet transfusions during the Screening Period
- Baseline organ dysfunction status
  - Cardiopulmonary symptoms (excluding hypertension)
  - Ventilatory/respiratory support, including mechanical ventilation
  - Presence of PRES
  - GI involvement (diarrhea, vomiting, GI pain, GI bleed)
  - Dialysis status

Any known COVID-19 exposure and the date of exposure will be provided in the listings.

7.2.3.3. Medical/Surgical History and Baseline Physical Examination

Medical history will be classified by System Organ Class (SOC) and PT using the latest available version of standardized MedDRA and will be reported by treatment group (Stage 1 Ravulizumab, Stage 2 Placebo, Stage 2 Rescue Ravulizumab, or Stage 2 Ravulizumab) and overall for the Safety Set. Baseline physical examination information will be summarized by treatment group and overall for the Safety Set.

7.2.4. Prior and Concomitant Medications/Therapies

Prior and concomitant medications (including vitamins and herbal preparations) and nonpharmacologic therapies will be summarized using the Safety Set. Prior medications or therapies are defined as medications or therapies taken in the 30 days prior to Day 1 (Stage 1) or within 30 days prior to randomization (Stage 2). Concomitant medications or therapies are defined as medications or therapies received by the participants during the Treatment-Emergent (TE) Period (see the definition in Section 9.3.1).

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) version in use by Alexion at the time of the analysis, while nonpharmacologic therapies (any therapeutic intervention, such as surgery/biopsy or physical therapy) will be coded using MedDRA.

Medication summaries including the number and percentages of participants by treatment group (Stage 1 Ravulizumab, Stage 2 Placebo, Stage 2 Rescue Ravulizumab, Stage 2 Ravulizumab) and overall using prior and concomitant medications will be presented by WHO-DDE Anatomical Therapeutic Chemical Level 3 and by WHO-DDE generic name. Nonpharmacologic therapies will be summarized similarly, but by MedDRA SOC and PT. Protocol-required vaccinations will be summarized similarly and will also be presented separately.

Prior and concomitant medications/therapies will be separately summarized for participants who are diagnosed with COVID-19 during the Treatment Period.

Additional HSCT for participants who undergo one or more HSCT following Day 1 will be summarized by treatment group:

- Number of additional HSCTs
- Transplant modality (type of donor): autologous, allogeneic
- Hematopoietic stem cell origin (product origin): bone marrow, peripheral blood stem cell, single cord blood unit, other
- Transplant indication: malignancy, hematologic malignancy, non-malignancy
- Conditioning regimen and regimen prescribed: myeloablative, non-myeloablative, reduced intensity
- Reason for HSCT
- Time on study for additional HSCT

7.3. Efficacy Analyses

The FAS is the primary analysis set for all efficacy analyses. The primary analysis and key secondary efficacy analyses will be repeated on the PPS as sensitivity analyses. The following descriptions of efficacy analyses focus on results from Stage 2. Efficacy data resulting from Stage 1 will be summarized in a similar manner without any treatment comparisons.

Multiplicity adjustment

The primary and key secondary endpoints will be tested sequentially. If the primary endpoint is statistically significant at 0.05, the key secondary endpoints will be tested using a hierarchical closed testing procedure. The secondary endpoints will be tested in the following order until a non-significant test is observed:

1. Overall survival by Week 26
2. Overall Survival by Day 100
3. Non-relapse mortality during the 26-week Treatment Period
4. Number of TMA response criteria met during the 26-week Treatment Period
5. Hematologic response during the 26-week Treatment Period
6. Change from Baseline in eGFR during the 26-week Treatment Period

If the previous endpoint does not achieve statistical significance, interpretation of subsequent endpoint(s) tests will not occur, and only nominal p-values will be provided.

7.3.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint of the study is EFS during a 26-week randomized Treatment Period, defined as the time from randomization until the first of the following two events: death and clinical worsening.

The null and alternative hypotheses for the primary analysis are as follows:

$$H_0: S(t)_{rav} = S(t)_{placebo} \text{ vs. } H_A: S(t)_{rav} \neq S(t)_{placebo}$$

where $S(t)_{rav}$ is the EFS over 26 weeks in the ravulizumab treatment group and $S(t)_{placebo}$ is the EFS over 26 weeks in the placebo treatment group. Hypothesis testing will be two-sided and performed at the 0.05 level of significance.

EFS will be analyzed as a time to event variable using FAS. The survival time will be calculated as the time in days from randomization to the date of clinical worsening or death, whichever is earlier. The criteria for clinical worsening must be confirmed by 2 independent samples collected at least 8 hours apart (ideally 24 hours apart) and the initial sample date would be used as the date of clinical worsening. The intercurrent events and censoring rules are included in Table 5. Events after treatment discontinuation will be included in the analysis. Participants who do not experience clinical worsening, death or an intercurrent event by Week 26 will be censored at the last date that they are known to be alive (last known alive date) or Day 183, whichever is earlier. Clinical worsening events will be restricted to those which are positively adjudicated by the CEAC.

Table 5: Censoring Rules for EFS

Endpoint	Situation	Date of event or censoring	Outcome (event or censored)
EFS	Death	Death date	Event *
	Clinical worsening	Date of clinical worsening	Event
	Additional HSCT	Date of additional HSCT	Censored
	Completion of treatment period at Week 26 or last known alive status	Day 183 or date of last known alive status (whichever is earlier)	Censored
*: if vital status determination is permitted by local law and regulation, then death information obtained after consent withdrawal will be included in the analysis.			

A log-rank test stratified by randomization stratification factors (acute GVHD status [no acute GVHD, Grade I-II acute GVHD, or Grade III-IV acute GVHD] and geographical region [Japan/rest of the world]), will be used for the hypothesis testing and will compare EFS through 26 weeks between the ravulizumab treatment group and the placebo treatment group. Kaplan-Meier (KM) curves will be displayed for each treatment group and the KM estimates and 95% CIs of EFS at Week 26 will be presented. Additionally, a Cox proportional hazards model will be used to estimate the hazard ratio (HR) and 95% CI of clinical worsening or death comparing ravulizumab treatment group and placebo. The stratification factors and treatment group will be included as fixed effects. Restricted mean survival will also be used to summarize the restricted mean survival time (RMST) at Week 26. The proportional hazards assumption will be tested using Schoenfeld residuals.

7.3.1.1. Subgroup Analysis

The primary efficacy endpoint EFS, and key secondary endpoints OS and non-relapse mortality at week 26 will be analyzed by subgroups. KM estimates and 95% CIs of EFS at Week 26 by subgroups will be presented. In addition, Cox proportional hazards models will be fit to estimate the HR and a forest plot of HR and 95% CI by subgroup will also be generated. Subgroups will include (but will not be limited to) the following:

- Acute GVHD status (no acute GVHD, acute Grade I-II, or acute Grade III to IV)
- Geographic region (Japan and rest of the world)
- Baseline weight (30 to < 40, 40 to < 60, 60 to < 100, ≥ 100 kg)
- Age at screening (12 to < 18 years old, ≥ 18 years old)
- Type of transplant (allogeneic, autologous)
- Gender (female, male)
- Time from the first TMA symptom or sign to randomization (≤ median, > median)
- Time from the first TMA symptom or sign to initiation of study treatment (≤ median, > median)
- Baseline platelet count (≤50,000, >50,000)
- Baseline LDH < or ≥ 2 upper limit of normal

- Time from TMA diagnosis to randomization (≤ median, > median)
- Time from TMA diagnosis to initiation of study treatment (≤ median, > median)
- Baseline proteinuria measured as urine protein:creatinine ratio (< 1 mg/mg, ≥ 1 mg/mg)
- GVHD and age subgroup combination
- GVHD and gender combination

Given that the number of participants in some subgroups may be limited, subgroup categories may be combined as appropriate. Additional subgroup analyses may be performed, such as the immunosuppressant therapies (IST) use at baseline, concurrent systemic infection including opportunistic infections (eg, bacterial other than N. meningitidis, viral or fungal).

7.3.1.2. Sensitivity Analyses

The following sensitivity analyses will be performed:

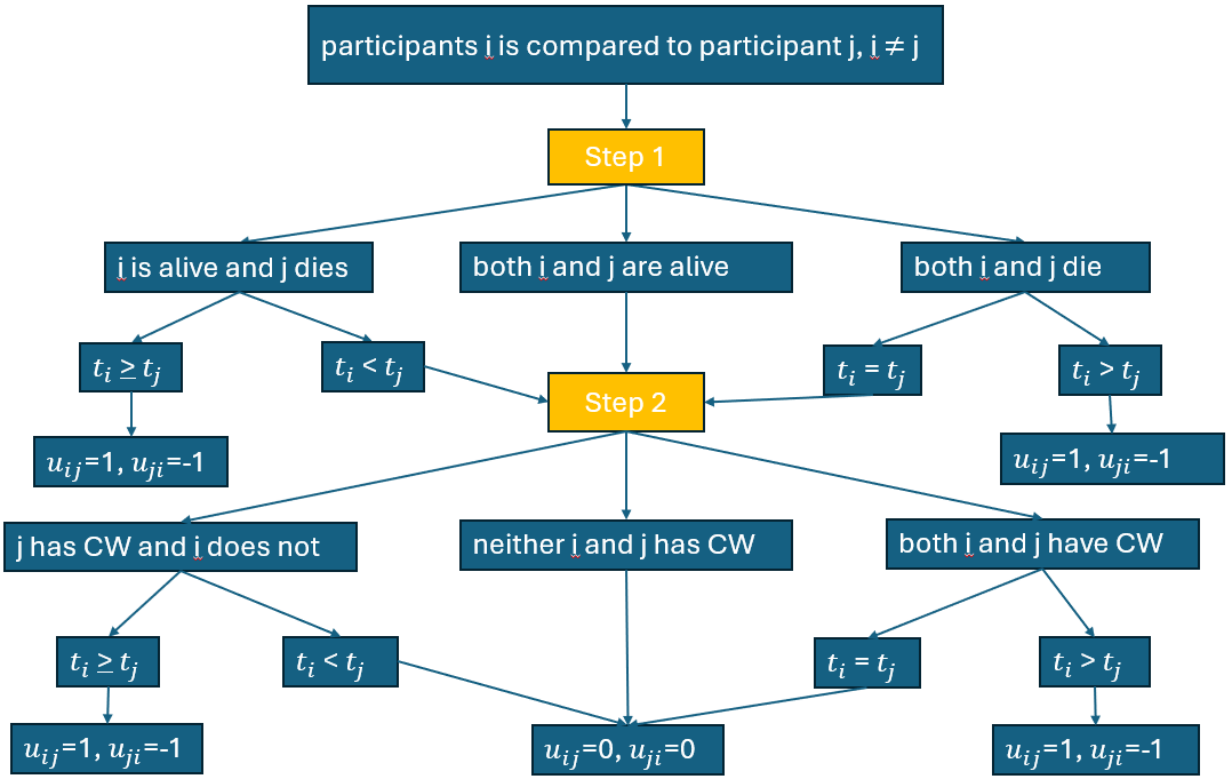
- The EFS analysis described above will be rerun using the ITT Set if it is not the same as the FAS.
- The primary analysis for the primary endpoint as described in Section 7.3.1 will be repeated in the PPS to determine if the results are materially different from the analysis based on the FAS.
- Another sensitivity analysis will be conducted by treating participants who take prohibited medication such as eculizumab or other agents that act on the complement pathway as an EFS event.
- The EFS endpoint will also be analyzed as a hierarchical combination of time to death and time to clinical worsening using the Win-Ratio (WR) approach.

This method compares all pairs of participants, including comparisons with participants belonging to the same treatment group. For any pair of participants, let

$$u_{ij}(i \neq j)\begin{cases} 1, if\ participant\ i\ does\ better\ than\ participant\ j\ (wins) \\ 0, if\ the\ comparison\ is\ undeterimined \\ -1, if\ participant\ i\ is\ worse\ than\ participant\ j\ (loses) \end{cases}$$

The score for participant *i* is the sum of u_{ij}over all pairwise comparisons of participant *i* with all other participants j. Hypothesis testing will be based on the F-S test (Finkelstein, 1999) and the treatment effect estimation will be based on the Win-Ratio method (Pocock, 2012). The scoring algorithm is shown in Figure 2, where t_i is time to death or clinical worsening within 26 weeks for the participant who die or has the clinical worsening event; and last known alive date or last known date without clinical worsening for the participant is alive or does not have the clinical worsening, respectively.

Figure 2: F-S Scoring Algorithm



The stratified F-S test statistic is based on the stratum-specific sum of these scores where the strata are defined by acute GVHD status [no acute GVHD, Grade I-II acute GVHD, or Grade III-IV acute GVHD] and geographical region [Japan/rest of the world]), resulting in a total of 6 strata (3 × 2).

Let D_i = 1 for participants in the ravulizumab group and D_i= 0 for participants in the placebo group. Using the u_{ij} for every pair of participants defined above, a score is assigned to each participant. The participants are divided into 6 strata (k = 1 to 6). Let A_k be the set of indices of the n_k participants in the k^{th} stratum and $U_i = \sum_{j \in A_k} u_{ij}$ for $i \in A_k$, then the test statistic is based on

$$T = \sum_k \sum_{i \in A_k} D_i U_i$$

Let m_k be the total number of participants in the k^{th} stratum who are in the ravulizumab group. Then, in the k^{th} stratum

$$E(D_i) = m_k/n_k, \text{ and}$$

$$Cov(D_i, D_j) = \frac{m_k(n_k - m_k)}{(n_k - 1)n_k^2}(\delta_{ij} n_k - 1)$$

Where $\delta_{ij}$is the Kronecker delta (valued as 1 if $i = j$ and 0 otherwise. Since $\sum_{i\in A_k} U_i = 0$, which means $E(T) = 0$ and

$$Var(T) = \sum_k \frac{m_k(n_k - m_k)}{n_k(n_k - 1)} \left(\sum_{i\in A_k} U_i^2\right).$$

The hypothesis of interest is tested by comparing $T/\sqrt{Var(T)}$ to the normal distribution. The p-value from the F-S test will be presented.

Let N_k be the total number of comparable pairs (no ties) in the k^{th} stratum and

$W_k = \sum_{i,j\in A_k} D_i(1 - D_j)I(U_{ij} = 1)$, where $I(U_{ij} = 1)$ is the indicator function. Then W_k is the number of wins in the ravulizumab group in the k^{th} stratum and$N_k - W_k$ is the number of wins in the placebo group in the k^{th} stratum.

The stratified WR statistic (Dong, 2018) is then

$$WR = \frac{\sum_k W_k / n_k}{\sum_k (N_k - W_k)/n_k}$$

where $1/n_k$ is considered as the weight in the k^{th} stratum. The SE of log (WR) will be estimated from an asymptotic normal distribution from the F-S test statistics as

$$SE(\log(WR)) = \frac{\log(WR)}{Z_{F-S}}$$

where Z_{F-S} is the Z-score from F-S test statistic. An approximately 95% CI of WR then can be estimated from the CI of log (WR).

7.3.2. Analyses of Key Secondary Efficacy Endpoints

All analyses for key secondary endpoints will be performed on the FAS, and selected secondary analyses will be performed on the PPS.

The key secondary endpoints analyses will be part of the hierarchical closed-testing procedure comparing results between the 2 randomized treatment groups and will be performed on the FAS.

7.3.2.1. Overall Survival

Overall survival at 26 weeks will be analyzed as a time to event variable. Survival time will be assessed as the number of days from randomization to death. Intercurrent events and censoring rules are included in Table 6. Participants who survive and have not had an intercurrent event will be censored at their last known date alive or Day 183, whichever is earlier. Deaths after treatment discontinuation will be included in the analysis. Considering the OS comparison of ravulizumab and placebo may be confounded by the potential benefit of ravulizumab treatment in patients randomized to placebo who experienced clinical worsening and received rescue treatment, several sensitivity analyses will be conducted.

Table 6: Censoring Rules for OS

Endpoint	Situation	Date of event or censoring	Outcome (event or censored)
OS	Death	Death date	Event *
	Additional HSCT	Date of additional HSCT	Censored
	Completion of treatment period at Week 26 or last known alive status	Day 183 or date of last known alive status (whichever is earlier)	Censored
*: if vital status determination is permitted by local law and regulation, then death information obtained after consent withdrawal will be included in the analysis.			

A log-rank test stratified by the randomization stratification factors will be used for the hypothesis testing to compare OS through 26 weeks between ravulizumab and placebo. Kaplan-Meier curves will be displayed for each treatment group and the KM estimates and 95% CIs of overall survival at Week 26 will be presented. Additionally, a Cox proportional hazards model will be used to estimate the HR and 95% CI of death comparing ravulizumab and placebo. The stratification factors and treatment group will be included as fixed effects. Restricted mean survival will also be used to summarize the restricted mean survival time at Week 26. The proportional hazards assumption will be tested using Schoenfeld residuals.

Additionally, the following sensitivity analyses will be performed for OS:

- Overall survival at Week 26 will be performed using the ITT Set if the FAS and ITT Set are different.
- An additional OS estimand will be used (the hypothetical policy) which will censor participants at the additional HSCT or the time of rescue therapy initiation, whichever is earlier.
- The analysis will be repeated on the PPS.
- Another sensitivity analysis will be conducted by treating participants who took prohibited medication such as eculizumab or other agents that act on the complement pathway as an event.

A similar approach will be applied to compare overall survival at 100 days and 52 weeks after randomization.

7.3.2.2. Non-relapse Mortality

Non-relapse mortality is death due to any cause, excluding death due to the primary disease progression or relapse. Time to non-relapse mortality is assessed as the time in days from randomization to an event of non-relapse death within the 26-week treatment period. Death due to primary disease will be treated as a competing risk. Intercurrent events and censoring rules are included in Table 7. Participants who are alive at the end of the analysis period and have not experienced an intercurrent event will be censored at their last known date alive or Day 183, whichever is earlier. The cumulative incidence function (CIF) for non-relapse mortality will be estimated using a competing risk analysis (Gray, 1988). The p-value from the stratified Gray's test for CIF equality, stratified by the randomization stratification factors will be presented.

Table 7: Censoring Rules for Non-relapse Mortality

Endpoint	Situation	Date of event or censoring	Outcome (event or censored)
Non-relapse Mortality	Non-relapse Death	Death date	Event *
	Primary Disease Relapse Related Death	Death date	Competing event *
	Additional HSCT	Date of additional HSCT	Censored
	Completion of treatment period at Week 26 or last known alive status	Day 183 or date of last known alive status (whichever is earlier)	Censored
*: if vital status determination is permitted by local law and regulation, then death information obtained after consent withdrawal will be included in the analysis.			

HR with 95% CI and p-value from Fine and Gray's subdistribution hazard model stratified by randomization stratification factors will be presented for comparing the 2 treatment groups.

Several sensitivity analyses will be conducted:

- The non-relapse mortality during 26-week treatment period will be performed using the ITT Set if the FAS and ITT Set are different.
- Fine and Gray's subdistribution hazard model stratified by stratification factors will be repeated on the PPS.

A similar approach will be applied to compare non-relapse mortality at Day 100 and Week 52 after randomization.

7.3.2.3. Number of TMA Response Criteria Met

The number of TMA response criteria met will be summarized by the number and percentage of participants in each category by treatment group. The Wilcoxon rank sum test stratified by the randomization stratification factors will be used to compare the number of TMA response criteria met.

Several sensitivity analyses will be conducted:

- The number of TMA response criteria met using data from local laboratories will be performed where central laboratory results are missing.
- General linear model adjusting the randomization stratification factors will be used to compare the treatment effect assuming the data are normally distributed.
- The analysis will be repeated using the PPS.
- The analysis will be performed using the ITT Set if the FAS and ITT Set are different.
- Another sensitivity analysis will be conducted by considering the participants taking prohibited medication such as eculizumab or other agents that act on the complement pathway as non-responders.

7.3.2.4. Hematologic Response

The criteria for hematologic response are presented in Section 5.1.2.

Number and percentage of participants achieving hematologic response by Week 26 by treatment group will be displayed using the FAS. The point estimate with 95% CI for the proportion of responders in each treatment group will be provided using the Mantel-Haenszel stratum-weighted estimator with the randomization stratification factors with p-values to compare the common risk difference.

Several sensitivity analyses will be conducted:

- Hematologic response using local laboratories when central laboratory results are missing will be repeated.
- The analysis will be repeated using the PPS.
- The analysis will be performed using the ITT set if the FAS set and ITT set are different.
- Another sensitivity analysis will be conducted by considering the participants taking prohibited medication such as eculizumab or other agents that act on the complement pathway as non-responders.

Hematologic response will also be summarized by treatment group over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each post-Baseline time point.

7.3.2.5. Estimated Glomerular Filtration Rate

Change from Baseline in eGFR will be included in the hierarchical testing procedure. The corresponding estimand will be the difference in the mean change from Baseline in eGFR at Week 26 between treatment groups in participants in the FAS. Handling of creatinine and eGFR values on dialysis is described in Section 9.3.12, and handling of platelet and hemoglobin values on platelet and/or RBC transfusions is described in Section 9.3.13.

The treatment comparison will be based on MMRM assuming MAR with the fixed categorical effects of treatment group, visit, interaction between treatment and visit, randomization stratification factors, and continuous effect of baseline eGFR as covariates. An unstructured covariance matrix will be used to model the within-participant variance. The least-squares means, SE of the estimates, p-values, and 2-sided 95% CIs combined from the multiply-imputed datasets will be provided for the change from Baseline within each treatment group, and for the comparison between the 2 treatment groups.

Several sensitivity analyses will be conducted:

- The analysis will be repeated using the ITT set if the FAS and ITT Set are different.
- Multiple imputation will be used to assess the robustness of comparative results, given the occurrence of missing data at post-Baseline time points. Different missing data pattern will be investigated. Non-monotone intermittent missing values will be imputed based on Monte Carlo Markov Chain (MCMC) method. For data with monotone missing pattern, the reason of missingness will be evaluated. Missing data following death will be imputed using 10% of worst change values. For other monotone missing pattern, a pattern-mixture model (PMM) with control-based pattern imputation imputation (Little, 1996; Ratitch, 2011) will be used under the “missing not at random” (MNAR)

assumption that missing values for participants in the ravulizumab group may imply these participants no longer receive the treatment. It is then reasonable to assume that the conditional distribution of the missing values, given observed data, is similar to the corresponding distribution of participants in the placebo group.

The SAS/STAT® procedure using the multiple imputation methodology (PROC MI and MIANALYZE) will be implemented for applying the PMM approach. Multiple imputation datasets with a monotonic missing pattern will be generated. Based on the datasets with a monotonic missing pattern, the control-based pattern imputation method under the PMM will be applied. The model for the missing observations is constructed from the observed data in the placebo group only and is the imputation model for missing values in the ravulizumab and placebo groups. The multiple imputed datasets will be analyzed using an analysis of covariance model with treatment group, baseline value of endpoint in analysis, and randomization stratification factors (acute GVHD status and geographic regions) as fixed effects. The estimates from all imputed datasets will be combined by Rubin's rule for an overall inference.

7.3.3. Analyses of Additional Secondary Endpoints

7.3.3.1. TMA Response

Number and percentage of participants who achieve TMA response during the 26-week randomized Treatment Period will be displayed using the FAS. The Mantel-Haenszel stratum-weighted estimator with strata defined by the stratification factor with the 95% CI for the common difference of the proportions between the 2 treatment groups will be presented.

A sensitivity analysis of TMA response using local laboratories when central laboratory results are missing will be repeated.

Another sensitivity analysis will be conducted by considering the participants taking prohibited medication such as eculizumab or other agents that act on the complement pathway as non-responders.

7.3.3.2. Time to TMA Response

Time to TMA response will be assessed for responders as the time in days from randomization to their first occurrence of TMA response during the 26-week treatment period. The following intercurrent events will be treated as competing risk: treatment discontinuation, clinical worsening, additional HSCT or death. Participants who do not have any response and have not experienced an intercurrent event will be censored at week 26 or last known alive date, whichever is earlier. CIF curves for TMA response will be generated for each treatment group. HR with 95% CI and p-value from Fine and Gray's subdistribution hazard model stratified by randomization stratification factors will be presented for comparing the 2 treatment groups.

7.3.3.3. TMA Response at and up to Specific Time Points

In addition to the primary analysis of TMA response during the 26-week Treatment Period, TMA response will be summarized by treatment group over time by presenting the number and proportion of responders along with a 2-sided 95% exact Clopper-Pearson CI for each post-

Baseline time point up to Week 26. The treatment difference in the proportions and 95% CIs based on Miettinen and Nurminen method will also be provided.

This analysis will be conducted using 2 different approaches following the composite endpoint strategy. The first one will present the number and proportion of responders at a specific time point for the participants who have data at that time. The second approach will present the cumulative number and proportion of responders up to a specific time point out of all participants in the FAS.

7.3.3.4. Other Response Endpoints

Other response endpoints, defined in Section 5.1.2, include the following:

- Response for individual components of TMA response criteria
- Partial TMA response, including separate presentations for participants with response to only 1 component, only 2 components, and at least 1, but not all components
- Hemoglobin response

All these response endpoints will be summarized for the 26-week Treatment Period.

Analysis of responses as binary outcomes

The response variables will be analyzed in the same way as the TMA response as described in Section 7.3.3.1 .

Time-to-response endpoints, defined in Section 5.1.2, include the following:

- Time to response for individual components of TMA response criteria assessed separately
- Time to hematologic response

The analysis of time to response endpoints will be performed in the same ways as time to TMA response as described in Section 7.3.3.2.

The above time-to-response endpoints will be assessed through the 26-week Treatment Period.

7.3.3.5. Hematologic Parameters

Hematologic parameters (haptoglobin, platelets, LDH, and hemoglobin) will be summarized by treatment group at Baseline and each post-Baseline time point for the observed value as well as the change from Baseline.

Additionally, the proportion of participants with schistocytes present out of those remaining in the study at a specific time point will be summarized by treatment group in the FAS.

7.3.3.6. Modified TMA Response

Number and percentage of participants achieving modified TMA response by Week 26 by treatment group will be displayed using the FAS. The Mantel-Haenszel stratum-weighted estimator with strata defined by the stratification factor with the 95% CI for the common difference of the proportions between the 2 treatment groups will be presented with p-values to compare the common risk difference.

7.3.3.7. Loss of Response

Loss of response will be summarized by treatment group in the FAS by calculating the point estimate and a 95% Clopper-Pearson CI for the proportion of participants with a loss of TMA response, among participants in the FAS who achieved TMA response defined following the composite endpoint strategy in the 26-week Treatment Period.

7.3.3.8. TMA Relapse

TMA relapse is assessed only for participants who maintain TMA response through the randomized Treatment Period; and the start date for assessing TMA relapse is the first day of the 26-week Follow-up Period (ie, Day 184). TMA relapse will be summarized by treatment group by calculating the point estimate and a 95% Clopper-Pearson CI for the proportion of participants with a TMA relapse during the 26-week Follow-up Period, among participants in the FAS who will have maintained TMA response during the 26-week Treatment Period defined following the composite endpoint strategy.

7.3.3.9. Duration of Response

The duration of response will be assessed by KM analysis as a time-to-event variable. It will be censored at the last day on study, or the last date known alive, whichever is earlier if a responder does not experience any events defined as loss of TMA response (during the 26-week Treatment Period) or TMA relapse (in the 26-week Follow-up Period) or death. Non-responders will be counted as an event with a duration of zero day. KM curves with the summary statistics (described in Section 7.1) will be generated for each treatment group.

7.3.3.10. Organ Dysfunction

Treatment effect on organ dysfunction will be evaluated during the 26-week Treatment Period and through 52 weeks in the following end organ systems: renal, cardiopulmonary, CNS, and GI.

Renal involvement:

Kidney function parameters (protein:creatinine ratio, serum creatinine, and eGFR) will be summarized by treatment group in the FAS at Baseline and each post-Baseline timepoint using descriptive statistics for continuous variables for the observed value as well as the change from Baseline.

The presence of renal dysfunction is defined in Section 5.1.2. The number and proportion of participants with renal dysfunction and with individual conditions (doubling of serum creatinine from Baseline, and requirement of dialysis) out of those remaining in the study at a specific time point by treatment group in the FAS. A 2-sided 95% Clopper-Pearson CI for the proportion will be provided. The treatment difference in the proportions and 95% CIs will also be provided. In addition, the shift tables describing the change of renal dysfunction status (yes or no) and of individual conditions from Baseline will be summarized by post-Baseline timepoints for each treatment group.

Cardiovascular and pulmonary involvement:

The presence of cardiopulmonary dysfunction, presence of hypertension, and use of any ventilatory or respiratory support, as defined in Section 5.1.2, will be summarized. An analysis

will present over time the number and proportion of participants with any cardiopulmonary dysfunction and with each symptom and condition for cardiopulmonary dysfunction out of those remaining in the study at a specific timepoint by treatment group in the FAS. A 2-sided 95% Clopper-Pearson CI for the proportion will be provided. The treatment difference in the proportions and 95% CIs will also be provided. These descriptive analyses will be repeated for the presence of hypertension and use of any ventilatory or respiratory support.

Additionally, the shifts from Baseline in ventilatory/respiratory support status (yes or no), hypertension status (yes or no), presence of cardiopulmonary dysfunction (yes or no) and individual symptoms/conditions will be summarized for all post-Baseline timepoints by treatment group in the FAS.

Also, the systolic and diastolic blood pressure will be summarized descriptively by treatment group in the FAS at Baseline and post-Baseline timepoints for observed values and for changes from Baseline.

CNS involvement:

The number and proportion of participants with CNS dysfunction, as defined in Section 5.1.2 out of those remaining in the study at a specific timepoint will be summarized at Baseline and post-Baseline timepoints by treatment group in the FAS. The shifts from Baseline in the presence of CNS dysfunction (yes or no) will also be summarized by post-Baseline timepoints. These descriptive analyses will be repeated for each sign and symptom of CNS dysfunction, including PRES, headache, confusion, visual loss, and seizures.

GI involvement:

The number and proportion of participants with GI dysfunction, as defined in Section 5.1.2 out of those remaining in the study at a specific time point will be summarized at Baseline and post-Baseline time points by treatment group in the FAS. The shifts from Baseline in the presence of GI dysfunction (yes or no) will also be summarized by post-Baseline time points and by treatment group in the FAS. These descriptive analyses will be repeated for each sign and symptom of GI dysfunction, including diarrhea, vomiting, pain, and GI bleeding.

For participants with GI bleeding, changes over time in the frequency and estimated volume of GI bleeding will also be summarized.

Time to first occurrence of each organ dysfunction

For each of the above organ systems, time to first occurrence of organ dysfunction, will be analyzed using a competing risk analysis with death as a competing event. The CIF estimates and 95% CI at fixed time points of interest will be provided for each organ dysfunction. Time to first occurrence of each organ dysfunction will be conducted for both the 26-week Treatment Period and through 52 weeks.

7.3.3.11. Subgroup Analysis for Secondary Efficacy Analyses

Subgroup analysis by time from TMA diagnosis to randomization (≤ median, > median) will be repeated for key secondary endpoints: OS, non-relapse mortality, number of TMA component criteria met, hematologic response, and change from Baseline in eGFR. The main analyses described in the corresponding sections of these endpoints will be used in the subgroup analysis.

If the number of participants in either one of the subgroups is < 10, only descriptive statistics will be provided for the subgroup analysis.

7.3.4. Exploratory Analyses

7.3.4.1. Biomarkers and Genetic Markers

Available exploratory endpoint biomarker data for analyses may include CCI [redacted] Summary statistics will be presented for the observed value, change from Baseline, and percent change from Baseline.

The incidence of specific complement dysregulation-related mutations will be summarized by treatment group and visit if evaluated.

The relationship between ravulizumab concentration and available biomarker data or the correlation between clinical benefit and key biomarkers may be assessed by graphical display. Exploratory analyses and potential relationships between clinical outcomes, PK/PD, TMA, genetic profile, and biomarker levels may also be performed on available data. Autoantibody results will be summarized if evaluated.

These analyses will be performed on the available biomarker and genetic data at the time of the primary analysis and on complete data at the end of study or in a separate report.

7.3.4.2. Clinical Outcomes Assessment

The following clinical outcomes will be analyzed using the FAS.

Health-Related Quality of life

Observed values and change from Baseline in EQ-5D-5L VAS and health state index score based on Time Trade-Off value set for the United States (US TTO) values, SF-12 physical and mental component scores (separately for adult and adolescent participants), and FACIT-Fatigue score will be summarized using descriptive statistics for continuous variables by treatment group in the FAS at Baseline and post-Baseline time point.

For the following endpoints, the MMRM as described in Section 7.1 will fit the data in the FAS at all post-Baseline time points to test whether changes differ between the 2 treatment groups at each time point:

- Change from Baseline in EQ-5D-5L VAS
- Change from Baseline in EQ-5D-5L index score
- Change from Baseline in SF-12 physical component score (separately for adults and adolescents)
- Change from Baseline in SF-12 mental component score (separately for adults and adolescents)
- Change from Baseline in FACIT-Fatigue score

In the main analysis for the above endpoints, the missing baseline values will not be imputed. Under the MAR assumption, missing baseline patient-reported outcome (PRO) responses will be imputed by the estimated value from a linear regression model of observed baseline PRO scores, adjusted for the corresponding randomization stratification factors.

Global Impression Scales

For Global Impression of Disease Severity and Change scales, PGI-S, CaGI-S, CGI-S, PGI-C, CaGI-C, and CGI-C, the observed number and proportion of respondents endorsing each category of the verbal rating scale will be presented by treatment group in the FAS at Baseline and post-Baseline time points. Change from Baseline on the Disease Severity scales (PGI-S, CaGI-S, and CGI-S) will be presented as the number and proportion of respondents shifting from the Baseline level to the post-Baseline level by treatment group in the FAS at each post-Baseline timepoint.

7.3.4.3. Health Resource Utilization

Hospitalizations will be summarized by treatment group in the FAS in a table presenting the number and proportion of participants requiring hospitalization, as well as the number of hospitalizations, the duration, and the reason for hospitalization. In addition, the number and proportion of participants requiring readmission due to TMA and the number of readmissions due to TMA will be summarized.

CCI [redacted] (defined in Section 9.3.13) will be summarized by treatment group in the FAS at Baseline and post-Baseline time points using the number and proportion of participants requiring CCI [redacted], the number of CCI [redacted], and the volume of CCI [redacted].

Outpatient medical encounters will be summarized by treatment group in the FAS using the number and proportion of participants requiring physician or emergency room visits during the analysis period and the underlying reason.

7.4. PK and PD Analyses

Individual PK/PD data will be collected for all participants. PK/PD analyses will be performed on the PK/PD Analysis Set.

Serum ravulizumab concentration will be summarized over time with descriptive statistics including the number of observations, arithmetic mean, SD, median, minimum, maximum, coefficient of variation, geometric mean, and geometric coefficient of variation at each scheduled sampling time point.

Graphs of mean serum ravulizumab concentration-time profiles will be constructed on the linear and semi-logarithmic scale over scheduled sampling time points. Graphs of serum concentration-time profiles for individual participants may also be provided according to the actual sampling time points.

The PD effects of ravulizumab will be evaluated by assessing the observed values, changes from Baseline, and percent changes from Baseline in serum free and total C5 concentrations at each scheduled sampling time point.

7.5. Safety Analyses

All safety analyses will be conducted on the Safety Set and based on the actual treatment received.

For participants who are randomized to placebo group and receive ravulizumab as rescue treatment, safety data collected before the first dose of ravulizumab (ie, initiation of rescue treatment) will be considered to have occurred while on placebo treatment, while safety data collected in the placebo group on or after the first dosing date of ravulizumab will be considered to have occurred while on ravulizumab treatment.

The treatment groups to be presented in the safety analyses include Stage 1 Ravulizumab, Stage 2 Placebo, Stage 2 Rescue Ravulizumab, Stage 2 Ravulizumab, and All Ravulizumab.

All safety data will be provided, by treatment group, in by-participant listings. No formal hypothesis testing is planned.

7.5.1. Study Duration, Treatment Compliance, and Exposure

Study duration will be calculated for the following analysis period as the "time in days" from the reference start day in the corresponding period to the end day of the period:

- Treatment Period
- Post-unblinding Rescue Treatment Period
- Follow-up Period
- Entire study period

Treatment compliance will be calculated as a percentage based on the number of infusions received in scheduled visits out of the number of infusions expected in scheduled visits until the last visit during the Treatment Period. For Stage 2 Placebo group, the treatment compliance is calculated using the scheduled infusions in the Placebo Treatment Period and the Post-unblinding Rescue Treatment Period separately.

Exposure will be calculated as the number of infusions received, including supplemental doses and rescue doses.

The study duration, treatment compliance, and exposure will be summarized by the treatment group in the FAS and the Safety Set, using descriptive statistics for continuous variables.

Supplemental dosing will be summarized by treatment group in the FAS and the Safety Set, using the number and percentage of participants who received supplemental doses and the number of supplemental doses per participant.

7.5.2. Adverse Events

The following definitions will be used for AEs:

- Pretreatment AEs: any AE that starts after providing informed consent/assent, but before the start of the first infusion of study drug (ravulizumab or placebo).
- TEAE: any AE that starts between the start of the first infusion of study drug and 8 months after the last infusion of study drug, inclusive. For participants in placebo

group who receive the rescue ravulizumab, TEAEs for the placebo arm only include AEs that occur before the first infusion of rescue ravulizumab. A TEAEs will be considered as emergent to rescue ravulizumab if it occurs after or on the first infusion date of rescue ravulizumab up to the earlier time of 8 months after the last infusion.

  - TEAE will be presented separately by treatment period and follow up period.

- Treatment-emergent SAE: a TEAE that is serious.
- Post-treatment AEs: any AE that starts 8 months or later after the last dose of study drug.

In addition, TEAE will be presented separately for the 26-week Treatment Period and the 26-week Follow-up Period.

The incidence of TEAEs, TEAEs leading to withdrawal from the study, TEAEs leading to study treatment discontinuation, drug-related TEAEs, TEAEs during study drug administration, and SAEs will be summarized by treatment group. A summary of TEAEs by SOC and PT will also be provided for participants who are diagnosed with COVID-19. All AEs will be coded using MedDRA Version 27.1 or higher and will be summarized by SOC and PT, and will include summaries by severity, and by relationship to study drug. AE summaries will include both the number of events and number and percentage of participants with each event based on the Safety Set. When calculating the percentage of participants, participants having multiple AEs within a category (eg, overall, SOC, and PT) will be counted once in that category. For severity/relationship tables, the participant's highest grade/most related event within a category will be counted. Percentages will be based on the number of treated participants in the Safety Set within a treatment group and overall. When calculating the number of events, all events will be provided in all tables, even for multiple AEs for the same participant. Tables will be sorted by descending frequency of SOC and by descending frequency of PT within an SOC.

Detailed by-participant listings of all AEs, SAEs, TEAEs leading to withdrawal from the study, and TEAEs leading to study treatment discontinuation will be provided.

7.5.2.1. Overall Summary of AEs

An overall summary of AEs and SAEs will be presented. The number of events (n) and number of participants with events (n, %) will be shown for the following event subcategories:

- Any TEAE
- TEAEs leading to withdrawal from the study
- TEAEs leading to study treatment discontinuation
- Drug-related TEAEs
- TEAEs during study drug administration
- TEAEs by severity grade

These statistics will be prepared separately for all AEs and SAEs. Additionally, the number and percentage of participants who died while on study will be presented.

7.5.2.2. AEs and SAEs by SOC and PT

The number of AEs and the number and percentage of participants with events will be presented by SOC and PT. Participants are counted once in each SOC and PT. Percentages will be based on the total number of treated participants in the treatment group. Non-serious AEs and SAEs (see the definition in Protocol Section 10.4) will be summarized similarly. The number of AEs and the number and percentage of participants with events will be presented by descending order of PT as well.

7.5.2.3. AEs and SAEs by SOC, PT, and Relationship

The number and percentage of participants with events will be presented by SOC and PT as described above by relationship (related, not related). If a participant has more than 1 occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. SAEs will be summarized similarly.

7.5.2.4. AEs and SAEs by SOC, PT, and Severity

The number and percentage of participants with events will be presented by SOC and PT as described above by CTCAE v5.0, severity grades (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5). If a participant has more than 1 occurrence of an AE, the most severe grade of occurrence will be used in the summary table.

7.5.2.5. Deaths, Other SAEs, and Other Significant Adverse Events

A listing of participant deaths will be produced, as well as a listing of AESIs (meningococcal infections are considered to be AESIs).

7.5.2.6. TEAE by subgroup

The overall summary of TEAEs and TEAE by SOC and PT term will be summarized by the following subgroups:

- Age at screening (12 - < 18, 18 - <45, 45 - <65, ≥ 65 years old)
- Sex (female, male)
- Race (white, black or African American, Asian, others)
- Baseline weight (30 to < 40, 40 to < 60, 60 to < 100, ≥ 100 kg)

7.5.3. Geographic region (Japan, rest of the world)Other Safety

7.5.3.1. Analyses for Laboratory Tests

Observed values and changes from Baseline in clinical chemistry, hematology, and urinalysis will be summarized descriptively by treatment group at Baseline and at each post-Baseline time point.

For laboratory results that can be classified as “normal,” “low,” or “high” based on normal range values, shifts from Baseline in classification will be summarized by treatment group for all post baseline time points. For the specific parameter, the denominator for the percentages is number

with non-missing at Baseline and post-Baseline. For purposes of analyses, laboratory results based upon standardized units will be used.

7.5.3.2. Vital Signs

Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, O_2 saturation, and temperature) and weight will be summarized descriptively by treatment group at Baseline and post-Baseline time points for observed values and for changes from Baseline.

7.5.3.3. Electrocardiograms

ECGs will be evaluated and the frequency and percentage of "normal," "abnormal, not clinically significant," or "abnormal, clinically significant" at each post-Baseline visit will be provided. Percentages are based on the number with an assessment at each visit.

Observed values and change from Baseline in ECG intervals (heart rate, PR, RR, QRS, QT, and QTcF) will be summarized descriptively by treatment group at Baseline and each post-Baseline time point.

7.5.3.4. GVHD Status

GVHD status assessed at Baseline and post-Baseline time points will be summarized descriptively as a categorical variable by treatment group. A shift table of post-baseline timepoint GVHD status from Baseline GVHD status will also be summarized.

7.5.3.5. Immunogenicity

The incidence of ADAs to ravulizumab will be summarized descriptively by treatment group at Baseline and each post-Baseline time point. In addition, the number and percentage of participants ever positive and always negative will be summarized. Any confirmed ADA positive samples will be tested for ADA titer and the presence of neutralizing antibodies to ravulizumab, these results will also be summarized.

7.6. COVID-19 Related Analyses

Following analysis will be performed to assess the pandemic impact of COVID-19 on the study efficacy and safety results as supplemental and sensitivity analyses.

The number and proportion of participants who experience following COVID-19 impact will be summarized by treatment group and visit in the FAS:

- Those who miss the scheduled visits due to COVID-19
- Those who miss the scheduled doses of study treatment due to COVID-19

The number of missing doses per participant will also be summarized by treatment group in the FAS.

If doses planned in 2 consecutive scheduled visits are missing due to COVID-19, the efficacy assessments from the target day of the first missing visit to the day of study drug reinitiating will be assumed to be missing even though the assessments may be collected. The missing efficacy assessments or visits due to COVID-19 impact will be handled in the same way as described in Section 7.1.1 under the assumption of MAR.

8. REFERENCES

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9. APPENDICES

9.1. Protocol Schedule of Events

Refer to Protocol Section 1.3 for the schedules of activities.

9.2. Sample Size, Power, and Randomization

Approximately 124 participants will be enrolled in the study. The sample size determination is based on the following assumptions:

- A log-rank test to compare EFS through the 26-week Treatment Period.
- Twenty-six week OS estimates for non-C5 inhibitor (C5i) treated patients in the literature, estimated to be approximately 30% (approx. 20% [Cho, 2008; Kraft, 2019; Oran, 2007], 18-40% [Wanchoo, 2018]).
- The EFS rate in the placebo treatment group is assumed to be similar to the OS rate for non-treated patients from the literature though with the following revisions:
    - Forty percent 26-week OS in the placebo treatment group is assumed considering the option for rescue in study ALXN1210-TMA-313 compared to the non-C5i treated patients from the literature (40% OS in placebo group and 30% OS in literature).
    - Thirty percent 26-week EFS in placebo group is assumed given EFS is a composite endpoint and includes clinical worsening events in addition to death
- The HR between ravulizumab and placebo is 0.45. Assuming an exponential distribution for time to the composite endpoint of clinical worsening or death, the 26-week EFS rate in the ravulizumab treatment group is 58%.
- 1:1 ravulizumab treatment group and placebo treatment group randomization ratio
- Two-sided significance level of 5%

With these assumptions, 119 participants are expected to experience 66 events, providing the study with 90% power. To secure 66 events, a conservative approach to enroll approximately 124 participants is proposed.

Participants will be randomized on Day 1 after the Investigator has verified that they are eligible. Permuted block randomization will be stratified by region (Japan and rest of the world) as well as GVHD status on the day of randomization (no acute GVHD, Grade I-II acute GVHD, or Grade III-IV acute GVHD), where grade is assigned using the International Bone Marrow Transplant Registry Severity Index for grading acute GVHD. Participants will be randomized 1:1 either to the ravulizumab treatment group or to the placebo treatment group. Randomization will be performed centrally using Interactive Response Technology (IRT) system.

9.3. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

9.3.1. Study Periods

Screening Period is defined as the period from the informed consent date to ththe day prior to the first infusion of study treatment (ie, placebo and ravulizumab).

The **end-of-study day** for a participant is defined as the latest of the last study visit, the last protocol specified assessment, or study discontinuation and is subsequently lost to follow-up.

Treatment Period is defined as the period from the first infusion to the earliest of the Day 183 Visit, the Early Discontinuation Visit, the end-of-study day, or the day just prior to the first infusion of rescue ravulizumab (for placebo-randomized participants who receive rescue ravulizumab as the rescue treatment), inclusive. The Treatment Period is the primary study period for efficacy analyses and is also referred to as the 26-week randomized Treatment Period.

For Stage 2 participants in the placebo group who receive ravulizumab as the rescue treatment, the **Post-unblinding Rescue Treatment Period** is defined as the period from the first infusion of rescue ravulizumab to the earliest of the Rescue Day 183 Visit, the Early Discontinuation Visit, or the end of study day, inclusive.

Follow-up Period, if applicable, is defined as the period from 1 day after the Treatment Period or the Post-Unblinding Rescue Period, whichever comes later, to the end of study day, inclusive. Participants who have an end of study day prior to the Day 183 Visit (or the Rescue Day 183 Visit) will not have a Follow-up Period.

For the purpose of safety analysis, the study period will also be divided into 3 segments per the definition of the Treatment Emergent Period:

The **Pre-treatment Period** is the period after the informed consent date and before the first dose date of study treatment.

The **Treatment Emergent (TE) Period** is the period from the first dose date of study treatment to 8 months after the last dose or the end of study day, whichever is earlier.

The **Post-treatment Period** is the period from 1 day after the TE Period to the end-of-study day. For participants whose TE Period ends at the end-of-study day, the Post-treatment Period is not applicable.

Table 8: shows the participants and study periods included in each treatment group in the 26-week analysis. The same approach will be followed in the final analysis.

Table 8: Participants and Study Periods Included in Each Treatment Group for the Primary Analysis at 26 Weeks

	Primary, Secondary, and Exploratory Efficacy Analyses	**Efficacy Analysis for Rescue Treatment Participants**	**Safety Analyses**	**PK, PD, and Immunogenicity Analyses**
Stage 1 Ravulizumab	Stage 1 participants, Treatment Period	Not applicable	Stage 1 participants, Treatment Period	Stage 1 participants, Treatment Period
Stage 2 Placebo	Stage 2 participants randomized to the placebo group, Treatment Period	Not applicable	Stage 2 participants in the placebo group who receive the rescue ravulizumab, Placebo Treatment Period	Not applicable

Table 8: Participants and Study Periods Included in Each Treatment Group for the Primary Analysis at 26 Weeks

	Primary, Secondary, and Exploratory Efficacy Analyses	Efficacy Analysis for Rescue Treatment Participants	Safety Analyses	PK, PD, and Immunogenicity Analyses
			Stage 2 participants in the placebo group who do NOT receive the rescue ravulizumab, Treatment Period	
Stage 2 Rescue Ravulizumab	Not applicable	Stage 2 participants in the placebo group who receive the rescue ravulizumab, Rescue Treatment Period	Stage 2 participants in the placebo group who receive the rescue ravulizumab, Rescue Treatment Period	Stage 2 participants in the placebo group who receive the rescue ravulizumab, Rescue Treatment Period
Stage 2 Ravulizumab	Stage 2 participants randomized to the ravulizumab group, Treatment Period	Stage 2 participants randomized to the ravulizumab group, Treatment Period	Stage 2 participants in the ravulizumab group, Treatment Period	Stage 2 participants in the ravulizumab group, Treatment Period
All Ravulizumab	Not applicable	Not applicable	Stage 1 participants, Treatment Period Stage 2 participants in the placebo group who receive the rescue ravulizumab, Rescue Treatment Period Stage 2 participants in the ravulizumab group, Treatment Period	Not applicable

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic

9.3.2. Definition of Baseline Values

Study baseline is defined as the last non-missing assessment value prior to the first dose of study treatment (data from Screening or Day 1, prior to date of first study infusion) or prior to the randomization if a participant is not treated with the study drug. Study baseline will be used in all efficacy analyses, including the delayed treatment effect analysis.

Rescue Treatment Period baseline is defined for participants in the placebo group who receive ravulizumab as the rescue treatment as the last non-missing assessment value prior to the first dose of rescue ravulizumab. Rescue treatment Baseline will be used in safety analyses.

For baseline values defined for safety laboratory parameters, in the event of duplicate samples from local and central laboratories, central laboratory results will be used to define baseline. Local laboratory results will only be used if no central laboratory results are available.

9.3.3. Change From Baseline

Change in values from Baseline will be calculated as follows:

Change in value = (subsequent value – Baseline value)

given that both the Baseline value and subsequent value are non-missing.

9.3.4. Percent Change from Baseline

Percent change in values from Baseline will be calculated as follows.

Percent change in value = (change in value / Baseline value) × 100

where change in value = (subsequent value – Baseline value), given that the Baseline value is non-missing and non-zero and the subsequent value is non-missing.

9.3.5. Duration Calculation

Duration from a start date to an end date (eg, time to event/response and response duration) will be calculated as follows: duration = (end date – start date + 1).

9.3.6. Dates and Points of Reference

For Stage 1, the reference start day will be the day of the first infusion date of ravulizumab.

For Stage 2, the reference start day of the primary, secondary, and exploratory efficacy analyses based on the randomized treatment will be the day of randomization, while the reference start day for the PK, PD, and safety analyses (including prior and concomitant medications, AEs, safety laboratory parameters, and immunogenicity assessment) will be the first infusion date of study treatment.

For Stage 2 participants in the placebo group who receive ravulizumab as the rescue treatment, the reference start day for safety analysis and delayed treatment effect analysis is defined as follows:

- Placebo Treatment Period: the reference start day is defined as the first infusion of placebo.
- Rescue Treatment Period: the reference start day is defined as the first infusion of rescue ravulizumab.

9.3.7. Analysis Visits

Summaries over post-Baseline time points or analyses at specific post-Baseline time points will be performed based on the list of visits described in the schedule of assessment of the protocol. For all assessments, the number of days from Baseline will be calculated using the following formula: (date of assessment) – (reference start day) + 1. Relative days prior to Day 1 are calculated as (date of assessment – reference start day). This number of days will be used to assign analysis visit.

The analysis visit assignment for a specific assessment will be based on visit windows around each scheduled visit for that specific assessment. The windows for each scheduled visit will go from the midpoint (in days) between the current visit and the previous scheduled visit to the

midpoint between the current visit and the subsequent scheduled visit. If the interval separating 2 scheduled visits is an even number of days, that middle day will be included in the later visit window and excluded from the prior visit window. For example, for an assessment with a scheduled visit on Day 71, a prior scheduled visit on Day 57, and a subsequent scheduled visit on Day 85, the window will start 64 days from Baseline and will go up to 77 days from Baseline.

Efficacy and safety assessments performed during the 26-week Treatment Period, if applicable, will be mapped to analysis visits according to the reference start day of the 26-week Treatment Period (defined in Section 9.3.6) and visit windows based on the target days of scheduled visits in the 26-week Treatment Period.

For Stage 2 participants in the placebo group who receive ravulizumab as the rescue treatment, efficacy assessments performed during Post-unblinding Rescue Treatment Period, if applicable, will be mapped to the analysis visits, as follows:

- According to the reference start day of Rescue Treatment Period (defined in Section 9.3.6) and visit windows based on the target days of scheduled visits in the Post-unblinding Rescue Treatment Period

For these participants, safety assessments in the 26-week Treatment Period (defined in Section 9.3.6), if applicable, will be mapped to analysis visits according to the reference start day in this period and target days of scheduled visits in the 26-week Treatment Period; safety assessments in the Post-unblinding Rescue Treatment Period, if applicable, will be mapped to analysis visits according to the reference start day in this period and target days of scheduled visits in the Post-unblinding Rescue Treatment Period.

9.3.8. Analysis Value

For all efficacy assessments, if there are multiple measurements within a visit window, the record at the scheduled visit will be used. If there are no measurements at the scheduled visit, the record at an unscheduled visit closest to the target day will be used. If there are multiple records with the same distance to the target day, the latest record will be used.

For all safety assessments, if there are multiple measurements within a visit window, then the record closest to the target day will be used. If there are multiple records within the same distance from the target day, the latest record will be used.

9.3.9. Adverse Events

The pretreatment AEs, TEAEs, and post-treatment AEs are determined by the start date of the AEs, as defined in Section 7.5.2. If the start date of an AE is completely missing, then the AE is considered as treatment emergent.

If the start date of an AE is partially missing, the AE start date will be imputed only as follows:

- If only the day is missing and the month and year are present
  - If the month and year are the same as the first dose date of study treatment, then assign to the day of the first dose date of study treatment.
  - If the month and year are not the same as the month and year of the first dose date of study treatment, then assign to the first day of the month.

- If the month and day are missing and only the year is present
  - If the year is the same as the year of the first dose date of study treatment, then assign to the month and day of the first dose date of study treatment.
  - If the year is not the same as the year of the first dose date of study treatment, then assign to 01 January.

The imputed AE start date will be used to classify pretreatment AEs, TEAEs, and post-treatment AEs.

9.3.10. Concomitant Medications/Therapies

In order to define concomitant for medications or therapies with completely missing start or stop dates, the following criteria will be used:

- If both start and stop dates of a medication or therapy are completely missing, this medication or therapy will be considered both prior and concomitant.
- If the start date of a medication or therapy is completely missing and the stop date is on or after the date of the first dose date of study treatment, that medication or therapy will be considered both prior and concomitant.
- If the stop date of a medication or therapy is completely missing and the start date is within the TE Period, that medication or therapy will be considered concomitant.

For medications with partial start dates, missing month will be imputed with January and missing day will be imputed with first day of the month. For medications with partial stop dates, missing month will be imputed with December and missing day will be imputed with the last day of the month.

9.3.11. Death Dates

For death dates, the following rules will be used for imputing partial dates:

- If only the day of the month is missing, the first of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive. If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive.

For OS and non-relapse mortality, if the imputed dates result in a negative duration, duration will be reset to 1 day.

9.3.12. Serum Creatinine and eGFR

Serum creatinine measurements are not reliable with concurrent dialysis. Therefore, all serum creatinine values obtained while a participant is on dialysis will be excluded from all analyses. The eGFR will be imputed with a value of 10 (in mL/min/1.73 m^2) while a participant is on dialysis. A participant will be considered on dialysis from the first day of dialysis through 5 days

after the end of dialysis. This rule will only be applied to postbaseline assessments of serum creatinine and eGFR.

The eGFR will be calculated based on creatinine using the CKD-EPI formula in participants ≥ 18 years of age:

$$\text{eGFR (mL/min/1.73 m}^2) = 142 \times \min(\text{Scr/k}, 1)^{\alpha} \times \max(\text{Scr/k}, 1)^{-1.200} \times 0.9938^{\text{age}} \times 1.012 \text{ [if female]},$$

where Scr is the creatinine value in mg/dL, k = 0.7 (if female) or 0.9 (if male), α = -0.241 (if female) or -0.302 (if male), and age is in years.

The eGFR will be calculated based on creatinine using the Bedside Schwartz formula in participants < 18 years of age:

$$\text{eGFR (mL/min/1.73 m}^2) = (0.41 \times \text{height in cm}) / \text{ creatinine in mg/dL}$$

9.3.13. Platelets and Hemoglobin

Platelet and hemoglobin measurements are not reliable with concurrent RBC and/or platelet CCI [redacted] Therefore, platelet values obtained on the day of a blood CCI [redacted] of platelets through 7 days after the CCI [redacted] will be excluded from all analyses. Hemoglobin values obtained on the day of a blood CCI [redacted] of either whole blood or packed RBCs through 7 days after the CCI [redacted] will be excluded from all analyses. This rule will only be applied to postbaseline assessments of platelets and hemoglobin.

9.3.14. EQ-5D-5L Scoring Algorithm for Health State Index

EQ-5D-5L and the EQ-5D-5L Proxy version 1 are assessed using the index scored according to the US TTO as well as the response on the VAS question.

The EQ-5D-5L health state index is derived by applying a formula that attaches values (or weights) to each of the levels in each dimension. The standard US TTO value set, the same for both proxy and self-completed versions, is used to assign a value based on the health state indicated on the questionnaire, as follows:

MOBILITY: 0.000 if response = 1, -0.096 if response = 2, -0.122 if response = 3, -0.237 if response = 4, -0.322 if response = 5

SELF CARE: 0.000 if response = 1, -0.089 if response = 2, -0.107 if response = 3, -0.220 if response = 4, -0.261 if response = 5

USUAL ACTIVITIES: 0.000 if response=1, -0.068 if response = 2, -0.101 if response = 3, -0.255 if response = 4, -0.255 if response = 5

PAIN/DISCOMFORT: 0.000 if response = 1, -0.060 if response = 2, -0.098 if response = 3, -0.318 if response = 4, -0.414 if response = 5

ANXIETY/DEPRESSION: 0.000 if response = 1, -0.057 if response = 2, -0.123 if response = 3, -0.299 if response = 4, -0.321 if response = 5

Health state index score = 1 + MOBILITY + SELF CARE + USUAL ACTIVITIES + PAIN/DISCOMFORT + ANXIETY/DEPRESSION

If data for some but not all dimensions are missing at a specific time point, data for the missing dimension(s) from the last available assessment prior to the time point with missing data will be used in the US TTO calculation. If all dimensions are missing, the last available US TTO score prior to the time point with missing data will be used.

Values prior to the first dose of ravulizumab will not be carried forward to post-dose values. For example, Baseline values will not be carried forward to post-Baseline values; likewise, values obtained for participants assigned to placebo will not be carried forward to post-rescue treatment values.

9.3.15. Scoring Algorithm for FACIT-Fatigue

Negatively stated items (all 13 items except for items An5 and An7) will be reversed by subtracting the response from "4." The FACIT-Fatigue total score will then be calculated by taking the sum of the items from the questionnaires, divided by the number of items answered, and then multiple by 13, the total number of items in the scale. A total score will not be calculated if more than 6 items are missing.

A higher total score indicates a better quality-of-life outcome.

9.4. Additional Subgroup Analysis

Additional subgroup analyses will be produced to support country-specific submissions. Unless otherwise specified, the endpoints and variables definitions and methods used for these outputs will be the same as described as the global study SAP.

9.4.1. Japanese Subgroup analysis

The following summary outputs will be produced for the subgroup of Japanese participants. These outputs may be used to support PMDA submission.

- Participants profile
    - Study disposition
    - Demographics and baseline disease characteristics
- Efficacy
    - EFS
    - Overall survival
    - TMA response and individual components of TMA response
- Safety
    - Overall summary of TEAEs
    - TEAEs and SAEs by MedDRA SoC and preferred term
    - TEAEs leading to study treatment discontinuation
    - TEAEs by relationship to study treatment
    - TEAEs by CTCAE Toxicity Grade

- PK/PD (Japanese subgroup and non-Japanese sub-group)
    - Serum concentration of ravulizumab
    - Pharmacodynamic parameters over time

9.4.2. East Asian Subgroup Analysis

The following summary outputs will be produced for the subgroup of east Asian participants. These outputs may be used to support NMPA submission.

- Participants profile
    - Study disposition
    - Demographics and baseline disease characteristics
- Efficacy
    - EFS
    - Overall survival
    - TMA response and individual components of TMA response
    - Number of TMA response criteria met
    - Non-relapse mortality
    - eGFR
- Safety
    - Overall summary of TEAEs
    - TEAEs and SAEs by MedDRA SoC and preferred term
    - TEAEs leading to study treatment discontinuation
    - TEAEs by relationship to study treatment
    - TEAEs by CTCAE Toxicity Grade
- PK/PD
    - Serum concentration of ravulizumab
    - Pharmacodynamic parameters over time

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