TITLE PAGE

STATISTICAL ANALYSIS PLAN

Version Number: 2.0

Protocol Title: A Phase 3, Open-label, Single-Arm, Multicenter Study of Ravulizumab in Addition to Best Supportive Care in Pediatric Participants (from 1 month to <18 years of age) with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplantation (HSCT)

Alexion Protocol Number: ALXN1210-TMA-314 Protocol Amendment 4

Brief Title: Ravulizumab in Pediatric Participants with TMA after HSCT

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for Study ALXN1210-TMA-314 is based on Protocol Version 4.0, dated 02 SEPT 2024.

SAP Version	Version Date	Change	Rationale
1.0	07 May 2021	Not applicable	Original version
2.0	09 OCT 2024	• Revised derivation of the primary endpoint • Added additional secondary endpoints: – Change from baseline in haptoglobin, platelets, LDH, and hemoglobin • Added detailed descriptions of estimands related to the primary endpoint/analysis • Added secondary endpoints: – CCI during the 26-week Treatment Period – Overall survival by Day 100 – Non-relapse mortality by Day 100 • Updated description of analyses sets to clarify that all participants who sign the informed consent will be included in the respective analysis sets.	To reflect changes made through protocol amendment 4

APPROVAL SIGNATURES

PPD

09-Oct-2024

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PPD

10-Oct-2024

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09-Oct-2024

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LIST OF ABBREVIATIONS

Abbreviation	Definition
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
ATC	Anatomical Therapeutic Chemical
BSC	best supportive care
C5	complement component 5
CI	confidence interval
CIF	cumulative incidence function
CNS	central nervous system
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DIC	disseminated intravascular coagulation
DMC	Data Monitoring Committee
EC	exclusion criteria
ECG	electrocardiogram
EFS	Event Free Survival
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ED	Early Discontinuation (Visit)
EoS	End of Study (Visit)
FAS	Full Analysis Set
GI	gastrointestinal
GVHD	graft versus host disease
HLA	human leukocyte antigen
HIV	human immunodeficiency syndrome
HSCT	hematopoietic stem cell transplant
HSCT-TMA	hematopoietic stem cell transplant-associated thrombotic microangiopathy
IC	inclusion criteria
IV	intravenous
KM	Kaplan Meier
LDH	lactate dehydrogenase
LLT	Lowest Level Term
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measure
PD	pharmacodynamic(s)
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic(s)
PPS	Per Protocol Set
PRES	posterior reversible encephalopathy syndrome
PT	Preferred Term
q4w	every 4 weeks
q8w	every 8 weeks
QoL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
REML	restricted maximum likelihood
SAE	serious adverse event

Abbreviation	Definition
SAS®	Statistical Analysis Software®
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
SOC	System Organ Class (MedDRA)
SOP	standard operating procedure
ST-HUS	Shiga toxin-related hemolytic uremic syndrome
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMA	thrombotic microangiopathy
ULN	upper limit of normal
VOD	veno-occlusive disease
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

This Statistical Analysis Plan describes the statistical methods for analyzing data for Study ALXN1210-TMA-314, Protocol Amendment 4.0, "A Phase 3, Open-label, Single-Arm, Multicenter Study of Ravulizumab in Addition to Best Supportive Care in Pediatric Participants (from 1 month to <18 years of age) with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplantation (HSCT)". Standard data presentation instructions, and table, figure, and listing specifications are contained in the Data Presentation Plan (DPP) in a separate document.

1.1. Objectives, Endpoints, and Estimands

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of ravulizumab plus BSC in the treatment of pediatric participants with HSCT-TMA	TMA response during the 26-week Treatment Period
Secondary	
To characterize TMA response after treatment with ravulizumab	• Time to TMA response during the 26-week Treatment Period • TMA response and time to response for each individual component of TMA response during the 26-week Treatment Period • Hematologic response 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

Table 1: Objectives and Endpoints

Objectives	Endpoints
	• Changes from baseline during the 26-week treatment Period and through 52 weeks in the following: – Haptoglobin – Platelets – LDH – Hemoglobin • CCI [redacted] during the 26-week Treatment Period
To assess improvement in organ dysfunction	• Change from baseline in TMA-associated organ dysfunction[a] in renal system, cardiovascular system, pulmonary system, CNS, and GI system through 26 weeks and 52 weeks
To assess TMA relapse	• TMA relapse during the Follow-up Period
To assess overall survival	• Overall survival by Day 100, 26 weeks and 52 weeks
To assess non-relapse mortality	• Non-relapse mortality by Day 100, during the 26-week Treatment Period and through 52 weeks
Pharmacokinetic and Pharmacodynamic Endpoints	
To assess PK/PD of ravulizumab in pediatric 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 plus BSC in pediatric participants with HSCT-TMA	• Incidence of treatment-emergent AEs and treatment-emergent SAEs • Changes from baseline in vital signs and laboratory parameters

Table 1: Objectives and Endpoints

Objectives	Endpoints
	• Incidence of ADAs and assessment of immunogenicity
Exploratory Objectives	
To assess the efficacy of ravulizumab plus BSC in the treatment of pediatric participants with HSCT-TMA	Event free survival during the 26-week Treatment Period defined as the time from Day 1 to the first of the following events: • Death • Clinical worsening
To assess biomarkers, including CCI in pediatric participants with HSCT-TMA	Changes from baseline in biomarkers, which may include, but are not limited to, CCI [redacted]
To assess improvement in QoL patient reported outcomes in pediatric participants with HSCT-TMA	Change from baseline in QoL as measured by PedsQL
To describe health resource utilization in pediatric participants with HSCT-TMA	• Number, reason, and duration of hospitalizations (including stays in intensive care unit) • CCI [redacted] Number of outpatient medical encounters (including physician or emergency room visits) and the underlying reason
To assess complement pathway genetic mutations in pediatric participants with HSCT-TMA	Frequency of specific complement dysregulation-related mutations

[a] Organ dysfunction is defined in Protocol Section 8.2.2.4.
Abbreviations: ADA = antidrug antibody; AE = adverse event; BSC = best supportive care; C5 = complement component 5; CNS = central nervous system; GI = gastrointestinal; HSCT-TMA = hematopoietic stem cell transplant-associated thrombotic microangiopathy; LDH = lactate dehydrogenase; PD = pharmacodynamic(s); PedsQL = Pediatric Quality of Life Inventory 4.0 Generic Core Scale; PK = pharmacokinetic(s); QoL = quality of life; CCI [redacted] SAE = serious adverse event; TMA = thrombotic microangiopathy

1.2. Study Design

ALXN1210-TMA-314 is an open-label, single-arm, multicenter Phase 3 study to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of ravulizumab administered by intravenous (IV) infusion in pediatric participants (from ≥28 days to < 18 years of age) with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). Eligible participants are those who received HSCT within 12 months prior to Screening and subsequently developed 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.

The study plans to enroll approximately 40 pediatric participants, with at least 35 participants evaluable for the primary analysis. The study will consist of 3 periods: a Screening Period of up to 7 days, a 26-week Treatment Period, and a 26-week Follow-up Period.

Participants will receive loading doses of ravulizumab IV on Day 1, Day 5, and Day 10 followed by maintenance dosing of ravulizumab IV on Day 15 and every 8 weeks (q8w) thereafter for participants weighing CCI kg, or once every 4 weeks (q4w) for participants weighing CCI kg. Participants will receive the following weight-based ravulizumab dosing regimen via IV infusion:

Weight[a]	Loading Phase Doses			Maintenance Doses
	Day 1	Day 5	Day 10	Starting Day 15
5 to < 10 kg	600 mg	300 mg	300 mg	300 mg q4w
10 to < 20 kg	600 mg	300 mg	300 mg	600 mg q4w
20 to < 30 kg	900 mg	300 mg	300 mg	2100 mg q8w
30 to < 40 kg	1200 mg	300 mg	300 mg	2700 mg q8w
40 to < 60 kg	2400 mg	600 mg	600 mg	3000 mg q8w
60 to < 100 kg	2700 mg	900 mg	900 mg	3300 mg q8w
≥ 100 kg	3000 mg	900 mg	900 mg	3600 mg q8w

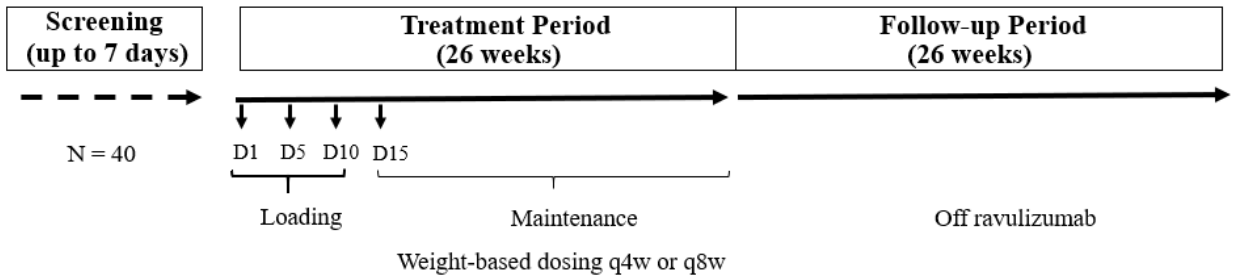
[a] Dose regimen will be based on body weight obtained at the study visit. If ravulizumab needs to be prepared prior to the visit, the weight from the previous visit may be used.
Abbreviations: q4w = every 4 weeks; q8w = every 8 weeks

Supplemental doses of ravulizumab will be administered following CCI [redacted] In addition, supplemental doses of ravulizumab will be allowed on an individual case basis for demonstrated clinical worsening (assessed and agreed upon by the Investigator and Alexion Medical Monitor).

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. Participants who discontinue ravulizumab early and agree to remain in the study should continue to attend the scheduled protocol visits according to the schedule of activities (SoA) for safety follow-up and collection of other data (Protocol Section 1.3).

For participants who discontinue study early or participants who are administered ravulizumab during the Follow-up Period, a safety follow-up phone call will be performed 8 weeks after the last dose of ravulizumab to collection information on concomitant medications, nonpharmacological therapies and procedures, and adverse events (AEs).

Figure 1: Study Design Schematic



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.
Abbreviations: ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif. Member 13; D = day; q4w = every 4 weeks; q8w = every 8 weeks; ST-HUS = Shiga toxin-related hemolytic uremic syndrome

1.3. 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 the Sponsor after consultation with the DMC. All appropriate regulatory authorities and Ethics Committees will be notified of any significant action.

2. STATISTICAL HYPOTHESES

This is an estimation study and no statistical test will be performed on the primary endpoint.

2.1. Multiplicity Adjustment

No statistical test will be performed and therefore no multiplicity adjustment is needed for the study.

3. ANALYSIS SETS

The following participant analysis sets are defined as follows:

Participant Analysis Set	Description
Full Analysis Set (FAS)	All participants who sign the informed consent and receive at least 1 dose of ravulizumab, excluding participants who enroll prior to availability of ST-HUS and/or ADAMTS13 laboratory results and are subsequently found to be ineligible after enrollment.
Per Protocol Set (PPS)	The Per Protocol Set (PPS) will consist of FAS participants who meet all of the following criteria: 1. Treatment compliance, defined in Section 4.5.1, is ≥ 80%. 2. Did not receive any disallowed medications or undergo any disallowed therapeutic procedures (see Protocol Section 6.5.2) during the Treatment Period. 3. Did not violate the following inclusion and exclusion criteria in the study: a. Met IC: i. IC #2: Participants received HSCT within the past 12 months at the time of Screening ii. IC #3: Confirmed HSCT-TMA diagnosis as required per protocol b. Did not meet EC: i. EC #3: Positive direct Coombs test ii. EC #4: Diagnosis or suspicion of DIC iii. EC #6: Diagnosis of VOD, regardless of severity iv. EC #7: Known human immunodeficiency syndrome (HIV) infection by HIV-1/HIV-2 test at Screening Validity of participants to the PPS will be reviewed and determined prior to database lock. The primary analysis and selected secondary efficacy analyses will be repeated on the PPS as sensitivity analyses.
Safety Set	All participants who sign the informed consent and receive at least 1 dose of ravulizumab
Pharmacokinetic and Pharmacodynamic Analysis Set (PK/PD)	All participants who sign the informed consent and receive at least 1 dose of ravulizumab and who have evaluable PK or PD data

- Efficacy analyses will be performed on the Full Analysis Set (FAS).
- The primary efficacy endpoint analysis, as well as selected secondary endpoint analyses, will also be performed on the Per Protocol (PP) Set.
- Safety analyses will be performed on the Safety Set.
- Pharmacokinetic and PD analyses will be performed on all participants who receive at least 1 dose of ravulizumab and who have evaluable PK and/or PD data.

4. STATISTICAL ANALYSES

4.1. General Considerations

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

Summary statistics will be computed and displayed by visit, where applicable. Descriptive statistics for continuous variables will minimally include the number of participants, mean, standard deviation (SD), minimum, median, and maximum. Continuous variables with values of "<XX.X" or ">XX.X" will be considered as "XX.X" for summary purposes. For categorical variables, frequencies and percentages will be presented. The Kaplan-Meier (KM) method will be used for the time to event analysis (e.g., overall survival, time to TMA response). Graphical displays will be provided as appropriate. The confidence interval (CI) will be constructed as 2-sided with 95% confidence level.

Day 1 for efficacy analyses will be the planned first day of ravulizumab administration and will be the first day of actual ravulizumab administration for safety analyses. Day 1 will be used for calculation of post-treatment study days.

Data listings will be provided for data collected or derived for analysis in the relevant analysis populations.

4.1.1. Handling of Dropouts or Missing Data

Intercurrent events

The strategies to handle the intercurrent events in the analysis include:

- Composite endpoint strategy where observed data prior to an intercurrent event will be used and worst outcome (e.g., no response in analysis of TMA response) will be assumed from the event onwards. The intercurrent events for composite endpoint strategy include treatment failures (defined in Section 4.2.1) and study discontinuation.
- Treatment policy strategy where all observed values will be used regardless of occurrence of an intercurrent event.
- Hypothetical strategy where missing values will be assumed from the event onwards. The intercurrent events for hypothetical strategy include treatment failures (defined in Section 4.2.1) and study discontinuation.

Missing data handling

The following missing data handling approaches will be used:

- A confirmatory result for individual TMA response components (details in Section 4.2.1) cannot be from an assessment that has 2 or more preceding consecutive missing scheduled assessments between itself and an earlier assessment when the TMA response criterion was met. This approach will also be applied to other response-type endpoints.
- The non-responder imputation 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 time-to-event endpoints (overall survival, time to TMA response, etc.), the missing data will be handled by censoring. Censoring mechanisms for these endpoints will be described in the analysis section.

For continuous endpoints with more than 1 postbaseline time point, the missing data will be handled by fitting the actually observed data with a mixed-effect model for repeated measures (MMRM) under the assumption of missing at random (MAR).

- Handling of creatinine and eGFR values on dialysis is described in Section 6.1.11, and handling of platelet and hemoglobin values on platelet and/or CCI is described in Section 6.1.12.
- Incomplete or missing dates will be imputed as described in Section 6.1.8, Section 6.1.9, Section 6.1.10.

Other missing data will not be imputed, unless otherwise specified.

4.2. Primary Endpoint(s) Analysis

4.2.1. Derivation of Endpoint(s)

The primary efficacy endpoint of the study is TMA response during the 26-week Treatment Period. TMA response is defined in Table 2, below.

Table 2: Overview of Thrombotic Microangiopathy Response

		TMA Response Parameter
TMA Response	Hematologic Response	If baseline platelet count ≤ 50,000/mm^3, the following criteria must be met: • Absolute platelet count > 50,000/mm^3 without platelet transfusion support during the prior 7 days If baseline platelet count > 50,000/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
	Renal Response	At least 50% reduction of proteinuria from baseline

Participants must meet each TMA response criterion at 2 separate assessments obtained at least 24 hours apart, and any measurement in between; and all intervals during which each criterion is met must overlap for at least one day to be classified as having met the primary efficacy endpoint. The first lab value used to assess TMA response 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 labs may be used in the absence of a valid central laboratory result. LDH must be assessed centrally for both measurements.

Time interval of response for individual TMA response criterion

The time interval for meeting individual TMA response criterion will be derived for each criterion by the following steps:

1. The initial response for each individual criterion needs to be confirmed by a second assessment ≥ 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.
2. For each individual criterion, loss of response is defined as the event of failing to meet the criterion at a subsequent visit after the positive response is established in Step 1 during the 26-week Treatment Period. The loss of individual component response must be confirmed by a second laboratory result at least 24 hours apart. For this criterion, if the second laboratory result does not confirm the loss, a positive response will be assigned to the prior visit not meeting the criterion. For platelets and proteinuria, local labs may be used in the absence of a valid central laboratory result. LDH must be assessed centrally for both measurements. The end of the time interval will be set as the date of last positive response prior to the loss of response. If loss of response is not observed for this criterion in the data by the end of the 26-week Treatment Period, the end of the time interval will be set as the date of last positive response.

In presence of missing central 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 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 TMA response criterion met during the time interval between 2 non-missing assessments. No response will be assigned to the two consecutive scheduled visits with missing values.

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

Assessment of no response due to treatment failures

Below intercurrent events will be considered as treatment failures:

- Meeting the criteria for clinical worsening to provide supplemental doses, as recorded on the electronic case report form (eCRF), and 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

The criteria for clinical worsening must be confirmed by 2 independent samples collected at least 8 hours apart. At least 1 of these samples must be analyzed by the central laboratory. Supplemental dosing for clinical worsening will be determined following assessment and agreement by the Investigator and Alexion Medical Monitor.

- Start of disallowed therapy as defined in the protocol
- Treatment discontinuation
- Additional HSCT
- Death at any time during the study

Under the composite endpoint strategy (Section 4.1.1), non-responder imputation will be employed as follows:

- if a participant meets the treatment failure rules as defined above, assume no response from the event of treatment failure onward for all 3 TMA response components.
- if a participant discontinues from the study for reasons other than treatment failures defined above, assume no response from the day of study discontinuation onward for all 3 TMA response components.

TMA response at participant level

The time interval of a positive TMA response is defined as the duration when all 3 TMA response criteria are met simultaneously.

In order to meet the composite TMA, all 3 intervals during which each criterion is met, after the non-responder imputation, must overlap for at least one day during the analysis period (e.g., during the 26-week Treatment Period for the primary endpoint analysis). Alternative strategies to define TMA response may be used in sensitivity analyses, such as the following:

1. Treatment policy strategy where all observed values will be used regardless of occurrence of an intercurrent event.
2. Hypothetical strategy where missing values will be assumed from the intercurrent event onward. The intercurrent events for hypothetical strategy could include treatment failures (defined in Section 4.2.1) and/or study discontinuation.

4.2.2. Main Analytical Approach

The primary efficacy endpoint of the study is TMA response during the 26-week treatment period as defined under composite endpoint strategy in Section 4.1.1. Missing values are handled as described in Section 4.1.1.

Formal statistical comparisons are not planned for this study. The proportion of participants who achieve TMA response during the 26-week Treatment Period and 95% exact Clopper-Pearson binomial CI will be summarized.

4.2.3. Subgroup Analysis

Summaries of efficacy endpoint, including the primary endpoint as the proportion of participants with TMA response with the 95% Clopper-Pearson CIs will be presented by subgroups. Subgroups will include (but not limited to):

- Gender (female, male)
- Geographical region (Japan and Rest of the World)
- Baseline weight (5 to < 10 kg, 10 to < 20 kg, 20 to < 30 kg, ≥ 30 kg)
- Age at Screening (Birth to < 2 years, ≥ 2 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years)
- Baseline Proteinuria Status (Yes [protein/creatinine ratio ≥ 1 mg/mg], No [protein/creatinine ratio < 1 mg/mg])
- Baseline Platelet Count (≤50,000 /mm^3, >50,000 /mm^3)
- Indication of transplant (hematologic malignancy, non-hematologic malignancy, non-malignancy)
- Type of transplant (allogeneic, autologous)
- eGFR (<15 mL/min/1.73m^2, ≥15 ml/min/1.73m^2)
- GVHD status (no GVHD, Grade I-II, or Grade III-IV)
- Time from the first TMA symptom or sign to first dose of study treatment (≤ median, > median)
- Time from TMA diagnosis to first dose date of study treatment (≤ median, > median)
- Receipt of supplemental doses during 26-week Treatment Period (yes, no)
- GVHD and age subgroup combination
- GVHD and gender subgroup combination

Given that the number of participants in some subgroups may be limited, subgroup categories may be combined, as appropriate. A Forest Plot of proportions with 95% CIs by subgroup will also be provided, if applicable.

4.2.4. Sensitivity Analyses

The following sensitivity analyses will be performed:

- The primary endpoint will be defined following the treatment policy strategy using all data in the 26-week Treatment Period, including the data obtained after the intercurrent events defined as treatment failures.
- The primary analysis for the primary endpoint as described in Section 4.2.2 will be repeated for the PPS.

4.3. Secondary Endpoint(s) Analysis

4.3.1. Derivation of Endpoints

The secondary efficacy endpoints of the study are the following:

1. Time to TMA response, defined as the days from Day 1 (Section 4.1) to the first day that the participant satisfies all the criteria for TMA response, following hypothetical strategy (Section 4.1.1), during the 26-week Treatment Period
2. Response for each individual component of TMA response (Section 4.2.1) during the 26-week Treatment Period
3. Time to response for each individual component of TMA response (Section 4.2.1), defined as time in days from Day 1 (Section 4.1) to first date of meeting individual response criterion, following hypothetical strategy (Section 4.1.1), during the 26-week Treatment Period.
4. Hematologic response as defined in Table 2 during the 26-week Treatment Period
5. Time to hematologic response, defined as time in days from Day 1 (Section 4.1) to first date of hematologic response following hypothetical strategy (Section 4.1.1), during the 26-week Treatment Period
6. Hemoglobin response is defined as the ability to maintain hemoglobin ≥ 10 g/dL without CCI [redacted] support during the prior 7 days. This 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.
7. Platelet response is defined as follows:
    a. If baseline platelet count ≤ 50,000/mm^3, the following criteria must be met:
        a. Absolute platelet count > 50,000/mm^3 without platelet transfusion support during the prior 7 days
    b. If baseline platelet count > 50,000/mm^3, the following criteria must be met:
        a. ≥ 50% increase in platelet count compared to baseline value without platelet transfusion support during the prior 7 days
8. Partial TMA response is defined as meeting ≥ 1, but not all, criteria for TMA response as defined in Table 2. The derivation is similar to that for the primary endpoint. Participants with partial TMA response are mutually exclusive to participants with TMA response. Partial response will be assessed during the 26-week Treatment Period.
9. 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 one or more TMA response criteria at a subsequent visit during the 26-week Treatment Period. At least one parameter must fail to meet the response criteria at 2 separate assessments obtained at least 24 hours apart, and any measurement in between. The occurrence of treatment failure events defined in Section 4.2.1 will also be treated as loss of TMA response.
10. 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

initial TMA response to first occurrence of loss of response during the 26-week Treatment Period, or TMA relapse during 26-week Follow-up period, or death.

11. Changes from baseline during the 26-week Treatment Period and through 52 weeks in the following:
    a. Haptoglobin
    b. Platelets
    c. LDH
    d. Hemoglobin
12. CCI [redacted] is defined in Table 3. The derivation is similar to that for the primary endpoint where participants must have met each response criterion, with each parameter meeting the requirement at 2 separate assessments obtained at least 24 hours apart, and any measurement in between; and all intervals during which each criterion is met must overlap for at least one day to be classified as having met the efficacy endpoint. CCI [redacted] will be assessed during the 26-week Treatment Period.

Table 3: Overview of CCI [redacted]

		CCI [redacted] Parameter
CCI [redacted]	CCI [redacted] 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
		CCI [redacted] from baseline and CCI [redacted][a] Or CCI [redacted] of LDH and [redacted] CCI [redacted]
	Renal response	At least 50% reduction of proteinuria from baseline

[a] 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).

13. 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 status will be assessed by urine protein/creatinine ratio, serum creatinine, and estimated glomerular filtration rate (eGFR) based on creatinine using the Bedside Schwartz formula in participants < 18 years of age (Section 6.1.11).

- Renal dysfunction will be defined as doubling of serum creatinine from baseline or requirement of dialysis. A participant will be considered as dialysis dependent:

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

  At postbaseline visit: if there is any dialysis within 5 days prior to the visit.

- Cardiopulmonary dysfunction will be defined as either presence of cardiopulmonary features (excluding hypertension and including, but not limited to, pulmonary hypertension, pleural effusion, pulmonary edema, pericardial effusion, serositis), or use of any ventilatory or respiratory support.
  - The presence of cardiopulmonary symptoms at baseline and postbaseline 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 eCRF page 'Non-Pharmacologic Therapies and Procedures'

  The presence of hypertension will also be assessed and recorded on the eCRF.

- Central nervous system dysfunction will be defined as confirmed posterior reversible encephalopathy syndrome (PRES), or any signs of headache, confusion, visual loss, or seizures at baseline and postbaseline visits, as recorded on the eCRF.
- Gastrointestinal dysfunction will be defined as presence of signs and symptoms of GI involvement including diarrhea, vomiting, pain, and bleeding at baseline and postbaseline visits, and recorded on the eCRF.

14. TMA relapse is defined only for participants who have achieved TMA response during the 26-week Treatment Period, as evidence of worsening hematologic and renal dysfunction due to TMA during the post-treatment Follow-up Period and requires treatment intervention, as determined by the investigator.
15. Overall survival at Day 100, 26 weeks and 52 weeks
    - Survival time will be assessed as the time in days from Day 1 (Section 4.1) to an event of death in the analysis period.
16. Non-relapse mortality through Day 100, 26 weeks and 52 weeks
    - 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 Day 1 (Section 4.1) to an event of non-relapse death in the analysis period.

4.3.2. Main Analytical Approach

All secondary analyses will be performed on the FAS.

4.3.2.1. Time to TMA Response

For time to TMA response, participants will be assigned as responders at the time of their TMA response. Cumulative incidence function (CIF) of TMA response will be estimated using competing risk survival analysis methods. 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 the latest date where all 3 TMA response components data are available within the 26 weeks period. CIF curves for TMA response will be generated. CIF estimates and 95% CIs at fixed time points of interest, including Week 26, will be provided.

Fine and Gray's subdistribution hazard model will be repeated for time to TMA response on the PPS as a sensitivity analysis.

4.3.2.2. 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 also be summarized over time by presenting the number and proportion of responders along with a 2-sided 95% exact Clopper-Pearson CI for each postbaseline time point, including time points of importance such as Week 26.

This analysis will be conducted using 2 different approaches following composite endpoint strategy. The first one will present the number and proportion of responders out of the participants in the FAS with available data. 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. The results from the cumulative approach at 26 weeks will be consistent with the primary analysis. This analysis will also be conducted on the PPS.

4.3.2.3. Other Response Endpoints

Other response endpoints, defined in Section 4.3.1, include:

- Hematologic response
- Response for individual 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
- Platelet response
- CCI [redacted]

Analysis of responses as binary outcomes

These response endpoints are defined following the composite endpoint strategy by assuming no response after treatment failures or study discontinuation.

Proportion of participants with positive responses during 26-week Treatment Period will be summarized by calculating the point estimate and a 95% CI for the proportion of responders. The CI will be based on exact confidence limits using the Clopper-Pearson method.

These responses will also be summarized for the FAS over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each postbaseline time point. This analysis will be conducted using 2 different approaches following composite endpoint strategy as described in Section 4.3.2.2.

Analysis of time to response

Time-to-response endpoints, defined in Section 4.3.2, include:

- Time to response for individual TMA response criteria, assessed separately
- Time to hematologic response

The analysis of the above time-to-response endpoints will be the same competing risk survival analysis methods as those described in Section 4.3.2.1.

4.3.2.4. Hematologic Parameters

Hematologic parameters (haptoglobin, platelets, LDH, and hemoglobin) will be summarized at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. Proportion of participants in the FAS with schistocytes present out of those remaining in the study at a specific time point will be assessed.

4.3.2.5. Loss of Response/Duration of Response

Loss of response will be summarized 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 will have achieved TMA response defined following the composite endpoint strategy.

Duration of response will be censored at the last day in the study if a responder does not experience any events defined as loss of TMA response. The duration of response will be assessed by KM analysis as a time-to-event variable in TMA responders. KM curves with the summary statistics, as described in Section 4.3.2.1 will be generated.

Sensitivity analysis will be performed by defining the loss of response using below alternative criteria:

- failing to meet at least 2 of 3 TMA response criteria, or
- failing to meet all 3 TMA response criteria

at a subsequent visit after TMA response is achieved. Above descriptive analyses for loss of response and the KM analysis of duration of response will be repeated using the alternative definitions of loss of response in the FAS.

A sensitivity analysis which includes all participants with non-responders censored at Day 1 will also be performed.

4.3.2.6. TMA Relapse

TMA relapse will be summarized by calculating the point estimate and a 95% Clopper-Pearson CI for the proportion of participants with a TMA relapse, among participants in the FAS who are TMA responders on Day 183 as defined following the composite endpoint strategy.

Time to TMA relapse/progression (defined in Section 4.3.1 is a clinically meaningful assessment of duration of TMA response, with the end of response defined as TMA relapse/progression or death. It will be censored at the last day on the study if TMA responders have not experienced any events defined as TMA relapse/progression. KM curves with the summary statistics, as described in Section 4.3.2.1 will be provided.

4.3.2.7. Organ Dysfunction

Treatment effect on organ dysfunction will be evaluated in the following end organ systems: renal, cardiopulmonary, CNS, and gastrointestinal.

Renal involvement:

Kidney function parameters (protein/creatinine ratio, serum creatinine, and eGFR) will be summarized in the FAS at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline.

Renal dysfunction is defined in Section 4.3.2. An analysis will present over time, 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 in the FAS. A 2-sided 95% Clopper-Pearson CI for the proportion will be provided. In addition, the shift tables describing the change of renal dysfunction (yes or no) and of individual conditions from baseline will be summarized by postbaseline time points.

A MMRM for change from baseline in eGFR at all postbaseline time points with visit and baseline eGFR as fixed effects will be used to describe the change of eGFR. The restricted maximum likelihood (REML) method will be used for estimation. An unstructured (co)variance structure will be used to model the within-subject variability. Other structures (e.g., first-order autoregressive, compound symmetry, and Toeplitz) will be explored by use of Akaike's information criteria should the unstructured (co)variance structure not result in adequate model convergence. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The least square means, standard error of the estimates, p-values, and 2-sided 95% CIs will be provided for each postbaseline time point.

In addition, the MMRM used in the main analysis of eGFR will be repeated in the PPS.

Cardiovascular and pulmonary involvement:

The presence of cardiopulmonary dysfunction, presence of hypertension, and use of any ventilatory or respiratory support 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 time point in the FAS. A 2-sided 95% Clopper-Pearson CI for the proportion will 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 postbaseline time points in the FAS.

In addition, the systolic and diastolic blood pressure will be summarized descriptively for the FAS at baseline and postbaseline time points for observed values and for changes from baseline.

CNS involvement:

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

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

Time to first occurrence of each organ dysfunction

For each of above organ systems, KM curves with summary statistics as described in Section 4.1 will be provided for the time to first occurrence of organ dysfunction, censored by the earlier time of last available assessment or death. If the organ dysfunction occurs at baseline for an organ system, the time to organ dysfunction will be set as 1 day.

A sensitivity analysis will be performed in the FAS to assess the treatment effects on the time to first occurrence of each organ dysfunction 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.

4.3.2.8. Overall Survival

Survival time will be assessed as the number of days from Day 1 to an event of death. Intercurrent and censoring rules are included in the table below.

Situation	Date of Event or Censoring	Outcome (Event or Censored)
Death	Death Date	Event
Additional HSCT	Date of additional HSCT	Censored
End of analysis period OR last known alive status	Date of end of analysis period OR Date of last known alive date, whichever is earlier	Censored

Participants who have not experienced an intercurrent event will be censored at their last available follow-up. A Kaplan-Meier cumulative distribution curve will be generated. A corresponding summary table will present the quartiles, along with corresponding 2-sided 95% CI of survival time. A sensitivity analysis will be repeated following the hypothetical strategy and will censor the participants at the occurrence of the intercurrent events: treatment discontinuation, or additional HSCT Another sensitivity analysis will be performed by repeating the KM analysis described above in the PPS.

4.3.2.9. Non-relapse Mortality

Non-relapse mortality is defined as participant's death due to any cause during the study, with the exception of death due to underlying disease progression or relapse (i.e., reason for HSCT). Time to non-relapse mortality is defined in Section 4.3.1. Progression/relapse-related deaths will be treated as a competing risk. Intercurrent events and censoring rules are included in Table xx. Participants 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 within the analysis period. Cumulative incidence function (CIF) curves for non-relapse mortality will be generated. CIF estimates and 95% CIs at fixed time points of interest, including Week 26, will be provided.

Situation	Date of Event or Censoring	Outcome (Event or Censored)
Non-relapse Death	Death Date	Event
Primary Disease Relapse Related Death	Death Date	Competing Event
Additional HSCT	Date of additional HSCT	Censored
End of analysis period OR last known alive date	Date of end of analysis period OR Date of last known alive date, whichever is earlier	Censored

Sensitivity analysis similar to that for the Time to TMA Response analysis will also be performed.

4.3.3. Other Subgroup Analysis

Subgroup analysis by time from TMA diagnosis to first dosing date of study treatment (≤ median, > median) will be repeated for key secondary endpoints: hematologic response, overall survival, change from baseline in eGFR, non-relapse mortality, and time to TMA response. The main analyses described in corresponding sections of these endpoints will be used in the subgroup analysis.

4.3.4. Sensitivity Analyses

Selected secondary efficacy analyses will be performed on the PPS, as necessary.

Sensitivity analyses of TMA response as well as TMA response parameters will be performed using local laboratories, where available, when central laboratories are missing.

4.4. Exploratory Analyses

4.4.1. Derivation of Endpoints

The exploratory endpoints of the study are as follows:

1. Event Free Survival (EFS) during the 26-week Treatment Period defined as the time from Day 1 to the first of the following events:

   - Death
   - Clinical worsening

   Clinical worsening is defined in the protocol 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

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

2. Changes from baseline in biomarkers, which may include, but are not limited to, CCI [redacted]
3. Incidence of specific complement dysregulation-related mutations
4. Change from baseline in quality of life (QoL), as measured by the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scale
5. Health resource utilization including:

   - Number, underlying 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

4.4.2. Main Analytical Approach

4.4.2.1. Event Free Survival

EFS time will be assessed as the number of days from Day 1 to an event of death, or clinical worsening, whichever occurs first. Participants who have not experienced an intercurrent event of additional HSCT and is event free will be censored at the last date that they are known to be alive (last known alive date) within 26 weeks. A Kaplan-Meier curve will be generated. A corresponding summary table will present the quartiles, along with corresponding 2-sided 95% CI, of EFS time.

4.4.2.2. Biomarkers and Genetic Markers

For blood and urine biomarker analyses, summary statistics will be presented for observed value, and change and percentage change from baseline. Available exploratory endpoint biomarker data

for analyses may include CCI [redacted]

The incidence of specific complement dysregulation-related mutations will be summarized by visit.

The relationship between ravulizumab concentration and biomarkers 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. Autoantibody results will be summarized if evaluated.

These analyses will be performed on the available biomarker data at the time of the primary endpoint analysis and on complete data at the end of study and may be reported separately.

4.4.2.3. Quality of Life

Quality of life will be evaluated using PedsQL 4.0 Generic Core Scale for participants ≥ 2 years and ≤ 18 years of age. There are 7 unique versions of the PedsQL, divided by age and reporting type, as shown in the table below:

Age Group	Self-reported	Parent-reported
2-4		√
5-7	√	√
8-12	√	√
13-18	√	√

For ages 2-4, there is a parent-reported instrument; whereas, for ages 5-18, both self-reported and parent-reported versions exist. For the purpose of summarization, results across age groups can be combined and summarized together. However, results from the self-reported and parent-reported versions will not be combined, with one exception. The parent-reported PedsQL for ages 2-4 may be combined with the self-reported versions for ages 5 and up, i.e., this version will be utilized in summaries of both parent- and self-reported PedsQL.

Each version of the PedsQL contains the same 4 individual scale scores (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning). Total and scale score calculations and missing value algorithms are provided in Section 6.3.1. These scores, along with summary scores (Psychosocial Health and Physical Health) and total scale score will be summarized across age groups in the FAS but separately for each reporting type (self and parent) at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. The missing baseline and postbaseline data will not be imputed for analyses.

4.4.2.4. Health Resource Utilization

Hospitalizations will be summarized at baseline and any time postbaseline by presenting the number and proportion of participants requiring hospitalization out of the number in the FAS, 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.

Transfusion requirements for RBCs or platelets (defined in Section 6.1.12) will be summarized in the FAS by presenting the number and proportion of participants requiring transfusions, the number of transfusions, and the volume of the transfusions at baseline and postbaseline time points.

Outpatient medical encounters will be summarized by presenting the number and proportion of participants requiring physician or emergency room visits and the underlying reason, out of the number in the FAS.

4.5. Safety Analyses

All safety analyses will be conducted on the Safety Set. Safety analyses will be presented separately for the 26-week Treatment Period and 26-week Follow-up Period.

All safety data will be provided in participant listings. No formal hypothesis testing is planned.

4.5.1. Study Duration, Treatment Compliance, and Exposure

Study duration will be calculated for the following analysis periods, as the time in weeks from the start day in corresponding period to the end day of the period:

- Treatment Period
- Follow-up Period
- Entire study period

Treatment compliance will be calculated as a percentage based on the number of infusions received at scheduled visits out of the number of infusions expected at scheduled visits, until the last visit during the Treatment Period.

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

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

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

4.5.2. Adverse Events (AEs)

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 ravulizumab.
- TEAE: any AE that starts between the start of the first infusion of ravulizumab and the earlier of either 8 months after the last infusion of ravulizumab or the end of study, inclusive. For participants who are retreated in the Follow-up Period, last infusion of ravulizumab will be the last infusion during retreatment.
- Treatment-emergent SAE: a TEAE that is serious.

- Post-treatment AE: any AE that starts > 8 months after the last infusion of ravulizumab.

The incidence of TEAEs, TEAEs leading to withdrawal from the study, TEAEs leading to study treatment discontinuation, drug-related TEAEs, TEAEs during study intervention administration, and serious adverse events (SAEs) will be summarized by treatment group. A summary of TEAEs by SOC and Preferred Term will also be provided for participants who are diagnosed with COVID-19. All AEs will be coded using MedDRA Version 23 or higher and will be summarized by SOC and Preferred Term and will include summaries by severity and by relationship to treatment. 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 percentage of participants, participants having multiple AEs within a category (e.g., overall, SOC, Preferred Term) 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. When calculating 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 SOCs and by descending frequency of Preferred Terms 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.

4.5.2.1. Overall Summary of Adverse Events

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 intervention 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 on study will be presented. AEs and SAEs by SOC and Preferred Term

The number of AEs and the number and percentage of participants with events will be presented by SOC and Preferred Term. Participants are counted once in each SOC and Preferred Term. Non-serious AEs and SAEs (see definition in Protocol Section 10.3.2) will be summarized similarly.

4.5.2.2. AEs and SAEs by SOC, Preferred Term, and Relationship

The number and percentage of participants with events will be presented by SOC and Preferred Term as described above by relationship (related, not related). If a participant has more than one

occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. SAEs will be summarized similarly.

4.5.2.3. AEs by SOC, Preferred Term, and Severity

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

4.5.2.4. Deaths 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 in this study).

4.5.3. Other Safety

4.5.3.1. Analyses for Laboratory Tests

Observed values and changes from baseline in clinical chemistry, hematology, coagulation, and urinalysis will be summarized descriptively at baseline and at each postbaseline time point.

For laboratory results that can be classified as normal, low, or high based on normal range values, shifts from baseline at each postbaseline visit will be summarized. Participants will be included in the summary for a given parameter and visit if they have a baseline and postbaseline value, and totals at baseline and postbaseline will be included. Vital Signs

Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, O_2 saturation, and temperature), along with weight will be summarized descriptively at baseline and postbaseline time points for observed values and for changes from baseline.

4.5.3.2. Electrocardiograms

Electrocardiograms will be evaluated and the frequency and percentage of normal, abnormal not clinically significant, or abnormal clinically significant at each postbaseline 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 at baseline and each postbaseline time point.

4.5.3.3. GVHD Status

GVHD status assessed at baseline and postbaseline time points will be summarized descriptively as a categorical variable.

4.6. Other Analyses

4.6.1. Pharmacokinetic and Pharmacodynamic Analysis

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-log 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 and percentage changes from baseline in serum free and total C5 concentrations at each scheduled sampling time point.

4.6.2. Immunogenicity

The incidence of ADAs to ravulizumab will be summarized descriptively at baseline and each postbaseline 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**.**

4.6.3. COVID-19 Related Analyses

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

The number and proportion of participants who experience the following impact due to COVID-19 will be summarized by 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 participants will also be summarized in the FAS.

If doses planned in two consecutive scheduled visits are missing due to COVID-19, the efficacy assessments from the target day of first missing visit to the day of study intervention reinitiation 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 ways as described in Section 4.1.1 under the assumption of MAR. Sensitivity analyses for the primary endpoint may be performed if, after applying above rule, the percent of missing efficacy assessments due to COVID-19 out of all scheduled assessments among all participants is more than 10%.

TMA response will be derived after setting missing values by the above rule, following the composite endpoint strategy. The descriptive summary and main analysis of TMA response during the 26-week Treatment Period will be repeated for the re-derived TMA response.

4.7. Planned Analyses

4.7.1. Dose Confirmation Analysis

An early analysis of the PK/PD data will be initiated when 10 evaluable 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 evaluable participants completing Visit 5 at Day 21 as part of the dose confirmation analysis to support adjustments to the dosing regimen and/or the transfusion-related supplemental dosing for ongoing participants. Alexion may also determine that additional participants need to be enrolled either prior to or during the dose confirmation analysis (e.g., if 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.

4.7.2. Interim Analysis

An interim analysis may be performed to provide interim descriptive analyses of participants as needed for regulatory milestones.

4.7.3. Primary Endpoint Analysis

A primary endpoint analysis will be conducted at the interim time point when all participants have been followed for the 26-week Treatment Period or have withdrawn from the 26-week Treatment Period. This analysis will also include available data on secondary efficacy endpoints and safety collected for the corresponding period.

4.7.4. Final Analysis

The final study analysis will be conducted at the end of the study. All analyses performed at the primary endpoint analysis will be repeated at Week 52, following 26 weeks of treatment.

4.8. Changes to Protocol-planned Analyses

4.8.1. Changes from Protocol Amendment 4.0 to SAP V2.0

Event Free Survival (EFS), which is defined as the time from Day 1 to the first of the events of Death or Clinical worsening during the 26-week Treatment Period, has been added as an endpoint for the exploratory analysis.

For time to TMA response, and time to response for individual TMA response criteria, Cumulative incidence function (CIF) of TMA response will be estimated using competing risk survival analysis methods.

The primary analysis for the overall survival will be based on treatment policy analysis strategy, so that death after treatment discontinuation could be included in the analysis.

4.8.2. Changes to Analyses Specified in the Previous Version of SAP

SAP Version	Version Date	Change	Rationale
1.0	7 May 2021	Not applicable	Original version

2.0	09 Oct 2024	Revised derivation of the primary endpoint	To align with PA2, based on rationale: '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/mm^3.'.
		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 endpoint/analysis	To add the estimands framework into endpoints.
		Added secondary endpoints: – CCI [redacted] during the 26-week Treatment Period – Overall survival by Day 100 – Non-relapse mortality by Day 100	CCI [redacted]
		Updated description of analyses sets to clarify that all participants who sign the informed consent will be included in the respective analysis sets.	To align with PA4
		For time to TMA response, and time to response for individual TMA response criteria, Cumulative incidence function (CIF) of TMA response will be estimated using competing risk survival analysis methods.	Updated to use more appropriate methodology for the analysis

		The primary analysis for the overall survival will be based on treatment policy analysis strategy.	To include death after treatment discontinuation in the analysis.

5. SAMPLE SIZE DETERMINATION

Approximately 40 participants will be enrolled in this study, with at least 35 participants evaluable for the primary analysis. This sample size is deemed appropriate to provide complete safety information and the necessary precision level for the planned estimation. Assuming a proportion of participants achieving TMA response of 50%, 40 participants would yield a 95% CI for the proportion of response with a half-width of approximately 16%.

6. SUPPORTING DOCUMENTATION

6.1. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

6.1.1. Study Periods

Screening Period is defined as the period from the informed consent date to the day prior to the first ravulizumab administration.

The **End-of-Study Day** for a participant is defined as the latest of last study visit, last protocol-specified assessment, or date of study disposition.

The **end-of-treatment day** is defined as the earliest of Day 183 visit, ED Visit, or end-of-study day. **Treatment Period** is defined as the period from the first infusion to the end-of-treatment day, inclusive.

Follow-up Period, if applicable, is defined as the period from 1 day after the end-of-treatment day to the End-of-Study Day, inclusive. Participants who have an end-of-study day prior to Day 183 visit will not have a follow-up period.

For the purpose of safety analysis, the study period will be also divided into 3 segments per the definition of the treatment-emergent (TE) period:

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

6.1.2. Definition of Baseline Values

Baseline for all parameters summarized during the Treatment Period is defined as the last non-missing value prior to the start of study treatment (data from Screening or Day 1, prior to date of first study infusion).

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

6.1.3. 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.

6.1.4. Percent Change from Baseline

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

% Change in Value = (Change in Value / Baseline value) x 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.

6.1.5. Duration Calculation

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

6.1.6. Analysis Visits

Summaries over postbaseline time points or analyses at specific postbaseline time points will be performed based on the list of visits described in the SoA of the protocol. For all assessments in the 26-week Treatment Period, the number of days from baseline will be calculated using the following formula: (date of assessment) - (date of Day 1 visit) + 1. This number of days will be used to assign the analysis visit number.

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 be 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 latter visit window and excluded from the former visit window. For example, for an assessment with a scheduled visit at Day 71, a prior scheduled visit at Day 57, and subsequent scheduled visit at Day 85, the window will begin at 64 days from baseline and end at 77 days from baseline.

6.1.7. 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 duration 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 duration from the target day, the latest record will be used.

6.1.8. Adverse Events

The pretreatment AEs, TEAEs, and post-treatment AEs are determined by the start date of the AEs, as defined in Section 4.5.2. 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 month and year are present,
  - If 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 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 month and day are missing, and only year is present,
  - If 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 year is not the same as the year of the first dose date of study treatment, then assign to January 1st.

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

6.1.9. 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 the 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.

6.1.10. 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 1st 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 overall survival and non-relapse mortality, if the imputed dates result in a negative duration, duration will be reset to 1 day.

6.1.11. 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 Bedside Schwartz formula in participants < 18 years of age:

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

6.1.12. Platelets and Hemoglobin

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

6.2. Study and Participant Characteristics

6.2.1. Participant Disposition

A summary of disposition will include the number and percentage of screened participants, screen failures, enrolled participants, and treated participants. In addition, the number and percentage of participants who discontinue from study treatment, 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 COVID-19 related reason) in the Treatment Period and Follow-up Period will be summarized for all enrolled participants. A table will also summarize the number and percentage of participants included, excluded, and the reasons for exclusion from each analysis set defined in Section 6 above.

6.2.2. Baseline Characteristics and Demographics

All demographics and baseline characteristics will be summarized using the FAS, the PPS, and the Safety Set.

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: Birth to < 2 years, ≥ 2 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years

- Baseline weight (kg): descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants in the following categories: 5 to < 10 kg, 10 to < 20 kg, 20 to < 30 kg, 30 to < 40 kg, 40 to < 60 kg, 60 to < 100 kg, ≥ 100 kg
- Baseline height (cm) by descriptive statistics for continuous variables
- Geographical region (Japan and Rest of the World)
- Presence of graft versus host disease (GVHD) (no GVHD, Grade I-II, or Grade III-IV)

6.2.3. Disease and Transplant Characteristics

All disease characteristics will be summarized using the FAS, the PPS, and the Safety Set.

The following characteristics will be summarized:

- 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 status (neutrophil and platelet)
- Time from TMA diagnosis to initiation of study treatment 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)
- Transfusion history
  - CCI [redacted] during Screening Period
  - Platelet transfusions during Screening period
- Baseline organ dysfunction status
  - Cardiopulmonary symptoms (excluding hypertension)
  - Ventilatory/respiratory support, including mechanical ventilation
  - Presence of PRES
  - Gastrointestinal involvement (diarrhea, vomiting, GI pain, GI bleed)
  - Dialysis status

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

6.2.4. Medical History and Baseline Physical Examination

Medical history will be classified by System Organ Class (SOC) and Preferred Term using the latest available version of standardized MedDRA and will be reported for the Safety Set. Baseline physical examination information will be summarized for the Safety Set.

6.2.5. 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 within the 30 days prior to the first ravulizumab administration. Concomitant medications or therapies are defined as medications or therapies received by the participants during the TE period (see definition in Section 6.1.1).

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.

Number and percentage of participants using prior and concomitant medications will be presented by WHO-DDE Anatomical Therapeutic Chemical (ATC) Level 3 and by WHO-DDE generic name. Nonpharmacologic therapies will be summarized similarly, but by MedDRA Class and Preferred Term. 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.

6.2.6. Protocol Deviations

Protocol deviations will be determined per the standard operating procedure (SOP) "Identification, Handling, and Documentation of Protocol Deviations" (SOP-G-CL-0044). The number and percentage of participants with specific protocol deviations will be summarized for all enrolled participants by important and non-important deviations. To ensure completeness of the list of protocol deviations, the following will be verified programmatically from the database, when applicable:

1. Participants who received any disallowed medication or underwent any disallowed therapeutic procedure
2. Participants who did not receive all of the planned number of infusions during the 26-week Treatment Period

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.

6.3. Instrument Scoring Details

6.3.1. PedsQL Scoring Algorithm

Each of the 7 PedsQL to be used in this study is divided into 4 dimensions: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. Each dimension contains a series of questions that are assessed on a Likert scale from 0 to 4, with 0 representing "Never" or "Not at all" and 4 representing "Always" or "Almost Always." Most questionnaires are on a 5-point Likert scale but the Young Child (Ages 5-7) is on a 3-point Likert scale.

All questions are reverse-scored and converted to a 0-100 scale. The following transformations are applied to the individual responses.

- 100 if response is 0
- 75 if response is 1
- 50 if response is 2
- 25 if response is 3
- 0 if response is 4

Each dimension score is calculated as the sum of the questions divided by the number of questions answered. If more than 50% of the questions are not answered, the scale score will not be computed.

The following scale, summary scores, and total scores are calculated:

- Physical Health Summary Score: same as Physical functioning dimension
- Psychosocial Health Summary Score: sum of all items in the Emotional, Social, and School dimensions divided by the number of questions answered in those dimensions.
- Total Score: sum of all items in all the scales divided by the number of questions answered.

Refer to Section 10.11.1 of the protocol for the specific PedsQL instruments used in this study.

7. REFERENCES

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ALXN1210-TMA-314 SAP Final V2.0

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