TITLE PAGE

Protocol Title: 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)

Alexion Protocol Number: ALXN1210-TMA-313

AstraZeneca D Code: D9284C00001

Amendment Number: Protocol Amendment 6

Compound: Ravulizumab (Sponsor code ALXN1210)

Study Phase: Phase 3

Brief Title: Ravulizumab in TMA after HSCT

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address: 121 Seaport Boulevard, Boston MA 02210, USA

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Sponsor Signatory:

This document has been e-signed in Alexion's electronic document management system. Please refer to last page for e-signature details.

PPD

Date

Alexion Pharmaceuticals, Inc.

Medical Monitor Name and Contact Information can be found in the Reference Manual distributed to study sites.

INVESTIGATOR'S AGREEMENT

I have read the study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 6 (15 Nov 2024)

This modification is considered to be substantial based on the criteria set forth in Regulation EU No 536/2014 of the European Parliament.

Overall Rationale for the Amendment:

This amendment revised the primary endpoint from "TMA Response during the 26-week Treatment Period" to "Event-free survival during the 26-week Treatment Period", a composite primary endpoint incorporating the first of the two following events: death and clinical worsening. This endpoint modification is founded on events which are clinically meaningful to physicians and patients, based on the feedback from medical experts and regulators, of which the most important and most relevant to establish ravulizumab treatment efficacy is death. This amendment revised the IA to remove the IA for SSR and proposes a new IA for early efficacy which may be conducted at the discretion of Alexion.

Number of TMA response criteria met during the 26-week Treatment Period was added as a secondary endpoint. The original primary endpoint of TMA response during the 26-week Treatment Period were moved to other secondary endpoints.

Lastly, minor grammatical and formatting changes including adding/defining abbreviations were made for consistency and clarity. Cross referencing to Tables and Sections were corrected throughout the protocol, where necessary.

See the table below for all the updates included in this amendment.

Section # and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis Section 3.1, Overview of Objectives and Endpoints Section 3.2, Definitions of Endpoints Global/as appropriate details regarding these endpoints have been included throughout the protocol.	Revised primary endpoint to: "Event-free survival during the 26-week Treatment Period defined as the time from randomization until the first of the two following events: death and clinical worsening."	Endpoint modified based on events which are clinically meaningful to physicians and patients, based on the feedback from medical experts, of which the most important and most relevant to establish ravulizumab treatment efficacy is death, as supported by the FDA and EMA in recent regulatory interactions.
	Added details for the new key secondary endpoint: "Number of TMA response criteria met during the 26-week Treatment Period."	Additional endpoint added based on healthcare provider feedback as these measures are considered clinically meaningful and should support the assessment of the efficacy of ravulizumab in this patient population.

Section # and Name	Description of Change	Brief Rationale
	Time to TMA response during the 26-week Treatment Period and the original primary endpoint of TMA response during the 26-week Treatment Period were moved to other secondary endpoints.	Endpoints moved to other secondary endpoints to reflect modification of the primary endpoint.
Section 3.2, Definitions of Endpoints	Added EFS definition.	To provide new endpoint definition.
	Added number of TMA response criteria met definition.	To provide new endpoint definition.
Section 4.1.2, Randomized Treatment Stage (Stage 2)	Number of participants updated to 124. SSR removed. Description of Follow-up Period updated.	Sample size and SSR updated based on new primary endpoint. Follow-up Period updated to reflect IA.
Section 4.2.2, Rationale for Primary Endpoint	Added rationale for EFS.	Updated to reflect the new primary endpoint.
Section 4.2.3, Rationale for Key Secondary Endpoints	Added rationale for survival, number of TMA response criteria met and hematologic response.	Modified to provide rationale for the key secondary endpoints.
Sections 6.5.5 and 8.1.4.5 Post-Interim Analysis Cross-Over Treatment	Added sections to reflect addition of an IA.	Added to provide details on IA.
Section 8.2.1.1Event-Free Survival	Event-Free Survival added: **"**Participants' survival status will be collected throughout the study. Information on any events of deaths and cause of death occurring during the study will be collected. For participants who discontinue the study early, vital status through 52 weeks will be assessed by the site through public records or telephone call. Clinical worsening as described in Table 6will be assessed and collected throughout the 26-week treatment Period.**"**	Updated to reflect the new primary endpoint.
Section 8.2.2.1.4 eGFR	Added eGFR assessment.	Updated for completeness.
Section 9.1.1 Primary Hypothesis	Primary hypothesis updated for EFS.	Updated to reflect the new primary endpoint.
Section 9.2 Sample Size Determination	Updated sample size.	Updated to reflect the new primary endpoint.

Section # and Name	Description of Change	Brief Rationale
Section 9.3 Populations for Analyses	Added ITT analysis Set and sensitivity analysis for the primary endpoint and key secondary endpoints using the ITT Set.	Updated as per FDA's recommendation.
9.4 Statistical Analyses, Section 9.4.1.1 Analyses of Primary Efficacy Endpoint	Updated to reflect change in primary endpoint: "The primary endpoint EFS will be analyzed as a time to event variable. The survival time will be calculated as the time in days from randomization to the date of clinical worsening or death, whichever is earlier. Intercurrent events and censoring rules are included in Table 12. 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." Censoring rules for EDS were added.	Updated to reflect the new primary endpoint.
Sections 9.4.1.2.1, 9.4.1.2.2, 9.4.1.3, 9.4.1.4.5, and 9.4.1.4.6	Updated to reflect change in key secondary endpoints.	Updated to reflect the new key secondary endpoint.
Section 9.4.1.4.3 Time to TMA Response	Updated to reflect change in other secondary endpoints.	Updated to reflect other secondary endpoints.
Section 9.4.1.5 Multiplicity Adjustment	Updated to reflect updated secondary endpoints.	Updated to reflect updated secondary endpoints.
Section 9.5.2 Interim Analysis	Added IA which may be conducted at the discretion of Alexion for early efficacy. Removed IA for sample size re-estimation.	Addition of an IA for efficacy to allow study stopping early for efficacy. Removal of IA for sample size re-estimation as not considered relevant anymore following the change of the primary endpoint.
Section 10.2, Mapping Objectives to Estimands	EFS added. Key secondary endpoints updated.	Updated per endpoint modification.

Section # and Name	Description of Change	Brief Rationale
Global	Minor grammatical and formatting changes including adding/defining abbreviations were made for consistency and clarity. Corrected cross referencing to tables and sections throughout the protocol where necessary. Added literature citations and references as applicable.	Minor editorial updates for consistency and clarity.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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)

Brief Title: Ravulizumab in TMA after HSCT

Regulatory Agency Identifier Number(s):

Registry	Identification
IND	128367
EU CT Number	2023-510107-22-00

Rationale:

Thrombotic microangiopathy is a rare, severe, and potentially fatal, post-transplant complication of HSCT that presents via endothelial injury and affects the kidney and other organs. Currently, there are no approved therapies for the treatment of patients with HSCT-TMA. Primary intervention for HSCT-TMA involves withdrawal of agents and/or treatment of conditions that trigger the TMA. However, in some patients, withdrawal of the offending agent and/or treatment of any associated trigger condition does not reverse the HSCT-TMA. Other supportive care options have limited clinical efficacy. Given the seriousness of the disease and limitations of the available interventions, there is a substantial unmet need for developing additional interventions that are efficacious and safe for patients with HSCT-TMA.

Complement plays a significant role in the pathogenesis of HSCT-TMA, and complement inhibition using eculizumab has demonstrated potential benefit in treating patients with HSCT-TMA in retrospective case reports with small sample sizes (Dvorak, 2019; Jan, 2019; Jodele, 2014a; Li 2019; Wanchoo, 2018) Since ravulizumab, like eculizumab, results in complete and sustained terminal complement inhibition, it is hypothesized that ravulizumab should be similarly effective in the treatment of HSCT-TMA. This study will assess the efficacy, PK, PD, and safety of ravulizumab in adult and adolescent participants with HSCT-TMA.

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: ○ Death ○ Clinical worsening[a]

Objectives	Endpoints
Secondary	
Key Secondary Endpoints	
To assess OS	• OS by Week 26 • OS 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:
	  ○ Haptoglobin
	  ○ Platelets
	  ○ LDH
	  ○ Hemoglobin
	• Modified TMA Response during the 26-week Treatment Period

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 through 26 weeks and 52 weeks
To assess TMA relapse	• TMA relapse during the Follow-up Period
To assess OS	• OS 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 and adolescent 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

[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

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

Overall Design Synopsis:

This is a two-stage, Phase 3, multicenter study of ravulizumab in adolescent (≥ 12 to < 18 years of age) and adult participants with HSCT-TMA. In Stage 1, the dosing regimen for participants with HSCT-TMA will be confirmed in an open-label, single-arm period. In Stage 2, participants will be randomized to receive either blinded ravulizumab plus BSC or matching placebo plus BSC. Eligible participants include adults and adolescents 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 will be conducted in two stages: a Dose Confirmation Stage (Stage 1) in at least 10 participants, followed by a Randomized, Double-Blind, Placebo-Controlled Treatment Stage (Stage 2) once an adequate dosing regimen has been confirmed in Stage 1.

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.

Stage 1 Treatment Period

During the Stage 1 Treatment Period, the participants enrolled in Stage 1 will receive the following weight-based ravulizumab dosing regimen via IV infusion:

Weight[a,b]	**Loading Phase Doses**			**Maintenance Doses Starting Day 15**
	Day 1	**Day 5**	**Day 10**	
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 the study intervention needs to be prepared prior to the visit, the weight from the previous visit may be used.

[b] In the event that a participant's weight drops below 30 kg after Day 1, contact the Medical Monitor or designee. If the participant's weight drops below 30 kg, the approved ravulizumab aHUS dosing for participants weighing ≥ 20 to < 30 kg will be used: a loading dose of CCI [redacted] and maintenance doses of CCI [redacted] CCI [redacted]

For participants in Stage 1, the PK and free 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. Any change in dosing regimen will be submitted for approval to the regulatory authority via a substantial protocol amendment prior to implementation, if required per local regulation. Several analyses may be conducted prior to the minimum of 10 participants completing Visit 5 at 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 the analysis (eg, if distribution of the initial 10 is not optimal) or after the analysis if the dosing regimen cannot be confirmed.

Stage 2 Treatment Period

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. The Stage 2 Treatment Period is randomized, double-blinded, and placebo-controlled.

Participants will be randomized on Day 1 in a 1:1 ratio to receive either ravulizumab plus BSC (ravulizumab treatment group) or matching placebo plus BSC (placebo treatment group). Randomization will be stratified at Stage 2 Baseline (Visit 1). Stratification will be based on geographical region (Japan and Rest of the World), and acute 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 randomized to the ravulizumab treatment group will be treated with IV ravulizumab for 26 weeks. Participants randomized to the placebo treatment group will be treated with matching placebo for 26 weeks. If the results of the efficacy assessment IA meet the pre-specified success criterion, the study may be stopped due to early efficacy (with no further enrollment) under the advisement of the study DMC. In this event, participants included in the study will continue through the Treatment and Follow-up Period as per the SoA. Additionally, participants randomized to the placebo treatment group will be offered to continue in the study and receive treatment with ravulizumab (following the SoA, Table 2 and Table 3) at the discretion of the PI and in consultation with the study Medical Monitor.

Supplemental doses of ravulizumab will be CCI [redacted] for participants in Stage 1 and Stage 2. In addition, participants in either treatment group who meet defined criteria for clinical worsening after Day 15 of the blinded Treatment Period will be eligible for rescue treatment and may be unblinded for the Investigator to determine appropriate rescue treatment. Any participant in the placebo treatment group who is to receive 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.

Follow-up Period

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. In the event that early efficacy is achieved via an IA, participants included in the study will continue through the Treatment and Follow-Up Period as per the SoA. Additionally, participants randomized to the placebo treatment group will be offered to continue in the study and receive treatment with ravulizumab (following the SoA, Table 2 and Table 3) at the discretion of the PI and in consultation with the study Medical Monitor.

Safety follow-up for participants who discontinue study intervention early, or withdraw from the study

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

For participants who discontinue study intervention and withdraw from the study, a Safety Follow-up phone call will be performed, if the participant agrees, 8 weeks after the last dose of study intervention to collect information on concomitant medications, nonpharmacological therapies and procedures, and AEs.

Disclosure Statement: This is a 2-stage study where Stage 1 is for ravulizumab dose confirmation (single-arm), and Stage 2 is randomized, double-blind, and placebo-controlled with 2 treatment groups.

Number of Participants:

Stage 1 will include at least 10 participants.

Stage 2 will include approximately 124 participants. A minimum of 10 adolescent participants ≥ 12 to < 18 years of age are planned to be enrolled in Stage 2.

Intervention Groups and Duration:

During Stage 1, all participants will receive ravulizumab plus BSC. During Stage 2, participants will be randomized 1:1 to receive either ravulizumab or matching placebo.

For each participant, the expected duration of study participation will be up to 53 weeks. This includes the Screening Period (of up to 1 week), the Treatment Period (26 weeks), and the Follow-up Period (26 weeks). If necessary, a Safety Follow-up phone call will be performed 8 weeks after the last dose of study intervention, if the participant agrees. The study duration is expected to be longer for participants randomized to the placebo treatment group who receive ravulizumab as a post-unblinding rescue treatment to allow them a 26-week ravulizumab Treatment Period followed by a 26-week Follow-up Period.

Data Monitoring Committee: Yes

1.2. Schema

Figure 1: Study Design Schematic

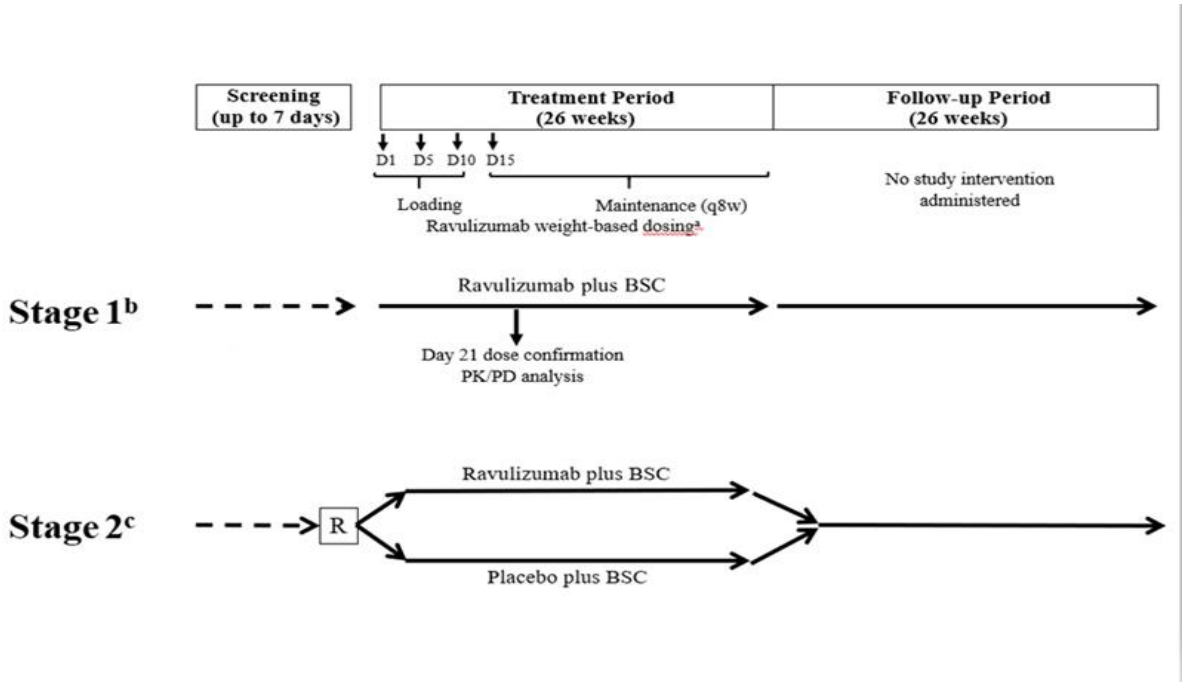


Figure 1: Study Design Schematic

Note: Stage 1 of this study will include at least 10 participants. Stage 2 will include approximately 124 participants.

[a] Initial weight based dosing (Stage 1): 30 to < 40 kg D1 = 1200 mg, D5 = 300 mg, D 10 = 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-blinded Treatment Period, followed by a Follow-up Period

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 prior to enrollment.

R = randomization

1.3. Schedule of Activities

Table 1: Schedule of Activities – Screening and Treatment Period (Stage 1 and Stage 2 Participants)

	SP	Treatment Period													Note
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information.**
Days	**-7 days**	**D1**	**D5**	**D10**	**D15**	**D21**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)			**-1**	**-1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
General Assessments/Procedures																
Informed consent/assent	X															Section 8.1.1
Inclusion/ Exclusion criteria assessment	X															Confirm clinical status before 1st dose of ravulizumab (Stage 1) or randomization (Stage 2)[a]
Medical history	X															
HSCT information	X															
Transfusion history	X															Section 8.1.7
Demographics	X															
Weight and height	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Height will only be collected at Screening, Day 71, and Day 183

Table 1: Schedule of Activities – Screening and Treatment Period (Stage 1 and Stage 2 Participants)

	SP	Treatment Period													Note
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information.**
Days	**-7 days**	**D1**	**D5**	**D10**	**D15**	**D21**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)			**-1**	**-1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
HIV-1/HIV-2 Test	X															Test at Screening or documented negative test within 6 months before Screening
ADAMTS13[a,c]	X															
ST-HUS screen [a,c]	X															
Coombs test, direct	X															
Pregnancy test (WOCBP only)	X	X	X	X	X					X			X		X	Serum pregnancy test at Screening and EoS/ED. Urine pregnancy test at all other timepoints. Additional urine testing when deemed necessary by the Investigator.[d]
Acute GVHD status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1: Schedule of Activities – Screening and Treatment Period (Stage 1 and Stage 2 Participants)

	SP	Treatment Period													Note
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information.**
Days	**-7 days**	**D1**	**D5**	**D10**	**D15**	**D21**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)			**-1**	**-1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
COA[e] (CaGI-S, CGI-S, PGI-S, EQ-5D-5L, EQ-5D-5L Proxy (version 1), SF-12, FACIT-Fatigue)	X						X					X			X	COAs to be completed prior to other study procedures and only SF-12 will be administered to adolescent participants
COA[e] (CaGI-C, CGI-C, and PGI-C)															X	COAs to be completed prior to other study procedures for adult participants
Dispense participant safety card	X															Instruct participants to carry safety card at all times and bring it to scheduled visits
Participant safety card review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants are to carry the card with them at all times until 8 months after the last dose of ravulizumab

Table 1: Schedule of Activities – Screening and Treatment Period (Stage 1 and Stage 2 Participants)

	SP	Treatment Period													Note
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information.**
Days	**-7 days**	**D1**	**D5**	**D10**	**D15**	**D21**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)			**-1**	**-1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
Physical examination	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Perform complete physical examination at Screening and Day 183 and abbreviated physical examination at all other visits.
Vital signs	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	2 consecutive blood pressure measurements obtained 1 minute apart are required at Screening; 1 measurement at all other visits. Vital signs will be collected pre- and post-dose at study intervention dosing visits.
ECG	X[b]														X	
Chest X-ray or CT-chest	X[b]														X	Section 8.3.4
Echocardiogram	X[b]														X	
Clinical laboratory tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Hematology, coagulation panel (Screening only), chemistry, and urinalysis/urine chemistry as described in Section 10.3[d, f]

Table 1: Schedule of Activities – Screening and Treatment Period (Stage 1 and Stage 2 Participants)

	SP	Treatment Period														Note
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information.**
Days	**-7 days**	**D1**	**D5**	**D10**	**D15**	**D21**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)			**-1**	**-1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
Prior medications and procedures	X															
Prophylactic antibiotic treatment	Continuous coverage															Refer to Section 8.1.8 for recommendations on prophylactic antibiotics and vaccinations
Concomitant medications	Continuous monitoring															
Concomitant procedures	Continuous monitoring															
Transfusion requirements	Continuous monitoring															Refer to Section 8.1.7 for instruction
Monitor for PRES	Continuous monitoring															Monitor at every visit for the development of seizures, headache, altered mental status and/or visual loss
AE	Continuous monitoring															
Medication error, drug abuse and misuse	Continuous monitoring															

Table 1: Schedule of Activities – Screening and Treatment Period (Stage 1 and Stage 2 Participants)

	SP	Treatment Period													Note
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information.**
Days	**-7 days**	**D1**	**D5**	**D10**	**D15**	**D21**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)			**-1**	**-1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
Survival status	Continuous monitoring															
Medical resource utilization	Continuous monitoring															
Pharmacokinetic and Pharmacodynamic Assessments																
PK/PD blood samples CCI	CCI															CCI
PK/PD blood samples CCI																
ADA blood samples	CCI															CCI
Biomarker/Future Biomarker Research																
Plasma and urine [d] samples for CCI	CCI															

Table 1: Schedule of Activities – Screening and Treatment Period (Stage 1 and Stage 2 Participants)

	SP	Treatment Period													Note
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information.**
Days	**-7 days**	**D1**	**D5**	**D10**	**D15**	**D21**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)			**-1**	**-1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
CCI																CCI
Plasma and urine [d] samples for CCI	CCI															
Blood samples for exploratory biomarker analysis CCI	CCI															CCI
Blood samples for exploratory biomarker analysis CCI																

Table 1: Schedule of Activities – Screening and Treatment Period (Stage 1 and Stage 2 Participants)

	SP	Treatment Period													Note
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information.**
Days	**-7 days**	**D1**	**D5**	**D10**	**D15**	**D21**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)			**-1**	**-1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
CCI																
Urine samples [d] for exploratory biomarker analysis CCI	CCI															CCI
Urine samples [d] for exploratory biomarker analysis CCI																
Blood and buccal swab samples for genetics analysis[i]	CCI															One blood and one buccal swab sample are to be collected at any visit.
Randomization/Administration of Study Intervention																
Randomization		X[j]														

Table 1: Schedule of Activities – Screening and Treatment Period (Stage 1 and Stage 2 Participants)

	SP	Treatment Period													Note
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information.**
Days	**-7 days**	**D1**	**D5**	**D10**	**D15**	**D21**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)			**-1**	**-1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
Study intervention administration (ravulizumab or placebo)[k]		X	X	X	X					X			X			Administer after all other required tests/procedures except post-dose sample collections.
Supplemental dosing of study intervention administration (ravulizumab or placebo)		CCI														For participants that receive CCI between CCI (refer to Section 8.1.4.3.1). Supplemental dosing may be completed CCI to the applicable supplemental dose schedule, as described within Section 8.1.4.3.1. If supplemental dosing is required at the same time as a scheduled study visit, the dosing can take place at that visit. The visit window for all other scheduled non-supplemental dosing activities at these visits, as displayed within the SoA, will remain unchanged.

Table 1: Schedule of Activities – Screening and Treatment Period (Stage 1 and Stage 2 Participants)

[a] 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. Investigators can re-test/repeat lab-based eligibility criteria that have not been met within the Screening Period. This re-testing is not allowed for those tests that are not expected to change such as ADAMTS13, HIV test, pregnancy test.

[b] Eligibility evaluation may be based on procedures (excluding laboratory assessments) conducted as part of the participant's routine clinical management and obtained during the Screening Period or ≤ 7 days prior to the start of the Screening Period. This excludes laboratory assessments which have separate criteria for use in eligibility evaluation.

[c] Participants may be enrolled prior to the availability of laboratory tests from the ST-HUS screen and ADAMTS13 test, except in the UK where all laboratory-based eligibility criteria must be met prior to enrollment.

[d] For participants CCI [redacted] may be collected using a CCI [redacted] Serum pregnancy test results obtained during routine clinical practice at timepoints between Screening and EoS/ED may be used in place of urine pregnancy test, when available.

e Participant-reported COAs will not be administered to participants deemed by the Investigator to be unable to self-report with these assessments at any protocol-specified time point. Caregiver-reported COAs, including EQ-5D-5L Proxy (version 1), should be completed by the same caregiver at each visit where the instruments are scheduled, if possible.

[f] Clinical laboratory samples should be taken pre-dose on dosing days. Follicle stimulating hormone levels will be measured during Screening only in order to confirm postmenopausal status.

[g] In the event a supplemental dose is administered at a non-dosing visit, pre- (T) dose samples should be collected instead of the any time (X) sample.

[h] It is acceptable to collect post-dose urine samples for biomarkers evaluation provided that the exact post-dose timing of sample collection is recorded.

[i] These samples are optional. They should only be collected from participants who consent to DNA collection.

[j] Only participants initially enrolled into Stage 2.

[k] Ravulizumab for participants in Stage 1, ravulizumab/placebo for participants in Stage 2 prior to unblinding for rescue, and for participants in the ravulizumab treatment group who are unblinded for rescue and the Investigator deems should continue ravulizumab treatment.

[l] The supplemental dosing regimen will be continued until no CCI [redacted] are administered in the CCI [redacted] following a maintenance dose.

Table 2: Schedule of Activities – Treatment Period (Participants Initially Randomized to the Placebo Treatment Group who Receive Ravulizumab as Post-unblinding Rescue Treatment or Following Determination of Early Efficacy Following IA)

	Treatment Period													**Note**
Visit	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**	**R11**	**R12**	**R13**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early**
Days	**D1**	**D5**	**D10**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)		**-1**	**-1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
General Assessments/Procedures														
Weight and height	X	X	X	X	X	X	X	X	X	X	X	X	X	Height will only be collected at Screening, Day 71, and Day 183
Pregnancy test (WOCBP only)	X	X	X	X				X			X		X	Serum pregnancy test at Screening and EoS/ED. Urine pregnancy test at all other timepoints. Additional urine testing when deemed necessary by the Investigator.[a]
Acute GVHD status	X	X	X	X	X	X	X	X	X	X	X	X	X	
COA[b] (CaGI-S, CGI-S, PGI-S, EQ-5D-5L, EQ-5D-5L Proxy (version 1), SF-12, FACIT-Fatigue)	X				X					X			X	COAs to be completed prior to other study procedures and only SF-12 will be administered to adolescent participants
COA[b] (CaGI-C, CGI-C, and PGI-C)													X	COAs to be completed prior to other study procedures for adult participants
Participant safety card review	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants are to carry the card with them at all times until 8 months after the last dose of ravulizumab
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	Perform complete physical examination at Day 183 and abbreviated physical examination at all other visits.

Table 2: Schedule of Activities – Treatment Period (Participants Initially Randomized to the Placebo Treatment Group who Receive Ravulizumab as Post-unblinding Rescue Treatment or Following Determination of Early Efficacy Following IA)

	Treatment Period													**Note**
Visit	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**	**R11**	**R12**	**R13**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early**
Days	**D1**	**D5**	**D10**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)		**-1**	**-1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	Vital signs will be collected pre- and post-dose at study intervention dosing visits.
ECG													X	
Chest X-ray or CT-chest													X	Section 8.3.4
Echocardiogram													X	
Clinical laboratory tests	X	X	X	X	X	X	X	X	X	X	X	X	X	Hematology, chemistry, and urinalysis/urine chemistry as described in Section 10.3[a,c]
Prophylactic antibiotic treatment	Continuous coverage													Refer to Section 8.1.8 for recommendations on prophylactic antibiotics and vaccinations
Concomitant medications	Continuous monitoring													
Concomitant procedures	Continuous monitoring													
Transfusion requirements	Continuous monitoring													Refer to Section 8.1.7 for instruction
Monitor for PRES	Continuous monitoring													Monitor at every visit for the development of seizures, headache, altered mental status and/or visual loss
AE	Continuous monitoring													

Table 2: Schedule of Activities – Treatment Period (Participants Initially Randomized to the Placebo Treatment Group who Receive Ravulizumab as Post-unblinding Rescue Treatment or Following Determination of Early Efficacy Following IA)

	Treatment Period													**Note**
Visit	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**	**R11**	**R12**	**R13**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early**
Days	**D1**	**D5**	**D10**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)		**-1**	**-1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
Medication error, drug abuse and misuse	Continuous monitoring													
Survival status	Continuous monitoring													
Medical resource utilization	Continuous monitoring													
Pharmacokinetic and Pharmacodynamic Assessments														
PK/PD blood samples CCI	CCI													CCI
PK/PD blood samples CCI														
ADA blood samples	CCI													CCI
Biomarker/Future Biomarker Research														
Plasma and urine[a] samples for CCI CCI	CCI													CCI
Plasma and urine[a] samples for CCI														

Table 2: Schedule of Activities – Treatment Period (Participants Initially Randomized to the Placebo Treatment Group who Receive Ravulizumab as Post-unblinding Rescue Treatment or Following Determination of Early Efficacy Following IA)

	Treatment Period													Note
Visit	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**	**R11**	**R12**	**R13**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early**
Days	**D1**	**D5**	**D10**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)		**-1**	**-1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
CCI														
Blood samples for exploratory biomarker analysis CCI CCI	CCI													CCI
Blood samples for exploratory biomarker analysis CCI CCI														
Urine samples[a] for exploratory biomarker analysis CCI CCI	CCI													CCI
Urine samples[a] for exploratory biomarker analysis CCI CCI														
Administration of Study Intervention														
Study intervention (ravulizumab)	X	X	X	X				X			X			Administer after all other required tests/procedures except postdose sample collections.

Table 2: Schedule of Activities – Treatment Period (Participants Initially Randomized to the Placebo Treatment Group who Receive Ravulizumab as Post-unblinding Rescue Treatment or Following Determination of Early Efficacy Following IA)

	Treatment Period													Note
Visit	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**	**R11**	**R12**	**R13**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early**
Days	**D1**	**D5**	**D10**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D127**	**D155**	**D183**	
Window (days)		**-1**	**-1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
Supplemental dosing of study intervention (ravulizumab)	CCI													For participants that receive CCI between CCI CCI CCI (refer to Section 8.1.4.3.1). Supplemental dosing may be completed CCI to the applicable supplemental dose schedule, as described within Section 8.1.4.3.1. If supplemental dosing is required at the same time as a scheduled study visit, the dosing can take place at that visit. The visit window for all other scheduled non-supplemental dosing activities at these visits, as displayed within the SoA, will remain unchanged.

[a] For participants CCI may be collected using a CCI Serum pregnancy test results obtained during routine clinical practice at timepoints between Screening and EoS/ED may be used in place of urine pregnancy test, when available.
[b] Participant-reported COAs will not be administered to participants deemed by the Investigator to be unable to self-report with these assessments at any protocol-specified time point. Caregiver-reported COAs, including EQ-5D-5L Proxy (version 1), should be completed by the same caregiver at each visit where the instrument is scheduled, if possible.
[c] Clinical laboratory samples should be taken pre-dose on dosing days.
[d] In the event a supplemental dose is administered at a non-dosing visit, pre- (T) dose samples should be collected instead of the any time (X) sample.
[e] It is acceptable to collect post-dose urine samples for biomarkers evaluation provided that the exact post-dose timing of sample collection is recorded.
[f] The supplemental dosing regimen will be continued until no CCI are administered in the CCI following a maintenance dose.

Table 3: Schedule of Activities – Follow-up Period

	Note			
Visit	**V15**	**V16**	**V17**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information**
Days (Window ± 7 days)	**D239**	**D295**	**D365 (EoS)/ED**	
General Assessments/Procedures				
Weight	X	X	X	
Pregnancy test (WOCBP only)			X	Serum test at EoS/ED. Additional urine testing when deemed necessary by the Investigator[a]
Acute GVHD status	X	X	X	
COA[b] (CaGI-S, CGI-S, PGI-S, EQ-5D-5L, EQ-5D-5L Proxy (version 1), SF-12, FACIT-Fatigue)	X		X	COAs to be completed prior to other study procedures and only SF-12 will be administered to adolescent participants
Physical examination	X	X	X	Perform complete physical examination at ED/EoS and abbreviated physical examination at all other visits
Vital signs	X	X	X	
ECG			X	
Chest X-ray or CT-chest			X	Section 8.3.4
Echocardiogram			X	
Clinical laboratory tests[a]	X	X	X	Hematology, chemistry, and urinalysis/urine chemistry as described in Section 10.3
Participant safety card review	X	X	X	Participants are to carry the card with them at all times until 8 months after the last dose of ravulizumab
Prophylactic antibiotics treatment	Continuous coverage			Refer to Section 8.1.8 for recommendations on prophylactic antibiotics and vaccinations
Concomitant medications	Continuous monitoring			
Concomitant procedures	Continuous monitoring			

Table 3: Schedule of Activities – Follow-up Period

	Note			
Visit	**V15**	**V16**	**V17**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information**
Days (Window ± 7 days)	**D239**	**D295**	**D365 (EoS)/ED**	
Transfusion requirements	Continuous monitoring			Refer to Section 8.1.7 for instruction
Monitor for PRES	Continuous monitoring			Monitor at every visit for the development of seizures, headache, altered mental status and/or visual loss
AE	Continuous monitoring			
Medication error, drug abuse and misuse	Continuous monitoring			
Survival status	Continuous monitoring			
Medical resource utilization	Continuous monitoring			
Pharmacokinetic and Pharmacodynamic Assessments				
PK/PD blood samples[c] CCI CCI	CCI			CCI
PK/PD blood samples[c] CCI CCI				
ADA blood samples[c] CCI CCI	CCI			
ADA blood samples[c] CCI CCI				
Biomarker/Future Biomarker Research				
Blood samples for exploratory biomarker analysis CCI CCI	X	X	X	

Table 3: Schedule of Activities – Follow-up Period

	Note			
Visit	**V15**	**V16**	**V17**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue early. After ED, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab, if the participant agrees, to collect AEs and concomitant medication information**
Days (Window ± 7 days)	**D239**	**D295**	**D365 (EoS)/ED**	
Urine samples[a] for exploratory biomarker analysis CCI CCI	X	X	X	

[a] For participants CCI may be collected using a CCI Serum pregnancy test results obtained during routine clinical practice at timepoints between Screening and EoS/ED may be used in place of urine pregnancy test, when available.

[b] Participant-reported COAs will not be administered for participants deemed by the Investigator to be unable to self-report with these assessments at any protocol-specified time point. Caregiver-reported COAs, including EQ-5D-5L Proxy (version 1), should be completed by the same Caregiver at each visit where the instrument is scheduled, if possible.

[c] PK/PD/ADA samples do not need to be collected for participants who were randomized to the placebo treatment group and who did not receive ravulizumab as post-unblinding rescue treatment.

2. INTRODUCTION

2.1. Study Rationale

Thrombotic microangiopathy is a rare, severe, and potentially fatal, post-transplant complication of HSCT that presents via endothelial injury and affects the kidney and other organs (Section 2.2.1) Currently, there are no approved therapies for the treatment of patients with HSCT-TMA. Primary intervention for HSCT-TMA involves withdrawal of agents and/or treatment of conditions that trigger the TMA. However, in some patients, withdrawal of the offending agent and/or treatment of any associated trigger condition does not reverse the HSCT-TMA. Other supportive care options have limited clinical response. Given the seriousness of the disease and limitations of the available interventions, there is a substantial unmet need for developing additional treatments that are efficacious and safe for patients with HSCT-TMA.

Complement plays a significant role in the pathogenesis of HSCT-TMA and complement inhibition using eculizumab has shown potential benefit in treating patients with HSCT-TMA (Section 2.2.2). Since ravulizumab, like eculizumab, results in complete and sustained inhibition of free C5, it is hypothesized that ravulizumab should be similarly effective in the treatment of HSCT-TMA. This study will assess the efficacy, PK, PD, and safety of ravulizumab in adult and adolescent participants with HSCT-TMA. The study design is described in Section 4.

2.2. Background

2.2.1. Thrombotic Microangiopathy after Hematopoietic Stem Cell Transplant

Thrombotic microangiopathy is a post-transplant complication of HSCT that may affect 10% to 35% of HSCT recipients (Dvorak, 2019; Jodele, 2015; Seaby, 2018). It presents via endothelial injury and affects the kidney and other organs. It is estimated that 30% of patients with HSCT-TMA will present with severe disease (Rosenthal, 2016), and in these cases, patients with HSCT-TMA develop systemic vascular injury manifesting in kidney damage, serositis, pulmonary hypertension, and multisystem organ failure. Survival of patients with HSCT-TMA at 1 year has been reported to range from 18% to 40% (Wanchoo, 2018). Severe HSCT-TMA is associated with long-term morbidity and mortality rates of approximately 80%. Studies have shown that the large majority of patients die within 6 months (Cho, 2008; Cho, 2010; Oran, 2007). Another study showed 9% OS of patients with severe HSCT-TMA who did not receive TMA targeted therapy (eg, eculizumab), with all mortality occurring within 10 months of the TMA diagnosis (Jodele, 2014b).

Endothelial injury is fundamental to the pathogenesis of HSCT-TMA, with dysregulated complement activation likely to be a consequence of the endothelial damage. Risk factors associated with HSCT-TMA development that also initiate endothelial damage include calcineurin inhibitors (CNIs), infections, and conditioning regimens (high-dose chemotherapy or total body irradiation); (Khosla, 2018; Masias, 2017).

Currently, there are no approved therapies for the treatment of HSCT-TMA. Primary intervention for HSCT-TMA involves withdrawal of the offending agent (eg, CNIs) and/or treatment of any trigger conditions (eg, treatment for infections) (Dvorak, 2019; Seaby, 2018). In

some patients, withdrawal of the offending agent and/or treatment of any associated trigger condition does not reverse the HSCT-TMA. Additional interventions are needed for these patients.

2.2.2. Complement Inhibition in HSCT-TMA

Complement has been shown to play a significant role in the pathogenesis of HSCT-TMA. One prospective study evaluated 100 consecutive HSCT recipients to determine the incidence of moderate and severe TMA and factors associated with poor overall outcomes, and found that elevated serum CCI [redacted], a marker of complement activation, was associated with very poor survival (Jodele, 2014b). Complement inhibition has shown favorable results in several studies of patients with HSCT-TMA (Jodele, 2016; Jodele, 2014a). This includes two single-arm, open-label, Investigator-led clinical studies which demonstrated the potential benefit of using eculizumab for treatment of severe HSCT-TMA in adult and pediatric patients. In both studies, patients were initially treated with eculizumab at the approved dose for atypical hemolytic uremic syndrome (aHUS) with additional eculizumab doses administered to keep eculizumab trough level > 99 µg/mL. The first study was conducted in 6 pediatric patients with severe HSCT-TMA; 4 out of the 6 patients had complete response (Jodele, 2014b). The second study was conducted in 18 patients with severe HSCT-TMA (3 were 19 to 29 years of age and the others were < 18 years of age). Of these, 61% had complete response (Jodele, 2016). These results support a hypothesis for terminal complement inhibition as a potential treatment for HSCT-TMA.

Ravulizumab is a humanized monoclonal antibody that, like eculizumab, binds to C5 and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin C5a and the formation of the CCI [redacted] Ravulizumab was designed through minimal targeted engineering to substitute 4 amino acids in the eculizumab heavy chain (Sheridan, 2018). These changes extend the half-life of ravulizumab relative to eculizumab, while preserving the high degree of specificity and selectivity of eculizumab for binding to C5 (Sahelijo, 2015). Both ravulizumab and eculizumab bind to the same site on C5. Ravulizumab is administered by IV infusion every 8 weeks (q8w). Ravulizumab, at a weight-based dosing regimen, is approved in multiple global regions for treatment of adult patients with NMOSD, gMG and adult and pediatric patients with PNH and aHUS. A detailed description of the chemistry, pharmacology, efficacy, and safety of ravulizumab is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Based on clinical experience and cumulative safety data from clinical studies of ravulizumab in PNH and aHUS, ravulizumab has been demonstrated to be generally well tolerated, and exposure to ravulizumab in humans has not raised any unexpected safety concerns.

Ravulizumab functions by blocking terminal complement; therefore, participants have increased susceptibility to serious infections, in particular *N meningitidis*. Specific risk mitigation measures available to support the safe use of ravulizumab in participants in this study are described in Table 4.

As with any therapeutic protein, administration of ravulizumab may lead to the development of antidrug antibodies (ADAs). Monitoring of immunogenicity is planned during this study, as described in Section 8.9. Intravenous administration of any investigational product may result in infusion reactions. Management of potential infusion reactions is described in Section 10.6.

Specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.7.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ravulizumab may be found in the Investigator's Brochure or local product labeling.

Table 4: Potential Risks and Mitigation Strategies

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Identified risk		
Meningococcal infection	Complement C5 inhibition is known to increase the susceptibility to infections caused by *N meningitidis*.	Participants must be vaccinated against all available serotypes of *N meningitidis* (A, C, Y, W135, and in addition serotype B [where available]) and when clinically feasible according to the national guidelines and recommendations for immune reconstitution and vaccination for HSCT-TMA patients. If participants cannot be vaccinated, they should be administered prophylactic antibiotics for the entire period they are treated with ravulizumab and for 8 months following their last dose of ravulizumab. Once vaccination is feasible according to national guidelines for immune reconstitution and vaccination after HSCT, participants must be vaccinated and antibiotic prophylaxis for meningococcal infections must be maintained for at least 2 weeks after vaccination. However, vaccination may not be sufficient to prevent meningococcal infection.
Potential risks		
Serious infection	Apart from the predictable risk of infection with *Neisseria* species, which is well known and directly	Increased awareness of healthcare professionals and participants about the potential risk of serious

Table 4: Potential Risks and Mitigation Strategies

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	related to the mechanism of action of ravulizumab, the mechanism that may lead to other serious infection in participants treated with ravulizumab remains unclear.	infection. Monitoring for signs and symptoms of serious infections will be conducted as part of routine safety assessments for this study. In addition to appropriate antibiotic coverage versus infection and opportunistic infections, guidelines for immune reconstitution and revaccination for HSCT patients will be followed.
Immunogenicity	Treatment with any therapeutic biologic has the potential to induce an immune response. Potential clinical consequences may include hypersensitivity, anaphylaxis or related type of reactions, or loss of efficacy. Fewer than 1% of participants in the ravulizumab Phase 2 and 3 studies had positive ADA samples.	Stop medication in the event of any drug related severe adverse events like systemic hypersensitivity or anaphylaxis. Monitoring for infusion reactions will be conducted as part of routine safety assessments for this study.
Pregnancy exposure/lactation	No studies of ravulizumab have been conducted in pregnant women. There are no data available on excretion of ravulizumab in breast milk.	Pregnant or nursing female participants are excluded from the clinical study. Participants enrolled in the study, and their spouses/partners, must use a highly effective or acceptable method of contraception (except in the UK) for a period of 8 months following the final dose of ravulizumab; for participants in the UK, only highly effective methods of contraception can be utilized. Breastfeeding should be discontinued during treatment and up to 8 months after treatment with ravulizumab.

2.3.2. Benefit Assessment

Hematopoietic stem cell transplant-associated TMA is a potentially fatal disease with limited treatment options, so development of new therapies is important to address unmet medical need. Although the efficacy of ravulizumab has not been previously studied in patients with HSCT-TMA, it represents an appropriate candidate for investigation due to the reported effectiveness of complement inhibition with eculizumab in patients with severe HSCT-TMA in previous studies (Jodele, 2014b; Jodele, 2016), as well as demonstrated efficacy and safety in treatment of aHUS, complement-mediated TMA, and other disorders of complement, including PNH. The scientific and therapeutic hypothesis for the potential benefit of ravulizumab in treatment of HSCT-TMA is discussed in Section 2.2.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the high unmet need for effective therapies for HSCT-TMA, the outcomes on this patient population with currently available care, along with the measures taken to minimize risk to participants in this study, the potential risks identified in association with ravulizumab are justified by the anticipated benefits that may be afforded to participants with HSCT-TMA.

3. OBJECTIVES AND ENDPOINTS

3.1. Overview of Objectives and Endpoints

The objectives and endpoints for Study ALXN1210-TMA-313 are provided in Table 5. A mapping of objectives to estimands is provided in Section 10.2.

Table 5: Mapping Objectives to 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 OS	• OS by Week 26 • OS 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

Table 5: Mapping Objectives to Endpoints

Objectives	Endpoints
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
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 through 26 weeks and 52 weeks
To assess TMA relapse	• TMA relapse during the Follow-up Period
To assess OS	• OS by Week 52
To assess non-relapse mortality	• Non-relapse mortality by Day 100, and through 52 weeks

Table 5: Mapping Objectives to Endpoints

Objectives	Endpoints
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 and adolescent 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] CCI [redacted] 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 symptoms 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)

Table 5: Mapping Objectives to Endpoints

Objectives	Endpoints
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

[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

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

3.2. Definitions of Endpoints

Event-Free Survival

EFS is defined as the time from randomization until the first of the two events during the 26-week Treatment Period: death and clinical worsening (defined in Table 6)

Table 6: ALXN1210-TMA-313 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

TMA Response

For TMA response (defined in Table 7), 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.

Table 7: Overview of Thrombotic Microangiopathy 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 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).

Number of TMA Response Criteria Met

The TMA response parameters (defined in Table 7) include: platelet response, normalization of LDH and absence of schistocytes, and renal response. A participant could meet 0, 1, 2, or 3 TMA response criteria during the 26-week Treatment Period. If the participants meet more than 1 TMA response criterion, the number of responses overlapping for at least 24 hours will be counted.

Modified TMA Response

For modified TMA response (defined in Table 8), 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.

Table 8: Overview of Modified Thrombotic Microangiopathy Response

		Modified 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).

Hematologic Response

The predetermined criteria for hematologic response are provided in Table 7.

Hemoglobin Response

Hemoglobin response is defined as the ability to maintain hemoglobin ≥ 10 g/dL without CCI [redacted] support. The criterion must be met at 2 separate assessments obtained at least 24 hours apart, and any measurement in between, and without CCI [redacted] support during the prior 7 days.

Platelet Response

Platelet response is defined as follows (see also Table 7):

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.

Partial Response

Partial response is when the participant meets ≥ 1, but not all, criteria for TMA response as defined in Table 7.

Loss of TMA Response

For participants that meet the criteria for TMA response during the 26-week Treatment Period, loss of TMA response is defined as when the participant fails to meet the criteria for one or more components of TMA response 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.

TMA Relapse

For participants that meet the criteria for TMA response during the 26-week Treatment Period, TMA relapse is defined 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.

Non-relapse Mortality

A participant's death due to any cause during the study, with the exception of death due to underlying disease progression or relapse.

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, double-blind, placebo-controlled, multicenter study of ravulizumab in adult and adolescent participants with HSCT-TMA. Participants with HSCT-TMA in whom the TMA persists for at least 72 hours after withdrawal or modification of any TMA triggering agent and/or treatment of any underlying trigger conditions will be enrolled.

The study will be conducted in two stages. The open-label, single-arm, Dose Confirmation Stage (Stage 1 [Section 4.1.1]) will confirm the ravulizumab dosing regimen for participants with HSCT-TMA. Once an adequate dosing regimen has been confirmed, a Randomized, Double-Blind, Placebo-Controlled Treatment Stage (Stage 2 [Section 4.1.2]) will be performed.

All participants enrolled (participants in Stage 1 and participants in Stage 2), may receive BSC as background therapy. Allowed and disallowed interventions for BSC are described in Section 6.5.1 and Section 6.5.3, respectively.

For all participants enrolled (participants in Stage 1 and participants in Stage 2), the study will consist of 3 periods (see study schema in Section 1.2):

- 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)
- A 26-week Follow-up Period

An independent DMC will be used for this study (Section 9.6).

4.1.1. Dose Confirmation Stage (Stage 1)

Participants enrolled in Stage 1 will receive the weight-based ravulizumab dosing regimen described in Section 8.1.4.1 while on BSC (Section 6.5.1). The proposed ravulizumab dosing regimen will be confirmed during Stage 1. A dose confirmation analysis will be initiated when at least 10 participants complete Visit 5 on Day 21 (Section 9.5.1). Pharmacokinetic and free C5 data collected in all participants at this time will be analyzed to confirm the adequacy of the initial dosing regimen to achieve and maintain complete inhibition of C5. Several analyses may be conducted prior to the minimum of 10 participants completing Visit 5 at Day 21 as part of the dose confirmation analysis to support adjustments to the dosing regimen and/or the CCI supplemental dosing for participants ongoing in Stage 1. Alexion may also determine that the additional participants may need to be enrolled either prior to or during the dose confirmation analysis (eg, if distribution of the initial 10 is not optimal) or after the analysis if the dosing regimen cannot be confirmed.

This analysis may result in adjustments to the dosing regimen for participants in Stage 1. Any changes to the dosing regimen will be submitted for approval to the regulatory authority via a substantial protocol amendment prior to implementation, if required per local regulation. The confirmed adequate dosing will be used for participants continuing in Stage 1 and all participants enrolled in Stage 2.

After the 26-week Treatment Period, Stage 1 participants will discontinue ravulizumab and will be managed by the Investigator, according to the standard of care, during the 26-week Follow-up Period.

See Section 7.2 for safety follow-up for participants who discontinue study intervention early and agree to remain in the study, and Section 7.3 for safety follow-up for participants who discontinue study intervention and withdraw from the study.

Supplemental doses of ravulizumab will be administered during the Treatment Period CCI [redacted] CCI [redacted] as outlined in Section 4.3.2 and Section 8.1.4.3.1. The dose confirmation analysis described above will also confirm both the dose regimen and the adequacy of the CCI [redacted] supplemental dosing of ravulizumab to achieve and maintain complete inhibition of C5. This analysis may result in adjustments to the CCI [redacted] supplemental dosing for participants in Stage 1. The confirmed supplemental dosing regimen will be used for participants continuing in Stage 1 and all participants enrolled in Stage 2.

4.1.2. Randomized Treatment Stage (Stage 2)

Once an adequate dosing regimen has been confirmed in Stage 1, approximately 124 participants will be enrolled in the Randomized, Double-Blind, Placebo-Controlled Treatment Stage (Stage 2). A minimum of 10 adolescent participants ≥ 12 to < 18 years of age are planned to be enrolled in Stage 2. Randomization will be stratified at Stage 2 Baseline (Visit 1). Stratification will be based on geographical region (Japan and Rest of the World), and acute GVHD status (no acute GVHD, Grade I to 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 GVHD" stratification group in the IRT system. In Stage 2, participants will be randomized in a 1:1 ratio to receive ravulizumab plus BSC (ravulizumab treatment group) or matching placebo plus BSC (placebo treatment group).

All participants in Stage 2 may receive BSC for the duration of the study or as long as deemed necessary by the Investigator. Participants randomized to the ravulizumab treatment group will receive ravulizumab at the weight-based dosing regimen confirmed in Stage 1 for 26 weeks. Participants randomized to the placebo treatment group will receive matching placebo for 26 weeks. If the results of the IA for efficacy assessment purpose meet the pre-specified success criterion, the study will discontinue further enrollment due to early efficacy at the time of the IA under advisement of the study DMC. In this event, participants included in the study will continue through the Treatment and Follow-up Period as per the SoA. Additionally, participants randomized to the placebo treatment group will be offered to continue in the study and receive treatment with ravulizumab (following the SoA, Table 2 and Table 3) at the discretion of the PI and in consultation with the study Medical Monitor

After the 26-week Treatment Period, participants will discontinue study intervention and will be managed by the Investigator, according to the standard of care, during the 26-week Follow-up Period. In the event that early efficacy is achieved via an IA, participants included in the study will continue through the Treatment and Follow-Up Period as per the SoA. Additionally, participants randomized to the placebo treatment group will be offered to continue in the study and receive treatment with ravulizumab (following the SoA, Table 2 and Table 3) at the discretion of the PI and in consultation with the study Medical Monitor.

Participants in either treatment group who meet defined criteria for clinical worsening after Day 15 of the blinded Treatment Period (Section 8.1.4.4) will be eligible for rescue treatment and may be unblinded for the Investigator to determine appropriate rescue treatment (see Section 6.3.2 for unblinding process).

Any participant in the placebo treatment group who is to receive ravulizumab as post-unblinding rescue treatment must enter a new 26-week ravulizumab Treatment Period (SoA Table 2) followed by a 26-week Follow-up Period. The study duration is expected to be longer for these participants since they will receive ravulizumab for 26 weeks followed by a 26-week Follow-up Period after the decision has been made to administer post-unblinding rescue treatment with ravulizumab.

See Section 7.2 for safety follow-up for participants who discontinue study intervention early and agree to remain in the study, and Section 7.3 for safety follow-up for participants who discontinue study intervention and withdraw from the study.

Supplemental doses of ravulizumab or placebo (for ravulizumab and placebo treatment groups, respectively) will be administered to participants CCI occurring during the Treatment Period, as outlined in Section 8.1.4.3.

4.2. Scientific Rationale for Study Design

The proposed development program for ravulizumab in HSCT-TMA has been designed based on ravulizumab aHUS clinical studies (Study ALXN1210-aHUS-311 and Study ALXN1210-aHUS-312), and published evidence supporting the benefit of eculizumab in patients with HSCT-TMA (Section 2.2.2). Given the role of complement in the pathogenesis of HSCT-TMA and the proven efficacy of complement inhibition in other complement dysregulation conditions such as aHUS and PNH, it is reasonable to hypothesize that ravulizumab should be similarly effective in the treatment of HSCT-TMA and it is anticipated to have a positive impact on the outcomes of patients with HSCT-TMA.

Since there is no approved standard of care for patients with HSCT-TMA, and current therapy consists of treatment of any underlying conditions and supportive measures, the benefit and safety of ravulizumab is being assessed in a randomized, double-blind, placebo-controlled study comparing BSC plus placebo vs BSC plus ravulizumab.

A randomized, double-blind, placebo-controlled study design is selected to provide the most robust evidence of the effectiveness of the intervention on disease progression and safety. Randomization minimizes the effects of baseline differences and confounding factors on the study population. The use of a placebo comparator allows for the true treatment effect of the intervention to be established while also allowing for study management, drug administration, and assessments to be conducted similarly between treatment groups, thus minimizing the potential for bias. A double-blind study ensures that assessment of non-response criteria is applied without bias across both treatment groups and eliminates the risk of prematurely offering post-unblinding rescue treatment, even though clinical worsening criteria are objective. A double-blind study minimizes bias towards interpretation of COAs.

4.2.1. Study Population and Treatment Duration

Hematopoietic stem cell transplant-associated TMA is a multisystem disorder usually presenting within 100 days after transplantation (Khosla, 2018). It has been described in children, adolescents, and adults after HSCT, in both the allogeneic and autologous setting, although most commonly in the former. Primary therapy for HSCT-TMA involves treatment of underlying conditions, such as withdrawal of any triggering agent (eg, CNIs) and/or treatment of any triggering conditions (eg, infections and/or GVHD). However, in some patients, this does not reverse the HSCT-TMA and additional interventions are required. The current study targets enrollment of such patients.

The length of treatment duration is based on the treatment duration reported in retrospective cohorts of patients with HSCT-TMA treated with eculizumab and feedback obtained from several transplant physicians around the world. It has been reported that a period of at least 23 weeks is required to observe hematological responses to therapy (Dvorak, 2019), while a significantly longer period may be required to achieve responses in renal parameters. In a retrospective cohort of 10 adult and adolescent patients with HSCT-TMA treated with eculizumab, hematological response was observed at 4 weeks in 7 of 10 patients with only one patient showing end organ recovery at 4 weeks after treatment (Jan, 2019).

4.2.2. Rationale for Primary Endpoint

Event-free survival is a robust composite primary endpoint, comprised of two clinically relevant components: death and clinical worsening.

Severe HSCT-TMA leads to death, the first component of the EFS composite primary endpoint, in approximately 80% of patients. Most of these deaths occur within 6 months of TMA diagnosis (Bohl, 2017; Kraft, 2019; Li, 2019; Oran, 2007). Survival of adult patients with HSCT-TMA at 1 year ranges from 18% to 40% (Wanchoo, 2018). In pediatric patients with HSCT, 1-year mortality is estimated to be 46.2% in patients with TMA versus 9.8% in patients without TMA. Within these pediatric patients with features of severe TMA, the OS at 1 year was 16.7% (Jodele, 2014b). In a retrospective review of 23,665 adult and pediatric HSCT patients (median age 49 years) from more than 500 centers worldwide, of which 3% had HSCT-TMA, 48% of patients with HSCT-TMA died within 6 months post-TMA and 58% died within 1 year. HSCT-TMA was associated with higher mortality (HR = 3.1, 95% CI = 2.8 – 16.3) (Epperla, 2020). Overall, these data confirm that reduction in mortality is clinically meaningful for physicians treating HSCT-TMA and is reflected in the first component of the proposed primary endpoint. The second component of the proposed primary endpoint is clinical worsening of TMA (defined in Table 6). Including the occurrence of clinical worsening at any time during the 26-week Treatment Period in the new proposed composite primary endpoint will capture participants who would, without intervention, likely have died, and is considered important to include in the primary endpoint definition.

4.2.3. Rationale for Key Secondary Endpoints

Survival is the most clinically meaningful endpoint in patients with HSCT-TMA as it remains a critical concern for treating physicians (<50% at 1 year; (Cho, 2008; Cho, 2010; Oran, 2007; Wanchoo, 2018)). This is consistent with previous recommendations from regulators and feedback from the scientific and medical community. The OS at Week 26 and Day 100 key

secondary endpoints will be evaluated in this study to better understand the potential of ravulizumab treatment in patients with HSCT-TMA.

Number of TMA response criteria met and hematologic response (as one of the TMA response criteria) contribute to assessing the response to therapy in the absence of standardized laboratory and clinical outcomes. The clinical factors incorporated into the response criteria are part of the diagnostic criteria; however, not all patients present with the same severity across these different markers and the resolution may vary between patients (Schoettler, 2023). These endpoints mimic clinical practice where response is evaluated across clinical markers for HSCT-TMA and understanding the individual components of the diagnostic criteria informs clinical decisions (Cho, 2010; Schoettler 2024).

Thrombotic microangiopathy response has 3 components, which encompasses the assessment of resolution or improvement of all the clinical hallmarks of TMA (ie, microangiopathic hemolytic anemia, thrombocytopenia, and end organ involvement, in particular, kidney involvement).

A change from baseline in eGFR will also be evaluated as key secondary endpoint to fully characterize the potential benefit of ravulizumab treatment.

Among patients who undergo HSCT, the main cause of mortality is relapse of the underlying disease (Styczynski, 2019). However, allogeneic HSCT can precipitate a multi-factorial cascade of events that are associated with significant early and late treatment-related mortality, including HSCT-TMA (Hahn, 2015). Therefore, non-relapse mortality will be evaluated as a key secondary endpoint to study the potential benefit of ravulizumab treatment for HSCT-TMA in transplant-related outcomes, independently of the underlying disease.

Other endpoints aimed to provide additional characterization of ravulizumab treatment effect are described in Section 3.

4.2.4. Rationale for Modified TMA Response

Modified TMA response introduces hemolysis parameter as ‘at least 50% reduction of LDH from baseline and absence of schistocytes’ as it is seen in clinical setting that LDH is often elevated for other reasons such as infections, malignancy, muscle injury, hepatic or renal disease, heart attack, etc (Farhana, 2024; Merck-Manual, 2024). The threshold for 'at least 50% reduction' was selected to be aligned with reduction required for other TMA response criteria and is considered clinically relevant by health care providers.

4.3. Justification for Dose

4.3.1. Ravulizumab

The ravulizumab dosing regimen for PNH and aHUS studies was selected based on comprehensive modeling and simulation of the Phase 1 and Phase 2 PK/PD data in healthy participants and participants with PNH. This dosing regimen provides for immediate, complete, and sustained inhibition of terminal complement activation for the entire treatment course in participants with PNH and aHUS. In clinical studies in both adult and pediatric participants with aHUS, the selected dosing regimen demonstrated immediate, complete, and sustained inhibition

of free C5, which led to complete TMA response in most participants and clinical benefit in additional participants.

The need for larger and more frequent doses is believed to be due to greater circulating C5 caused by the severe and continuous endothelial damage leading to complement activation, as well as more frequent bleeding events necessitating CCI and resulting in faster eculizumab clearance) (Jodele, 2020).

Changes in population PK-derived systemic eculizumab clearance were noted during the first several weeks of eculizumab treatment in pediatric patients with HSCT-TMA (Jodele, 2016). Significant interpatient variability in eculizumab clearance, ranging from 16 to 237 mL/hr/70 kg, was noted during the induction phase. Mean drug clearance normalized for weight during the first week of therapy was 3.5-fold higher than during the fifth week. The effect on eculizumab clearance is thought to be driven by an increase in total complement activation, resulting from endothelial damage that may result from the HSCT and/or myeloablative treatment pre-transplant. Higher concentrations of circulating complement complexes are expected to bind more of the anti-C5 drug, thereby leading to a faster clearance of eculizumab relative to other indications (aHUS or PNH; (Jodele, 2016)). This increased clearance appears during the first few weeks of treatment, with the clearance declining over time and approaching the clearance estimates seen in patients with aHUS and PNH by the third week.

The objective for dose selection in this complement-amplified population is to ensure immediate, complete, and sustained terminal complement inhibition. Using the final aHUS population PK model, simulations were conducted assuming similar ravulizumab clearance changes as seen with eculizumab over the first few weeks of treatment. The initial dosing regimen is predicted to maintain ravulizumab drug concentrations above the target PK threshold to ensure immediate, complete, and sustained terminal complement inhibition.

Given the large safety margin for ravulizumab observed in the PNH and aHUS programs to date, the focus of dose selection is to ensure sufficient ravulizumab plasma concentrations to sustain complete suppression of serum free C5 at all times. To accomplish this, modeling and simulation were employed using both ravulizumab data and data from experience with eculizumab in patients with HSCT-TMA.

The adequacy of the initial dosing regimen and CCI supplemental dosing regimen outlined in Section 8.1.4.1 will be confirmed using PK/PD data during Stage 1 as described in Section 4.1.1. Ten participants are considered sufficient to characterize the impact of disease and CCI on ravulizumab PK and PD in patients with HSCT-TMA. Several analyses may be conducted prior to the minimum of 10 participants completing Visit 5 at Day 21 as part of the dose confirmation analysis to support adjustments to the dosing regimen and/or the CCI supplemental dosing for ongoing participants. Alexion may also determine that the additional participants may need to be enrolled either prior to the dose confirmation analysis (eg, if distribution of the initial 10 is not optimal) or after the analysis if the dosing regimen cannot be confirmed. The PK and PD of ravulizumab in patients with aHUS is currently characterized from data in 85 pediatric and adult patients with aHUS.

If the initial dosing regimen is not considered appropriate, the dosing regimen will be modified for subsequent participants enrolled in in Stage 2. Any changes to the dosing regimen (including

changes in CCI [redacted]) will be submitted for approval to the regulatory authority via a substantial protocol amendment prior to implementation, if required per local regulation.

4.3.2. CCI [redacted]

Supplemental doses of ravulizumab (Stage 1 participants and Stage 2 participants randomized to the ravulizumab treatment group) will be administered to participants who receive CCI [redacted] (likely connected with bleeding) during the Treatment Period to address the anticipated increased ravulizumab clearance CCI [redacted] (Section 8.1.4.3.1). The supplemental dose of ravulizumab in these situations has been selected based on PK simulations and is predicted to maintain drug concentrations above the target drug threshold required to maintain complete terminal complement inhibition at all times. These supplemental doses will be confirmed at the time of Stage 1 dose confirmation analysis and adjusted before Stage 2 if necessary.

Placebo will be administered to Stage 2 participants randomized to the placebo treatment group who receive CCI [redacted] during the Treatment Period, due to the nature of the double-blind Treatment Period.

4.3.3. Post-unblinding Rescue Treatment

During Stage 2, participants who meet the criteria for clinical worsening described in Section 8.1.4.4 are eligible for rescue treatment. The Investigator is encouraged to contact the Medical Monitor to confirm that a participant meets the criteria for clinical worsening. Each participant who meets the criteria will be eligible for rescue treatment and may be unblinded for the Investigator to determine appropriate rescue treatment (see Section 6.3.2 for unblinding process). If ravulizumab is selected as the post-unblinding rescue treatment, the rescue ravulizumab dosing regimen will be the confirmed adequate dosing regimen used in Stage 2 (Section 8.1.4.2).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant or the Safety Follow-up call, if the participant agrees (Section 7.3), in the study globally.

5. STUDY POPULATION

- 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.
- If any laboratory results are not available ≤ 14 days prior to the start of the Screening Period, these assessments must be conducted during the Screening Period. 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. In the UK, if a local laboratory result for ST-HUS is used to confirm eligibility prior to enrollment, the ST-HUS test must still be repeated at the central laboratory; however, these results are not required prior to enrollment.
- If a participant is found not to meet eligibility based on laboratory results for the ST-HUS screen and ADAMTS13 activity tests following enrollment, the participant must be discontinued and will be replaced. Participants discontinued following enrollment based on ST-HUS screen and ADAMTS13 test results will not be counted towards the total sample size as described in Section 9.2.
- Eligibility evaluation may be based on procedures (excluding laboratory assessments) conducted as part of the participant's routine clinical management and obtained during the Screening Period or ≤ 7 days prior to the start of the Screening Period. This excludes laboratory assessments which have separate criteria for use in eligibility evaluation. See Section 1.3, SoA, for all details.
- Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Age

1. Participant must be ≥ 12 years of age at the time of signing the ICF or assent form

Type of Participant and Disease Characteristics

2. Adult and adolescent participants who received HSCT for any reason within the past 12 months at the time of Screening
3. Participants must have HSCT-TMA that persists despite initial management of any triggering condition (persists for at least 72 hours after management of triggering agent/condition):
   - Withdrawal or dose reduction of the triggering agent (eg, CNIs)
   - Treatment of any underlying infection
   - Treatment of underlying GVHD

4. A TMA diagnosis, based on meeting all of the following criteria during the Screening Period and/or ≤ 14 days prior to the Screening Period:
   a. De novo thrombocytopenia, defined as the presence of one or more of the following 3 conditions:
      – Reduction in platelet count ≥ 50% from pre-TMA value;
      – Platelet count ≤ 50000/mm^3;
      – Increased platelet transfusion dependence as shown by a rise of less than 10×10^9/L 24 hours [redacted]
   b. Any one of the following markers of hemolysis:
      – LDH > ULN for age;
      – Presence of schistocytes ≥ 2 per HPF or ≥ 1% in peripheral blood smear;
   c. Proteinuria on spot urinalysis where proteinuria is defined as protein/creatinine ratio ≥ 0.5 mg/mg.
   d. De novo anemia OR the presence of hypertension, where:
      – De novo anemia is defined as the presence of any one of the following 3 conditions 1) a new decline in hemoglobin to ≤ 10 g/dL; 2) a > 1.5 g/dL drop in hemoglobin over any 14-day period; or 3) an increased transfusion dependence, defined as the need to administer [redacted] in order to maintain hemoglobin at the clinically determined transfusion threshold
      – Hypertension is defined as the presence of any one of the following 3 conditions: 1) a systolic pressure ≥ 139 mm Hg or a diastolic pressure > 80 mm Hg on 2 consecutive measurements at least 1 minute apart; 2) requirement for new antihypertensive medication after HSCT (for a participant not on antihypertensive medication prior to HSCT); or 3) for participants with underlying hypertensive disease, a change in their antihypertensive regimen or the addition of new antihypertensive agents required to treat hypertension

Weight

5. Body weight ≥ 30 kg at Screening or ≤ 7 days prior to the start of the Screening Period (date of consent).

Sex

6. Male or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

- Male participants:

Male participants must agree to use contraception as detailed in the protocol (Section 10.9.2.2) during the Treatment Period and for at least 8 months after the final dose of study intervention and refrain from donating sperm during this period.

- Female participants:

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and meets at least one of the following conditions:

– Not a WOCBP (Section 10.9.1)

OR

– Is a WOCBP and using a highly effective or acceptable contraceptive method (except in the UK) as described in Section 10.9.2.1 during the Treatment Period and for at least 8 months (generally 5.5 terminal half-lives) after the final dose of study intervention; for participants in the UK, only highly effective methods of contraception can be utilized.

The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention. A WOCBP must have a negative serum pregnancy test at Screening and a negative urine pregnancy test before the first dose of study intervention. Serum pregnancy test results obtained during routine clinical practice at timepoints between Screening and EoS/ED may be used in place of urine pregnancy test, when available. Additional requirements for pregnancy testing/reporting during and after study intervention administration are described in Section 10.9.3 The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Other Inclusion Criteria

7. Participants must be vaccinated against meningococcal infections if clinically feasible, according to national guidelines and recommendations for immune reconstitution after HSCT (if national guidelines and recommendations are not available, international guidelines or institutional guidelines must instead be followed). Participants < 18 years of age must be re-vaccinated against *Hib* and *Streptococcus pneumoniae* if clinically feasible, according to institutional guidelines for immune reconstitution after HSCT. All participants should be administered coverage with prophylactic antibiotics according to institutional post-transplant infection prophylaxis guidance including coverage against *N meningitidis* for at least 2 weeks after meningococcal vaccination. Participants who cannot receive meningococcal vaccine should receive antibiotic prophylaxis coverage against *N meningitidis* the entire Treatment Period and for 8 months following the final dose of study intervention.

Informed Consent

8. Participants or their legally authorized representative must be capable of giving signed informed consent/assent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Known familial or acquired ADAMTS13 deficiency (activity < 5%).
2. Known ST-HUS as demonstrated by a positive test for Shiga toxin or culture of Shiga toxin producing bacteria.
3. Positive direct Coombs test result which in the judgment of the Investigator is indicative of a clinically significant immune-mediated hemolysis not due to TMA.
4. Clinical diagnosis of DIC in the judgement of the Investigator, utilizing the ISTH scoring criteria outlined in Section 10.13.
5. Known bone marrow/graft failure for the current HSCT.
6. Diagnosis of VOD, unresolved at the time of Screening, according to the EBMT criteria outlined in Section 10.14.
7. Known HIV infection evidenced by a positive HIV-1 or HIV-2 antibody titer obtained at Screening. A documented negative HIV-1 and HIV-2 test within 6 months prior to Screening is also acceptable to confirm eligibility.
8. Unresolved meningococcal disease.
9. Presence of sepsis requiring vasopressor support within 7 days prior to enrollment.
10. Pregnancy or breastfeeding.
11. Hypersensitivity to murine proteins or to one of the excipients of ravulizumab.
12. Any ongoing or history of medical or psychological conditions unrelated to HSCT-TMA that, in the opinion of the Investigator or Alexion, could increase the risk to the participant by participating in the study or confound the outcome of the study. This includes, but is not limited to, major cardiac, pulmonary, renal, endocrine, or hepatic disease.
13. Respiratory failure from any cause requiring mechanical ventilation (including intubation, BiPAP, or CPAP) within 72 hours prior to enrollment.
14. Acute and/or chronic heart failure with an ejection fraction ≤ 40%.

Prior/Concomitant Therapy

15. Previously or currently treated with a complement inhibitor.

Prior/Concurrent Clinical Study Experience

16. Participation in an interventional treatment study of any therapy (approved or unapproved) being evaluated for TMA within 30 days before Day 1 in this study or within 5 half-lives of that interventional treatment, whichever is greater.

5.3. Lifestyle Considerations

There are no lifestyle restrictions for this study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently treated with ravulizumab (for Stage 1 participants) or are not randomized to either treatment group (for Stage 2 participants). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any AEs, including any SAEs and any related concomitant medication, occurring during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved, may be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

Refer to Section 1.3 SoA for study intervention dosing schedules and Section 8.1.4 for detailed dosing instructions.

Intervention Name	**Ravulizumab**	**Placebo**
Type	Biologic	Placebo
Dose formulation	30 mL single-use vial. Each vial contains 300 mg of ravulizumab (10 mg/mL) in 10 mM sodium phosphate, 150 mM sodium chloride, 0.02% polysorbate 80, and water. pH 7.0	30 mL single-use vial. Formulated as a matching sterile, clear, colorless solution with the same buffer components, but without active ingredient
Physical description	Liquid solution practically free from particles	Liquid solution practically free from particles
Unit dose strength(s)	300 mg (10 mg/mL concentrated solution)	Placebo
Dosage level(s)	Weight-based dosing [a]	Weight-based dosing [a]
Route of administration	IV infusion	IV infusion
Use	Experimental	Placebo comparator
IMP or AxMP	IMP	IMP
Sourcing	Provided centrally by Alexion or contracted manufacturing organization	Provided centrally by Alexion or contracted manufacturing organization
Packaging and labeling	Ravulizumab will be provided in glass vials and stoppered with a butyl rubber stopper with aluminum overseal and flip-off cap. Ravulizumab will be supplied in kits and labeled as required per country requirement	Placebo will be provided in glass vials and stoppered with a butyl rubber stopper with aluminum overseal, and flip-off cap. Placebo will be supplied in kits and labeled as required per country requirement.

[a] Detailed information of ravulizumab dosing regimen is provided in Section 8.1.4.

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any product complaints to productcomplaints@alexion.com within 1 business day. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical trial material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.
    b. The pharmacist or other designated individual will maintain records of study intervention delivered to the study site, the inventory at the study site, the distribution to and use by each participant, and the return of materials to Alexion for storage or disposal/destruction of materials at the study site. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the study intervention and study participants.
    c. The Investigator will maintain records that adequately document that the participants were administered the correct study treatment kits and reconcile the products received from the drug dispensing center. Investigational product will not be returned to Alexion or disposed of until accountability has been fully monitored.
4. Further guidance and information for the final disposition of used and unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

To minimize bias, the study will be conducted in a randomized, double-blind, placebo-controlled manner.

6.3.1. Randomization

Participants will be randomized on Day 1 in Stage 2. Permuted block randomization will be stratified by region (Japan and Rest of the World) as well as acute GVHD status on day of randomization (no acute GVHD; Grade I-II acute GVHD; and Grade III-IV acute GVHD where grade is assigned using the International Bone Marrow Transplant Registry Severity Index for grading acute GVHD Section 10.15). 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 will be randomized 1:1 either to the ravulizumab treatment group or to the placebo treatment group. Randomization will be performed centrally using IRT.

6.3.2. Blinding

All investigative site personnel, Alexion staff, Alexion designees, staff directly associated with the conduct of the study, and all participants will be blinded to participant treatment assignments for the Stage 2 26-week Treatment Period. The double-blind will be maintained by using identical study drug kits and labels for ravulizumab and placebo. The placebo will have an identical appearance to that of ravulizumab (Section 6.1). The randomization code will be maintained by the IRT provider.

Data that may potentially unblind the treatment assignment (serum PK concentration, study intervention preparation, treatment allocation, biomarker data, or other specific laboratory data) should be handled with caution to maintain the integrity of the blind and minimize the potential for bias.

Under normal circumstances and unless otherwise specified, the randomized treatment assignment should not be broken until all participants in Stage 2 have completed the 26-week Treatment Period or withdrawn from the study and the interim database lock is finalized for primary endpoint analysis.

In case of urgent medical situation to ensure participant safety, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. The date and reason that the blind was broken must be recorded in the source documentation.

When an AE is unexpected or related and serious, the blind will be broken for that specific participant only. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, Investigators, etc.) and those responsible for data analysis and interpretation of results, such as biometrics personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Independent Ethics Committees (IECs), and/or Institutional Review Boards (IRBs).

Participants may also be unblinded for rescue treatment if they meet the criteria for clinical worsening described in Section 8.1.4.4. The Investigator is encouraged to contact the Medical Monitor to confirm that a participant meets the criteria for clinical worsening.

Any participant who is unblinded during the Stage 2 Treatment Period may remain in the study; however, only those participants who meet the criteria for clinical worsening are eligible for rescue therapy as defined in Section 8.1.4.4.

Any participant who is unblinded as a result of early efficacy determined by IA will be offered treatment with ravulizumab at the discretion of the PI.

More information on blinding/unblinding will be provided in the blinding/unblinding plan.

6.4. Study Intervention Compliance

During this study, participants will receive dosing with study intervention directly from the Investigator or designee, under medical supervision at the study site. The date and time of each dose administered in the clinic will be recorded in the source documents and in the case report form (CRF). The dose of study intervention and study participant identification will be confirmed at the time of dose preparation by a member of the study site staff other than the person administering the study intervention.

For additional information on study intervention compliance and management, refer to the Pharmacy Manual.

6.5. Concomitant Therapy

6.5.1. Allowed Medication and Therapies

In this study, all participants will receive BSC as background therapy. Best supportive care will be determined by the Investigator according to institutional practices and participant characteristics. Best supportive care measures include but are not limited to:

- Transfusion support:
  - Transfusion support should be provided as required per institutional guidelines and based on the participant's clinical condition. In general, transfusion support is recommended as follows per the JAPC:
    a. CCI [redacted] should be considered in participants with hemoglobin ≤ 7 g/dL or in participants with symptomatic anemia (eg, dyspnea and/or tachycardia) with hemoglobin ≤ 8 g/dL. CCI [redacted] CCI [redacted]
    b. Prophylactic platelet transfusions should be given to participants as required with a transfusion trigger of 10×10^9/L.
    c. An increase in the platelet transfusion threshold to 20×10^9/L is justified in participants who are febrile and/or receiving antibiotic therapy for suspected bacterial or fungal infection.
- Corticosteroids
- Dialysis
- Antihypertensive medications

Supportive care measurements should be recorded in the appropriate CRF.

Medicines and therapies that are not allowed are outlined in Section 6.5.3.

6.5.2. Hematopoietic Stem Cell Transplant Following Day 1

Participants who undergo one or more additional HSCT procedures following Day 1 will be allowed to continue in the study. The Investigator will determine the best care options for the individual participant, including treatment with ravulizumab. All AEs must continue to be reported even if the Investigator considers that the event is due to conditioning regimen or the additional HSCT. Other considerations include:

- If a new SAE is reported following the additional HSCT, the Investigator must include in the report details on the causality as it relates to the additional HSCT and the conditioning regimen, in addition to standard SAE reporting requirements.
- The additional HSCT must be reported as an SAE within 24 hours of awareness that the procedure took place.
- Vaccination administered prior to the new HSCT will no longer provide protection against infection due to *N meningitidis*; therefore, participants should initiate or continue to receive antibiotic prophylaxis until revaccination is feasible as described in Section 8.1.8, Vaccination and Antibiotic Prophylaxis.
- The Investigator must contact the Medical Monitor to determine whether a temporary pause in the study intervention is appropriate, as well as the duration of the pause.

Data on any additional HSCT procedures will be captured in the CRF in the same manner as described in Section 8.1.6.

6.5.3. Disallowed Medicine and Therapy

Eculizumab or other agents that act on the complement pathway and TPE/plasma transfusion are not permitted during the Treatment Period. During the Follow-up Period, participants may receive treatments based on standard of care.

Experimental interventions or therapies being evaluated for TMA are not permitted at any time during the study.

6.5.4. Post-unblinding Rescue Treatment

The criteria for receiving post-unblinding rescue treatment during the Treatment Period for clinical worsening is outlined in Section 8.1.4.4. The selection of rescue treatment will be at the discretion of the Investigator. However,

- Eculizumab is prohibited
- If ravulizumab is selected as post-unblinding rescue treatment, then concomitant administration of TPE/plasma transfusion is prohibited.

Post-unblinding rescue treatment administration will be recorded in the CRF.

6.5.5. Post-Interim Analysis Cross-Over Treatment

If the results of the IA for efficacy assessment purpose meet the pre-specified success criterion, the study may be stopped for early efficacy at the time of the IA under recommendation of the study DMC. In this event, participants included in the study will continue through the Treatment and Follow-up Period as per the SoA. Additionally, participants randomized to the placebo treatment group will be offered the option to cross over and receive treatment with ravulizumab (following the SoA for post-unblinding rescue patients, see Table 2 and Table 3) at the discretion of the PI and in consultation with the study Medical Monitor.

6.6. Dose Modification

The adequacy of the proposed dosing regimen (including CCI) will be confirmed through analysis of Stage 1 PK/PD data (as described in Section 4.1.1). If the proposed dosing regimen does not result in the anticipated degree of free C5 inhibition, the dosing regimen will be modified (increased) for subsequent participants according to PK/PD data, which will be submitted for approval to the regulatory authority via a substantial protocol amendment prior to implementation, if required per local regulation. Refer to Section 8.1.4.1 for instruction on ravulizumab dose modification.

6.7. Intervention After the End of the Study

Ravulizumab will not be administered to participants after the end of the study, unless required by local regulations.

Upon completion of the last study visit, participants will return to the care of their treating physician.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Temporary Interruption of Study Intervention Administration

In rare instances, it may be necessary for a participant to temporarily pause treatment with study intervention. During this temporary interruption of treatment with study intervention, the participant will continue to complete scheduled study visits and procedures according to the SoA (see Section 1.3).

Participants may be considered for temporary interruption of study intervention, at the discretion of the Investigator to ensure participant safety if any of the following occur during the study:

- An adverse event that, in the opinion of the Investigator precludes treatment with study intervention
- Suspicion of contraceptive failure or suspicion of pregnancy
- While monitoring abnormal laboratory tests if the Investigator judges this is necessary

In the event of a temporary interruption of study intervention administration, the Investigator should notify the Medical Monitor as soon as feasible. The Investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the subject during a pause in treatment with study intervention. If the Investigator judges that it is safe to restart dosing, the Investigator must reach agreement with the Medical Monitor on plan to resume treatment. If the Investigator or Medical Monitor decide not to resume treatment with study intervention, the subject must be permanently discontinued from treatment, complete ED visit, and enter the 26-week follow-up period. Doses not administered for the reasons mentioned above do not constitute protocol deviations and should be noted in the dosing log with the reason for not administering the dose of study intervention.

When available at the time of decision to interrupt treatment with study intervention, Investigators should include in the eCRF the participant's weight and any relevant local laboratory results.

7.2. Permanent Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study intervention.

If a participant is found not to meet eligibility based on laboratory results for the ST-HUS screen and ADAMTS13 activity tests following enrollment, the participant must be discontinued and a Safety Follow-up phone call will be performed, if the participant agrees, 8 weeks after the last dose of study intervention to collect information on concomitant medications, nonpharmacological therapies and procedures, and AEs. Additional visits after the Safety Follow-up phone call are not required. Participants should be considered for discontinuation from intervention if any of the following occur during the study:

1. Serious hypersensitivity reaction
2. Severe uncontrolled infection

3. Use of disallowed medication as defined in Section 6.5.3
4. Pregnancy or planned pregnancy
5. Presence of clinical worsening despite receiving supplemental doses of study intervention
6. Alexion or the Investigator deems it is necessary for the participant

If the study intervention is definitively discontinued, every effort should be made to have the participant continue in the study. If the participant agrees to remain in the study, the participant should continue to attend the scheduled protocol visits according to the SoA for safety follow-up and collection of other data (Section 1.3).

If the participant does not agree to continue with the SoA visits, the participant should be discontinued from the study (Section 7.3).

7.3. Participant Discontinuation/Withdrawal from the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the Screening procedures. The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and CRF.
- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the decision to withdraw the participant from the study is made, the participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant discontinues from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- At the time of discontinuing from the study, the following activities should be completed if possible:
  - Early discontinuation (ED) assessments to be performed as indicated in the SoA. See Table 3 (SoA, Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant agrees, a Safety Follow-up phone call will be performed 8 weeks after the last dose of study intervention to collect information on concomitant medications, nonpharmacological therapies and procedures, and AEs.
- Information about survival status at Day 100, 26 weeks and 52 weeks after first dose of ravulizumab (for participants in Stage 1) or post-randomization (for participants in Stage 2) should be collected. If a participant's survival status is not available at the

time of discontinuation, sites should attempt to collect the status (eg, via public records, or telephone call).

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- If a participant is deemed lost to follow-up, information about survival status at Day 100, 26 weeks and 52 weeks after first dose of ravulizumab (for participants in Stage 1) or post-randomization (for participants in Stage 2) should be collected. If a participant's survival status is not available at the time, sites should attempt to collect the status (eg, via public records, or telephone call).

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

7.5. Replacement

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. If any laboratory results are not available ≤ 14 days prior to the start of the Screening Period, these assessments must be conducted during the Screening Period. 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. In the UK, if a local laboratory result for ST-HUS is used to confirm eligibility prior to enrollment, the ST-HUS test must still be repeated at the central laboratory; however, these results are not required prior to enrollment. If a participant is found not to meet eligibility based on laboratory results for the ST-HUS screen and ADAMTS13 activity tests following enrollment, the participant must be discontinued and will be replaced. These participants will not be counted towards the total sample size as described in Section 9.2.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- As described in Section 1.3 SoA, procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for Screening or baseline purposes.
- Any clinically significant abnormal laboratory test results or other clinically significant abnormal safety assessments should be reported as AEs.

8.1. General Assessments and Procedures

8.1.1. Informed Consent/Assent

The Investigator or qualified designee must obtain a signed and dated ICF for each participant and/or their legally authorized representative prior to conducting any study procedures. The process for informed consent/assent is outlined in Section 10.1.3. All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the Screening procedures.

Participants ≥ 12 to < 18 years of age at time of signing assent during Screening Period who turn 18 years of age while enrolled on-study should be re-consented when they turn 18 years of age.

8.1.2. Inclusion/Exclusion Criteria

All inclusion (Section 5.1) and exclusion (Section 5.2) criteria must be reviewed by the Investigator or qualified designee to ensure the participant qualifies for study participation.

8.1.3. Demographics

A review of demographic parameters, including age, gender, race, and ethnicity will be performed.

8.1.4. Study Intervention Administration

At the scheduled dosing visits (Section 1.3), IV administration of study intervention should be performed after all other tests and procedures have been completed, excluding the postdose sample collections (PK/PD/biomarkers) and postdose vital signs.

Dose regimen will be based on body weight obtained at the study visit. If the study intervention needs to be prepared prior to the visit, the weight from the previous visit may be used.

As indicated in the SoA, when a pregnancy test is required and a dose of study intervention is scheduled to be administered on the same day, results from the pregnancy test must be available prior to dosing.

Refer to Section 6 for additional information on study interventions including preparation, handling, storage, and accountability.

8.1.4.1. Study Intervention Administration - Stage 1

In Stage 1, ravulizumab will be administered by IV infusion according to the dosing regimen in Table 9. The dose confirmation analysis will be triggered when at least 10 participants complete Visit 5 on Day 21 and will include all PK/PD data collected by that time. Several analyses may be conducted prior to the minimum of 10 participants completing Visit 5 at Day 21 as part of the dose confirmation analysis to support adjustments to the dosing regimen and/or the CCI supplemental dosing for participants ongoing in Stage 1. This analysis will confirm the adequacy of the initial dosing regimen and supplemental dosing regimen to achieve and maintain complete suppression of C5 throughout the dosing interval. If necessary, additional participants may be enrolled into Stage 1 either prior to or during the analysis (eg, if distribution of the initial 10 is not optimal) or after the analysis if the dosing regimen cannot be confirmed. This analysis may result in an adjusted dosing regimen for participants in Stage 1 and the participants enrolled in Stage 2. Participants in Stage 1 will receive the adjusted dosing regimen for the remainder of the Treatment Period.

Table 9: Initial Dosing Regimen

Weight[a,b]	Loading Phase Doses			Maintenance Doses Starting Day 15
	Day 1	Day 5	Day 10	
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 the study intervention needs to be prepared prior to the visit, the weight from the previous visit may be used.

[b] In the event that a participant's weight drops below 30 kg after Day 1, contact the Medical Monitor or designee. If the participant's weight drops below 30 kg, the approved ravulizumab aHUS dosing for participants weighing ≥ 20 to < 30 kg will be used: a loading dose CCI and maintenance doses of CCI CCI

8.1.4.2. Study Intervention Administration - Stage 2

Participants in Stage 2 randomized to the ravulizumab treatment group will receive blinded doses of ravulizumab according to the confirmed dosing regimen resulting from Stage 1 PK/PD analysis (Section 8.1.4.1). Participants randomized to the placebo treatment group will receive blinded doses of matching placebo.

8.1.4.3. Supplemental Dosing of Study Intervention

Supplemental doses of study intervention are allowed during the Treatment Period following administration of the first Maintenance Dose on Day 15 as follows:

- Supplemental doses in participants CCI (Section 8.1.4.3.1)
- Supplemental doses for participants who demonstrate clinical worsening in Stage 1 (as defined in Section 8.1.4.3.2)

8.1.4.3.1. Supplemental Dosing of Study Intervention CCI

Following administration of the first Maintenance Dose on Day 15, participants who receive any CCI following a maintenance dose will be administered supplemental doses of study intervention according to body weight (ie, maintenance dose according to Table 9). Supplemental doses of study intervention will not be administered during the loading phase or be required following CCI

Participants who receive any CCI following a maintenance dose should be administered a supplemental dose of study intervention CCI following every maintenance dose as outlined in the SoA (Section 1.3).

The supplemental dosing regimen will be continued until CCI in the CCI following a maintenance dose and will be resumed if CCI CCI following a subsequent maintenance dose.

Supplemental doses of study intervention may be administered at non-dosing scheduled visits according to the SoA Section 1.3. For a supplemental dosing visit that does not align with a scheduled visit, an unscheduled supplemental dosing visit may be scheduled. The following are the minimum assessments that must be performed during any supplemental dosing visit in which ravulizumab is administered:

- Urine pregnancy test (WOCBP only, if indicated)
- Predose PK/PD blood sample collection
- Vital signs

The supplemental doses will be evaluated as part of the dose confirmation analysis described in Section 4.1.1.

8.1.4.3.2. Supplemental Dosing of Ravulizumab for Clinical Worsening in Stage 1

Supplemental doses of ravulizumab will be allowed during the Treatment Period (Stage 1) following administration of the first Maintenance Dose on Day 15 for participants who demonstrate clinical worsening. 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

The criteria for clinical worsening must be confirmed by 2 independent samples collected at least 8 hours apart (ideally 24 hours apart). At least 1 of these samples must be analyzed by the central laboratory. Supplemental dosing for clinical worsening (ie, maintenance dose according to Table 9) will be determined following assessment and agreement by the Investigator and Alexion Medical Monitor.

If a participant meets the criteria for clinical worsening, the Investigator may opt to administer additional treatment with ravulizumab or other medicines or therapies (except therapies which are not permitted during the Treatment Period (Section 6.5.3).

Supplemental dosing may be administered at scheduled visits according to the SoA Section 1.3. For a supplemental dosing visit that does not align with a scheduled visit, an unscheduled supplemental dosing visit may be scheduled. The following are the minimum assessments that must be performed during any supplemental dosing visit in which ravulizumab is administered:

- Urine pregnancy test (WOCBP only, if indicated)
- Predose PK/PD blood sample collection
- Vital signs

8.1.4.4. Post-unblinding Rescue Treatment in Stage 2

Following administration of the first Maintenance Dose on Day 15 in Stage 2, participants who meet defined criteria for clinical worsening will be eligible for rescue treatment and may be unblinded for the Investigator to determine appropriate rescue treatment (see Section 6.3.2 for unblinding process).

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

The criteria for clinical worsening must be confirmed by 2 independent samples collected at least 8 hours apart (ideally 24 hours apart). At least 1 of these samples must be analyzed by the central laboratory.

Prior to unblinding, it is recommended that the Investigator discuss with the Medical Monitor whether or not the participant meets the criteria for clinical worsening.

If a participant is unblinded for meeting clinical worsening criteria, it is expected that the Investigator will administer post-unblinding rescue treatment. Unblinding for rescue treatment should only occur if the Investigator believes that the participant would benefit from rescue treatment.

The selection of post-unblinding rescue treatment will be at the discretion of the Investigator; however, the prohibited therapies as outlined in Section 6.5 still apply.

If the participant is determined to be randomized to the placebo treatment group:

- Participants initially randomized to the placebo treatment group who receive ravulizumab as post-unblinding rescue treatment will be administered the ravulizumab dosing regimen confirmed in Stage 1 and will start a new 26-week Treatment Period following the SoA Table 2. The Investigator is requested to also inform the Alexion Medical Monitor that unblinding has occurred.

If the participant is determined to be randomized to the ravulizumab treatment group:

- Participants have the option to continue the study and receive ravulizumab according to SoA Table 1
- Supplemental dosing of ravulizumab or rescue treatment with other therapies will be determined following assessment and agreement by the Investigator and Alexion Medical Monitor
- The participant may be discontinued from study intervention (Section 7.2)

The following assessments must be performed during any post-unblinding rescue treatment in which study intervention is administered:

- Urine pregnancy test (WOCBP only, if indicated)
- Predose PK/PD blood sample collection
- Vital signs

8.1.4.5. Post-Interim Analysis Cross-Over Treatment

In the event an IA is performed and early efficacy is achieved, participants assigned to placebo will be offered unblinded treatment with ravulizumab at the discretion of the Investigator. In this scenario, participants will follow the SoA in Table 2 and Table 3 and complete all the listed procedures through 52 weeks of additional participation.

8.1.5. Medical History

The participant's relevant medical history, including prior and concomitant conditions/disorders (including TMA diagnosis), treatment history, and family history of relevant diseases will be evaluated at Screening by the Investigator and documented in the source documents and CRF.

8.1.6. Hematopoietic Stem Cell Transplant Information

Information to be collected includes transplant modality, hematopoietic stem cell origin, transplant indication, history of prior HSCT, conditioning regimen, presence of acute GVHD, engraftment status, and any other transplant complication(s) or relevant information on the peritransplant period.

For participants who undergo one or more additional HSCT procedures following Day 1, information to be collected on the additional HSCT includes transplant modality, hematopoietic stem cell origin, transplant indication, history of prior HSCT, and conditioning regimen.

8.1.7. Transfusion History and Transfusion Requirements During the Study

The number and volume of CCI during the Screening Period should be documented on the transfusion CRF log. The information to be collected includes date of the transfusion, number of units, and volume of each blood component given.

CCI during the study must be recorded on the CCI CRF. The information to be collected includes date of the transfusion, number of units, and volume of each blood component given.

8.1.8. Vaccination and Antibiotic Prophylaxis

Due to its mechanism of action, the use of ravulizumab increases the participant's susceptibility to infection due to *N meningitidis*. To reduce the risk of infection, participants must be vaccinated against *N meningitidis* if clinically feasible according to national guidelines and recommendations for immune reconstitution and vaccination after HSCT*. When clinically feasible according to national guidelines and recommendations for immune reconstitution and vaccination after HSCT*, vaccines against serotypes A, C, Y, W135, and in addition serotype B (where available) must be administered, to prevent common pathogenic meningococcal serotypes. Participants must be administered prophylactic antibiotics for meningococcal infection until at least 2 weeks after vaccination. Participants who cannot be vaccinated must be on antibiotic prophylaxis as outlined in Table 10.

Once vaccination is feasible according to national guidelines for immune reconstitution and vaccination after HSCT*, participants must be vaccinated. Antibiotic prophylaxis must not delay vaccination and should not be used in place of vaccination in participants who are eligible for vaccination according to national guidelines for immune reconstitution and vaccination after HSCT*.

As HSCT results in immunosuppression due to ablative therapy, concomitant medication, or due to underlying disease, vaccine antibody titers will decrease 1 to 4 years after the transplant if the patient is not revaccinated. Sites must follow the relevant immune reconstitution guidelines or local practice guidelines for immune reconstitution for re-vaccination of participants who have undergone HSCT.

Vaccination may not be sufficient to prevent meningococcal infection; therefore, consideration should be given per national guidance and local practice on the appropriate use of prophylactic antibacterial agents. All participants must be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

If clinically feasible, participants < 18 years of age must also be vaccinated against *Hib* and *S. pneumoniae* according to the appropriate immune reconstitution guidelines and participants who have undergone HSCT must be re-vaccinated. Participants who cannot be vaccinated must receive antibiotic prophylaxis for the entire period they are treated with ravulizumab and for 8 months following the final dose of ravulizumab. Once vaccination is feasible according to national guidelines for immune reconstitution and vaccination after HSCT*, participants must be vaccinated. Antibiotic prophylaxis must not delay vaccination and should not be used in place of vaccination in participants who are eligible for vaccination according to national guidelines for immune reconstitution and vaccination after HSCT*.

Vaccination status and administration of any vaccines, including those for *N meningitidis*, *Hib*, and *S. pneumoniae*, will be recorded on the CRF.

*If national guidelines and recommendations are not available, international guidelines or institutional guidelines must instead be followed. "Clinically feasible" means that the patient is considered immune competent and able to mount an immune response following vaccination.

Participants will be provided a safety card to carry with them at all times and for 8 months after the final dose of study intervention (Section 8.3.10).

Table 10: Prophylactic Antibiotics for Participants who Cannot be Vaccinated

	Prophylactic Antibiotic Administration
Stage 1 participants and Stage 2 participants randomized to the ravulizumab treatment group	Must be administered prophylactic antibiotics for the entire period they are treated with ravulizumab and for 8 months following the final dose of ravulizumab
Stage 2 participants randomized to the placebo treatment group	Must be administered prophylactic antibiotics for the duration of the blinded Treatment Period and can stop antibiotic treatment after unblinding (either for clinical worsening during the Treatment Period, or in the Follow-up Period)
Participants randomized to placebo treatment group who receive ravulizumab as post-unblinding rescue treatment or post-Interim Analysis cross-over treatment	Must be administered prophylactic antibiotics for the entire period they are treated with ravulizumab and for 8 months following the final dose of ravulizumab

8.2. Efficacy Assessments

8.2.1. Primary Efficacy Assessments

8.2.1.1. Event-Free Survival

Participants' survival status will be collected throughout the study. Information on any events of deaths and cause of death occurring during the study will be collected. For participants who discontinue the study early, vital status through 52 weeks will be assessed by the site through public records or telephone call. Clinical worsening as described in Table 6 will be assessed and collected throughout the 26-week Treatment Period.

8.2.2. Secondary Efficacy Assessments

8.2.2.1. Key Secondary Efficacy Assessments

8.2.2.1.1. Overall Survival and Non-Relapse Mortality

Participants' survival status will be collected throughout the study. Information on any events of deaths and cause of death occurring during the study will be collected. Information about survival status at Day 100, 26 weeks, and 52 weeks after first dose of ravulizumab (for participants in Stage 1) or post-randomization (for participants in Stage 2) should be collected. If

a participant's survival status is not available at the time of discontinuation, sites should attempt to collect the status (eg, via public records, or telephone call).

8.2.2.1.2. Number of TMA Response Criteria Met

Laboratory assessments to determine the number of TMA response criteria met will be performed according to the SoA (Section 1.3) and Section 10.3 and assessed against predetermined criteria for TMA response (defined in Section 3.2).

8.2.2.1.3. Hematologic Response

Clinical laboratory assessments will be performed according to the SoA (Section 1.3) and Section 10.3, and assessed against predetermined criteria for hematologic response (Section 3.2).

8.2.2.1.4. eGFR

Serum creatinine will be collected according to SoA (Section 1.3) and Section 10.3. eGFR will be calculated based on creatinine using the CKD EPI formula.

8.2.2.2. Other Secondary Endpoints

8.2.2.2.1. Additional Characterization of TMA Response

For time to TMA response, partial response, loss of TMA response, TMA relapse, and durationof response, the relevant clinical laboratory assessments will be performed according to the SoA (Section 1.3) and Section 10.3, and assessed against predetermined criteria for TMA response.

8.2.2.2.2. Hemoglobin Response and Platelet Response

Clinical laboratory assessments will be performed according to the SoA (Section 1.3) and Section 10.3, and assessed against predetermined criteria for platelet response (Section 3.2).

8.2.2.2.3. Organ Dysfunction

Change from baseline in organ dysfunction (end organ involvement, ie, renal system, cardiovascular system, CNS, pulmonary system, GI system) will be described for participants in each randomized treatment group and in participants who received post-unblinding rescue treatment with ravulizumab. The following parameters to assess organ dysfunction will be assessed:

- Renal dysfunction: Kidney function status will be assessed by measuring protein/creatinine ratio, serum creatinine, and calculating eGFR. For participants who require dialysis, change from baseline in dialysis requirements will be recorded.
- Cardiopulmonary involvement: Chest X-rays and/or chest CT, ECG, and echocardiography to assess the presence of signs of pulmonary or cardiovascular involvement (including, but not limited to, pulmonary hypertension, pleural effusion, and pulmonary edema) will be performed. In addition, use of any ventilatory or respiratory support will be reported in the participant’s CRF, along with associated oximetry.

- Hypertension will be assessed by blood pressure measurement at every visit as part of vital signs collection, and analysis of concomitant medications to control the hypertension.
- Central nervous system involvement: Participants will be assessed at every visit for signs of PRES, including headache, confusion, visual loss, and seizures. If PRES is suspected, confirmatory MRI will be performed (Section 8.3.6).
- Gastrointestinal involvement: Participants will be assessed for signs and symptoms of GI involvement (eg, diarrhea, vomiting, pain, and bleeding). The frequency and estimated volume of GI bleeding will be recorded in the participant's CRF.

8.3. Safety Assessments

8.3.1. 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.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Additional physical examinations can be performed as medically indicated during the study at the Investigator's discretion.
- Height and weight will also be measured and recorded.

8.3.2. Vital Signs

- Body temperature (°C or °F), heart rate, respiratory rate, systolic and diastolic blood pressure (mm Hg), and pulse oximetry will be assessed.
- Blood pressure and heart rate measurements will be assessed with the participant in a seated or supine position using a completely automated device. Manual techniques will be used only if an automated device is not available or not reliable.
- As permitted by clinical setting, blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements. Site-specific institutional guidelines may be utilized for these assessments.
- O_2 saturation (%) will be collected using pulse oximetry.
- Vital signs will be collected predose and postdose at ravulizumab dosing visits.

8.3.3. Electrocardiograms

- Single 12-lead ECGs will be conducted to obtain heart rate, PR, QRS, QT, and QTc intervals. (QT interval will be corrected for heart rate using Fridericia's formula [QTcF].)
- Participants must be supine for ECG collection.
- The Investigator or Sub-Investigator will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be recorded in the source documents and the CRF.
- Additional ECGs can be performed if clinically indicated.

8.3.4. Chest X-ray or Computed Tomography Chest

Chest X-rays (portable or posteroanterior and lateral views) or CT-chest as determined by clinical need or availability should be obtained while the participant is at full inspiration at the timepoints specified in the SoA. Additional chest X-rays or CT scans of chest can be performed, if clinically indicated, to ensure participant appropriate follow-up. The Investigator or designee Sub-Investigator will be responsible for reviewing the X-rays or CT scan to assess the clinical significance of the results. These assessments will be recorded in the source documents and the CRF. Particular attention should be paid to determine whether signs of pulmonary or cardiovascular involvement are present (including, but not limited to, pulmonary hypertension, pleural effusion, and pulmonary edema).

8.3.5. Echocardiogram

Transthoracic echocardiography will be performed as per the SoA. Additional echocardiograms can be performed if clinically indicated to ensure participant appropriate follow up. The Investigator or designee Sub-Investigator will be responsible for reviewing the echocardiogram to assess the clinical significance of the results. These assessments will be recorded in the source documents and the CRF. Particular attention should be paid to determine whether signs of pulmonary hypertension (right ventricular dysfunction, tricuspid regurgitation) or serositis (pericardial effusion) are present.

8.3.6. Magnetic Resonance Imaging

The occurrence of PRES must be evaluated as part of the assessment of TMA-related organ dysfunction. If a participant has symptoms of PRES at study entry or develops symptoms during the study, an MRI should be performed to look for bilateral white matter abnormalities in the vascular watershed areas consistent with PRES. If the presence of PRES is confirmed, MRIs will be performed upon resolution of symptoms and at the EoS/ED Visit, if clinically warranted (Section 1.3). Mandatory MRI for resolution of PRES is not standard of care but is permitted if deemed appropriate by the Investigator. Additional MRIs may be performed during the study, upon discussion between the Investigator and the Alexion Medical Monitor.

8.3.7. Immunogenicity

Immunogenicity assessments are described in Section 8.9.

8.3.8. Clinical Safety Laboratory Assessments

- See Section 10.3 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the final dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - All protocol-required laboratory assessments, as defined in Section 10.3, must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE, or dose modification), then the results must be recorded in the source document.

8.3.8.1. Virus Serology

Human immunodeficiency virus testing for HIV-1 and HIV-2 is required of all participants prior to enrollment. A documented history of negative HIV-1 and HIV-2 tests within 6 months prior to Screening is acceptable. Participants who are HIV positive will not be enrolled.

8.3.9. Pregnancy

8.3.9.1. Pregnancy Testing

Pregnancy testing will be performed as described in the SoA (Section 1.3) and Section 10.3.

8.3.9.2. Pregnancy Data

- Pregnancy data from female participants and female spouses/partners of male participants will be collected and followed from the signing of the ICF until the outcome of the pregnancy is known, even if the participant discontinues study intervention or withdraws from the study. Any female participant who becomes pregnant while participating in the study will be discontinued from the study intervention. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.9.

- For all Alexion products, both in development or post-approval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The corresponding infant will be followed-up for 3 months postpartum.
- Pregnancy is not considered as an AE (Section 10.9.3) unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly) (Section 8.4). Elective abortions without complications should not be reported as AEs.

8.3.10. Participant Safety Card

Before the first dose of the study intervention, a Participant Safety Card will be provided to participants to carry with them at all times until 8 months after the final dose of study intervention.

The card is provided to increase participant awareness of the risk of meningococcal infections and promote quick recognition and disclosure of any potential signs or symptoms of infection experienced during the course of the study and to inform participants on what actions must be taken if they are experiencing signs or symptoms of infection.

At each visit throughout the study, the study staff will ensure that the participant has the Participant Safety Card.

8.3.11. Prior and Concomitant Medication Review

It is important for the Investigator or designee to review each medication the participant is taking before starting the study and at each visit (Section 1.3) and record relevant changes in the CRF.

8.3.11.1. Prior Medications and Procedures

Prior medications and/or vaccines (including vitamins, herbal preparations, and those discussed in the exclusion criteria [Section 5.2]) and procedures (any therapeutic intervention, such as mechanical ventilation, renal replacement therapy, surgery/biopsy, or physical therapy) that the participant receives or undergoes within 30 days prior to Day 1 (Stage 1) or within 30 days prior to randomization (Stage 2) will be recorded. Please refer to the inclusion/exclusion criteria for prior medication considerations for eligibility. In addition, use of certain medication is not allowed during the study (Section 6.5.3). Information regarding the HSCT procedure should be recorded on the HSCT information CRF page.

Prior medications and procedures must be recorded in the participant's source document/medical chart and CRF (unless otherwise noted) along with:

- Reason for use (indication)
- Dates of administration including start and end dates (if the participant is expected to continue on the medication during the study, it should be recorded as continuing)

- Dosage information including dose and frequency (this information will be recorded in the source documents but not required on the CRF)

8.3.11.2. Concomitant Medications and Procedures

Concomitant medications (including any medication, vitamin, herbal preparation or supplement) and procedures (defined in Section 6.5) are those received on or after Day 1 (for Stage 1), or after the start of ravulizumab or placebo IV infusion for participants in Stage 2. This includes any supportive care medications and procedures, antibiotic prophylaxis, GVHD prophylaxis or treatment, and vaccinations. At each study visit, participants will be questioned about any new medication or nondrug therapies or changes to concomitant medications and nondrug therapies since the last visit. Concomitant medications must be recorded in the participant's source document/medical chart and CRF (unless otherwise noted) along with:

- Reason for use (indication)
- Dates of administration including start and end dates (if the participant is expected to continue on the medication during the study, it should be recorded as continuing)
- Dosage information including dose and frequency (this information will be recorded in the source documents but not required on the CRF)

Any concomitant medication deemed necessary for the participant's care during the study, or for the treatment of any AE, along with any other medications, other than those listed as disallowed medications in Section 6.5.3, may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded as described above, in the participant's source document/medical chart and CRF page.

Data regarding transfusion of blood components should be recorded on the transfusion CRF page, including date of transfusion, type of blood component administered, number of units and volume of each blood component given.

The Medical Monitor should be contacted if there are any questions regarding prior or concomitant therapy.

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.4.

All AEs will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.4.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF Form until the EoS Visit (Section 1.3).

For participants who discontinue study intervention but remain in the study, all AEs and SAEs will be collected until the EoS Visit (Section 1.3).

For participants who receive CCI supplemental dose(s) of ravulizumab, all AEs and SAEs will be collected until the EoS Visit.

For participants who discontinue from the study, all AEs and SAEs will be collected until the Safety Follow-up call (8 weeks after the final dose of ravulizumab) if the participant agrees; however, for the participants who withdraw consent all AEs and SAEs will be collected until the time of withdrawal.

All SAEs will be recorded and reported to Alexion or the designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.4.4. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE data after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.4.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow-up on each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Section 10.4.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

- SUSARs (defined in Section 10.4.2) must be reported according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SUSAR, SAE, or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Under EU CTR 536/2014 regulation, events other than SAEs (eg, unexpected events) that may impact the benefit-risk balance should be reported. See definitions in Section 10.4.5.
- In the European Union, Alexion will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No. 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

8.4.5. Medication Error, Drug Abuse, and Drug Misuse

Medication error, drug abuse, and drug misuse will be collected from signing of the ICF through the last scheduled procedure shown in the SoA (Section 1.3).

8.4.5.1. Timelines

If an event of medication error, drug abuse, or drug misuse occurs during the study, then the Investigator or other site personnel will report to Alexion or designee immediately but no later than 24 hours of when they become aware of it.

The full definitions and examples of medication error, drug abuse, and drug misuse can be found in Section 10.5.

8.4.5.2. Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP that either causes harm to the participant or has the potential to cause harm to the participant.

8.4.5.3. Drug Abuse

Drug abuse is the persistent or sporadic intentional, non-therapeutic excessive use of IMP for a perceived reward or desired non-therapeutic effect.

8.4.5.4. Drug Misuse

Drug misuse is the intentional and inappropriate use of IMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

8.4.6. Adverse Events of Special Interest

Meningococcal infections are considered to be AESIs.

8.5. Treatment of Overdose

For this study, any dose of IMP (study intervention) greater than that specified in the protocol will be considered an overdose.

Alexion does not recommend specific treatment for an overdose.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

In the event of an overdose or suspected overdose, the Investigator should:

- Capture and forward the event, with or without associated AEs, to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Overdose Report Form within 24 hours of awareness.
- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities (as medically appropriate and at least until the next scheduled follow-up).
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration (infusion start and stop dates) of the overdose.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics and Pharmacodynamics

- Blood samples will be collected for determination of serum ravulizumab, free C5, and total C5 concentrations at the timepoints specified in the SoA (Section 1.3). The timing of sampling may be altered during the course of the study, based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Samples collected for PK/PD analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.6.1. Collection of Samples for PK/PD Analyses

Instructions for the collection and handling of biological samples, including blood volume requirements, is provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.

- Samples for PK/PD analyses will be collected at the specified timepoints for all participants in Stage 1, all blinded participants in Stage 2, participants randomized to

the ravulizumab treatment group who are unblinded, and all unblinded participants randomized to the placebo treatment group who receive ravulizumab as rescue treatment.

  - Predose PK and PD blood samples will be collected within 90 minutes before administering study intervention at visits specified in the SoA (Section 1.3). The predose blood sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose.
  - Postdose PK and PD blood samples will be collected within 60 minutes after completing study intervention infusion. The postdose blood samples will be drawn from the participant's opposite, non-infused arm.
  - PK/PD blood samples at a non-dosing visit can be collected at any time during the visit. In the event a supplemental dose is administered at a non-dosing visit, predose samples should be collected instead of the any-time sample.

- In the event of an unscheduled visit, PK and PD blood samples will be collected as soon as possible.
- Predose PK and PD samples will be collected for all supplemental doses of study intervention administered.

8.7. Genetics

Exploratory genetics will be performed only in countries where the applicable regulatory authorities permit exportation of biological samples for this purpose. For participants in applicable countries who sign an additional optional consent, whole blood and buccal swab samples for exploratory genetics may/will be collected at the time point specified in the SoA Section 1.3). Exploratory genetics may be performed to investigate genetic variants in genes that may be associated with complement dysregulation or metabolism or efficacy of ravulizumab. Please refer to the Laboratory Manual for details on sample collection, including sample requirements.

Information regarding DNA sample retention and future genetics research is provided in Section 10.10.

8.8. Biomarkers

8.8.1. Exploratory Biomarker Research

Blood and urine samples for biomarker research will be collected predose from all participants at the time points specified in the SoA (Section 1.3) except in countries where the applicable regulatory authorities prohibit exportation of biologic samples for this purpose.

Whenever possible, collection of biomarker samples during the study, including samples collected during the Screening Period, should be performed prior to the participant receiving CCI or dialysis.

Biomarkers will be measured and include, but are not limited to, assessments of the following:

CCI [redacted]



Information regarding biomarker sample retention and future biomarker research is provided in Section 10.11.

8.9. Immunogenicity Assessments

Antidrug antibodies will be evaluated in serum samples collected predose (within 90 minutes prior to the start of ravulizumab or placebo IV infusion) from all participants at time points specified in the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention. These samples will be tested by Alexion or Alexion's designee.

Serum samples will be screened for antibodies binding to ravulizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of ravulizumab.

The detection and characterization of antibodies to ravulizumab will be performed using a validated assay method. Samples collected for detection of antibodies to ravulizumab will also be evaluated for ravulizumab serum concentration to enable interpretation of the antibody data. Confirmed antibody positive samples will be further evaluated for antibody titer and the presence of neutralizing antibodies.

8.10. Exploratory Assessments

8.10.1. Clinical Outcomes Assessments

Participant-reported COAs (Patient Global Impression of Severity [PGI-S], Patient Global Impression of Change [PGI-C], EuroQol 5-Dimension 5-Level [EQ-5D-5L], Functional Assessment of Chronic Illness Therapy [FACIT] Fatigue, and 12-Item Short Form Survey [SF-12]) should be administered electronically by the Investigator or a qualified site staff at visits specified in the SoAs (Section 1.3). These assessments may be recorded on paper if electronic devices are unavailable or cannot be used.

Caregiver-reported COAs (EQ-5D-5L Proxy [version 1], Caregiver Global Impression of Change [CaGI-C], and Caregiver Global Impression of Severity [CaGI-S]) should be administered prior to learning any updated clinical results/outcomes at that specific time point. The measures should also be administered electronically by the Investigator or a qualified site staff at visits specified in the SoAs (Section 1.3). These assessments may be recorded on paper if electronic devices are unavailable or cannot be used.

Clinicians should report the COAs (Clinician Global Impression of Change [CGI-C] and Clinician Global Impression of Severity [CGI-S]) at visits specified in the SoAs (Section 1.3).

The questionnaires will be completed in the eCRF (ie, in an electronic format) by the Investigator.

The following order should be followed when performing assessments for adult participants:

1. Participant-reported COAs
2. Caregiver-reported or clinician-reported COAs
3. Other study procedures

For adolescent participants, SF-12 will be the only COA to be administered.

All COAs should be completed in a quiet room, as clinically permitted.

If the Investigator deems that the participant is not able to self-report using any of these instruments at a protocol-specified time point, then they will not be administered to the participant. Every effort should be made to ensure that COA's are administered at all visits specified in the SoAs (Section 1.3).

8.10.1.1. Global Impression Scales

8.10.1.1.1. Global Impression of Severity

The PGI-S, CaGI-S, and CGI-S single-item measure of participant's TMA symptom severity requires the participant, caregiver, and clinician, respectively, to report TMA symptom severity at each scheduled timepoint. The question is scored on a 7-point Likert scale ranging from 1 to 7, anchored at 1 = "None" and 7 = "Very severe".

The CaGI-S and CGI-S measures will be used to support the evaluation of impression of the severity of TMA symptoms in the participant due to the severity of the participant's symptoms at the baseline and initial assessments. The CGI-S will also be used to evaluate the clinician's impression of the severity of the participant's TMA symptoms.

The individual PGI-S, CaGI-S, and CGI-S will be evaluated as potential anchors to support the derivation and interpretation of meaningful change for other clinical outcome assessment endpoints in this trial.

8.10.1.1.2. Global Impression of Change

The PGI-C, CaGI-C, and CGI-C single item measure of change in participant's TMA symptom severity requires the participant, caregiver, and clinician, respectively, to report change from baseline in the participant's TMA symptom severity at the end of the Treatment Period (Day 183).

The question is scored by a 7-point Likert scale ranging from 1 to 7, anchored at 1 = "Very much improved" and 7 = "Very much worse".

The individual PGI-C, CaGI-C, and CGI-C will be evaluated as potential anchors to support the derivation and interpretation of meaningful change for other clinical outcome assessment endpoints in this trial.

8.10.1.2. EuroQoL 5-Dimensions 5-Level

The EQ-5D-5L is a self-reported, standardized instrument to measure health-related quality of life (HRQoL) and has been used in a wide range of health conditions (Section 10.12.2).

The EQ-5D-5L Proxy (version 1) (Section 10.12.2.2) will be used in addition to the participant EQ-5D-5L. It will be administered following the same administration schedule as the participant EQ-5D-5L version.

8.10.1.3. Short-Form Health Survey 12 Item

The SF-12™ Questionnaire (SF-12™ Health Survey© 1996, 2000 by Medical Outcomes Trust and Quality Metric Incorporated), 4-week recall period version, is a self-assessed, standardized instrument to measure HRQoL and has been used in a wide range of health conditions (Section 10.12.3). In the SF-12 Questionnaire, subjects are instructed to rate their health and capacity to perform activities of daily living in eight domains 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 determined and are used to determine the physical and mental component summary scores as described in the SF-12 manual. The summary scores of adult participants will be transformed to a 0–100 scale as described in the SF-12 manual.

8.10.1.4. Functional Assessment of Chronic Illness Therapy-Fatigue

The FACIT-Fatigue Scale (Version 4) is a short, 13-item, self-reported, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week (Section 10.12.4). The level of fatigue is measured on a five-point Likert-type scale (0 = not at all fatigued; 1 = a little bit fatigued, 2 = somewhat fatigued, 3 = quite a bit fatigued, and 4 = very much fatigued). All items contribute to the sum score with equal weight.

8.10.2. Medical Resource Utilization and Health Economics Data

Medical resource utilization and health economics data associated with medical encounters, concomitant medication use, and other indicators of health resource utilization will be collected. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct descriptive economic exploratory analyses and will include, but are not limited to:

- Number, reason, and duration of hospitalizations (including stays in intensive care unit, (if applicable)
- Number, frequency, and volume of RBC and/or platelet transfusions
- Number of outpatient medical encounters (including physician or emergency room visits) and the underlying reason

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

For the primary analysis, EFS in the ravulizumab treatment group will be compared to the placebo treatment. EFS is calculated as the time in days from randomization to the date of the first event of death or clinical worsening. The estimand corresponding to the primary efficacy analysis is described in Section 10.2. Hypothesis testing will be two-sided and performed at the 0.05 level of significance.

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.

9.2. Sample Size Determination

Approximately 124 participants are planned to be enrolled into the study. The sample size 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-C5i-treated patients in the literature, estimated to be approximately 30% [approximately 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:
  - 40% 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).
  - 30% 26-week EFS in the placebo group is assumed given EFS is a composite endpoint and includes clinical worsening events in addition to death.
- The hazard ratio 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. Approximately 124 participants will be randomized to increase the likelihood of observing 66 events.

9.3. Populations for Analyses

The analysis sets are defined in Table 11. These definitions for analysis sets will be applied for participants enrolled in both Stage 1 and Stage 2 of the study. However, data from each stage

will be analyzed and reported separately, except for selected safety analyses which may combine results from both stages.

Table 11: Analysis Sets

Analysis Set	Description
Safety Set	All participants who sign the informed consent and receive at least 1 dose of study intervention.
ITT Analysis Set	The ITT Set includes all participants who sign the informed consent and are randomized in Stage 2.
Full Analysis Set	All participants who sign the informed consent and are randomized in Stage 2, excluding[a] participants who enroll prior to availability of ST-HUS and ADAMTS13 laboratory results and are subsequently found to be ineligible after enrollment.
All-Enrolled Set	All participants who sign the informed consent and are randomized in Stage 2 or are enrolled in Stage 1.
Pharmacokinetic and Pharmacodynamic Analysis Set	All participants who sign the informed consent and receive at least 1 dose of ravulizumab and who have evaluable pharmacokinetic or pharmacodynamic data.
Per Protocol Set	Will be defined in the statistical analysis plan.

[a] ST-HUS and TTP are different forms of TMA with different treatment modalities than what is being studied within Study ALXN1210-TMA-313. Because ST-HUS and TTP are different forms of TMA, they are part of the exclusion criteria. To avoid confounding the efficacy results, patients who are found to be ineligible after randomization due to ST-HUS or ADAMTS13 testing will be discontinued and replaced. These patients will also be excluded from the primary efficacy analysis. This is in alignment with ICH E9 guidance which indicates that it is justifiable to exclude randomized subjects from the Full Analysis Set who fail to satisfy major entry criteria (eligibility violations).

- Efficacy analyses will be performed on the FAS.
- Sensitivity analysis for primary endpoint and key secondary endpoints will be run using the ITT Analysis Set if the FAS and ITT Analysis Set are different.
- The primary efficacy endpoint analysis, as well as selected secondary endpoint analyses, will also be performed on the PP Set.
- Safety analyses will be performed on the Safety Set.
- PK and PD analyses will be performed on all participants who receive at least 1 dose of ravulizumab and who have evaluable PK or PD data.

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate SAP. Summary statistics will be computed and displayed by treatment group, and by visit, where applicable, and by stratification factors, when relevant. Descriptive statistics for continuous variables will minimally include the number of participants, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. Graphical displays will be provided as appropriate. The significance level is 0.05 for two-sided tests and 0.025 for one-sided tests, unless specified otherwise.

Analyses will be performed using the SAS® software Version 9.4 or higher.

The main set of analyses will focus on comparing results in the FAS between the 2 randomized Stage 2 treatment groups (ravulizumab treatment group and placebo treatment group). Descriptive statistics will be provided for Stage 1 efficacy data.

The primary endpoint EFS will be analyzed as a time to event variable. The survival time will be calculated as the time in days from randomization to the date of clinical worsening or death, whichever is earlier. Intercurrent events and censoring rules are included in Table 12. 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.

Table 12: 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
	Withdrawal of consent	Date of withdrawal of consent	Censored

For secondary endpoints that will be assessed as time to event or change from baseline, the main analyses will be performed by adopting the treatment policy strategy. Sensitivity analyses for secondary endpoints will be performed by adopting the hypothetical policy strategy. The p-values from sensitivity analyses for efficacy endpoints are for descriptive purpose only and not adjusted for multiplicity. Details on sensitivity analyses will be provided in the SAP.

To evaluate the delayed treatment effect of ravulizumab, the efficacy data collected from the start of post-unblinding rescue treatment will be summarized separately for participants in the placebo treatment group who receive ravulizumab as the rescue treatment. The baseline to assess the delayed treatment effect will be assigned as the last non-missing value prior to the first dose of study intervention.

Analyses of the primary endpoint will be performed by subgroups including, but not limited to the presence of acute GVHD, geographical region, and baseline weight. Further details will be provided in the SAP.

9.4.1. Efficacy Analyses

Efficacy analyses will be performed using the FAS, which will exclude participants who enrolled prior to availability of ST-HUS and ADAMTS13 laboratory results and were subsequently found to be ineligible after enrollment. The FAS was selected as the primary efficacy population to ensure the exclusion of participants with TTP or ST-HUS as potential confounders in the

efficacy analyses, as these conditions present similarly to the target population but have distinct clinical prognosis and management.

Sensitivity analyses for primary endpoints and key secondary endpoints will be run using the ITT Set if it is not the same as the FAS.

The primary analysis and selected secondary efficacy analyses will also be performed on the PP Set as sensitivity analyses as necessary.

Estimands corresponding to the primary and key secondary efficacy objectives can be found in Section 10.2.

9.4.1.1. Analyses of Primary Efficacy Endpoint

The EFS will be analyzed as a time to event variable using the FAS. A log-rank test stratified by randomization stratification factors (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 to compare EFS through 26 weeks between the ravulizumab treatment group and the placebo treatment group. 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 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 at Week 26. The proportional hazards assumption will be tested.

9.4.1.2. Analyses of Key Secondary Efficacy Endpoints

9.4.1.2.1. Overall Survival

OS will be included in the hierarchal testing procedure. Survival time will be assessed as the number of days from randomization to an event of death. Intercurrent events and censoring rules are included in Table 13. Participants who survive will be censored at their last known date alive within the analysis period. KM cumulative distribution curves will be generated for each treatment group in the FAS. A log-rank test stratified by randomization stratification factors will be used to obtain the p-value for comparing the 2 survival curves by 26 weeks and by Day 100. A corresponding summary table will present by treatment group the first quartile, median, and third quartile, along with corresponding 2-sided 95% CI, of survival time, and KM estimates with 95% CI at 26 weeks and Day 100 post-randomization. Restricted mean survival will also be used to summarize the restricted mean survival time at Week 26. The proportional hazards assumption will be tested.

Table 13: Censoring Rules for Overall Survival

Endpoint	Situation	Date of Event or Censoring	Outcome (event or censored)
	Death	Death date	Event
	Additional HSCT	Date of additional HSCT	Censored

Table 13: Censoring Rules for Overall Survival

Endpoint	Situation	Date of Event or Censoring	Outcome (event or censored)
OS	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
	Withdrawal of consent	Date of withdrawal of consent	Censored

Additionally, a similar approach will be applied to compare OS by 52 weeks after randomization. This analysis will not be part of the hierarchal testing procedure.

A sensitivity analysis of OS will be performed using the hypothetical estimand which will censor patients at the time of rescue treatment initiation.

9.4.1.2.2. Non-relapse Mortality

Non-relapse mortality will be included in the hierarchal testing procedure. 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 (causing HSCT). Time to non-relapse mortality is assessed as the number of days from randomization to an event of non-relapse death. Death due to primary disease will be treated as a competing risk (Gray, 1988). Intercurrent events and censoring rules are included in Table 14. 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 within the analysis period. CIF for non-relapse mortality will be estimated using a competing risk analysis, treating disease progression related death as a competing risk. P-value from stratified Gray's test for equality of the CIF, stratified by the randomization stratification factors will be presented for comparing the 2 treatment groups.

Table 14: 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
	Withdrawal of consent	Date of withdrawal of consent	Censored

9.4.1.3. Number of TMA Response Criteria Met

The TMA response components include: 1) platelet response, 2) normalization of LDH response and absence of schistocytes, and 3) renal response. A participant could meet 0, 1, 2, or 3 TMA response criteria during the 26-week Treatment Period. If the participants meet more than 1 TMA response criterion, those responses must overlap for at least 24 hours.

Under the composite endpoint strategy, NRI will be employed as follows:

If a participant does not meet any TMA response component during the 26-week Treatment Period before the occurrence of the intercurrent events: treatment discontinuation, clinical worsening, or additional HSCT, the participant will be classified as having no TMA response criteria met.

The number of TMA response criteria will be summarized by the number and percentage of the 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.

9.4.1.3.1. Hematologic Response

The criteria for hematologic response are presented in Table 7.

The corresponding estimand for hematologic response during the 26-week randomized Treatment Period is the difference in proportion of participants achieving hematologic response by Week 26 between treatment groups in participants in the FAS. Analyses will be based on a composite strategy where participants will be considered as non-responders if they do not achieve a hematologic response prior to the occurrence of any of the following intercurrent events: treatment discontinuation, rescue treatment unblinding, death, or additional HSCT.

The p-value comparing the proportions of hematologic response between the two treatment groups will be based on the Mantel-Haenszel stratum-weighted estimator with strata defined by randomization stratification factors and NRI will be used to handle missing data. The point estimate and 95% CI for the proportion of responders in each treatment group will be provided. The first lab value used to assess hematologic response will be based on central laboratory results; the second (confirmatory) laboratory value will be assessed based on the earliest value obtained ≥ 24 hours after the first value. For platelets, local laboratories may be used for the second (confirmatory) value in the absence of a valid central result. LDH must be assessed centrally for both measurements. LDH must be assessed centrally for both measurements. The CI will be based on exact confidence limits using the Clopper-Pearson method.

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 postbaseline time point. This analysis will be conducted using 2 approaches described in Section 9.4.1.4.

9.4.1.3.2. eGFR

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. This analysis will follow a hypothetical strategy where data collected after any of the following intercurrent events will not

be utilized for analysis: treatment discontinuation, rescue treatment unblinding, death, or additional HSCT.

The treatment comparison will be based on an MMRM with the fixed categorical effect 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 error. The specified MMRM analysis can produce valid statistical inference under MAR missing data mechanism assumption.

9.4.1.4. Analyses of Other Secondary Endpoints

9.4.1.4.1. TMA Response

TMA response during the 26-week Treatment Period between treatment groups for participants will be analyzed using the FAS. The criteria for TMA response are presented in Table 7. A composite strategy will be applied where participants will be classified as non-responders if they do not have any TMA response observed prior to any of the following intercurrent events: treatment discontinuation, rescue treatment unblinding, death, or additional HSCT. For participants who do not experience one of the intercurrent events, above, TMA response will be assessed using all available assessments within the 26-week randomized Treatment Period. The first laboratory 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 ≥ 24 hours after the first value. Additionally, for platelets and proteinuria, local laboratories may be used for the second (confirmatory) value in the absence of a valid central result. LDH must be assessed centrally for both measurements.

The proportion of participants who achieve TMA response during the 26-week randomized Treatment Period will be summarized for each treatment group. The primary analysis will be based on a CMH test stratified by randomization stratification factors at a 5% significance level, comparing the proportion of participants achieving TMA response during the 26-week randomized Treatment Period between the 2 treatment groups in the FAS. The analysis will be performed according to the randomized treatment assignment. NRI will be used to handle missing data.

Sensitivity analyses of hematologic response, renal response, individual TMA response parameters, and TMA response will be performed using local laboratories, where available, when central laboratory results are missing.

9.4.1.4.2. TMA Response at and up to Specific Time Points

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

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 (assessed as in the primary analysis of TMA response) at a specific time point out of the participants who are still in the study up to this time point. The second approach will present the cumulative number and proportion of responders up to a specific time point out of all participants randomized.

9.4.1.4.3. Time to TMA Response

Time to TMA response will be assessed as the time in days from randomization to their first occurrence of TMA response and analyzed as a time to event endpoint. The following intercurrent events will be treated as competing risk: treatment discontinuation, rescue treatment unblinding, 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-week period. CIF curves for TMA response will be generated for each treatment group. HR with 95% CI and p-value from Fine and Gray's sub-distribution hazard model stratified by randomization stratification factors will be presented for comparing the 2 treatment groups.

9.4.1.4.4. Individual Components of TMA Response

Response to each individual component of TMA response (Table 7) during the 26-week randomized Treatment Period will be summarized by treatment group by calculating the point estimate and a Clopper-Pearson 95% CI for the proportion of responders.

These responses 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 postbaseline time point. This analysis will be conducted using the 2 approaches described in Section 9.4.1.3.

9.4.1.4.5. Time to Response for Individual TMA Response Criteria

Time to response for each criterion of TMA response (Table 7) will be assessed separately. Participants will be assigned as responders for a specific criterion at the time of first response for that criterion since randomization and analyzed as a time to event endpoint. The following intercurrent events will be treated as competing risk: treatment discontinuation, rescue treatment unblinding, 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 the individual TMA response component data are available within the 26 weeks period. 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.

9.4.1.4.6. Time to Hematologic Response

Time to hematologic response will be assessed as time in days from randomization to first occurrence of hematologic response. The following intercurrent events will be treated as competing risk: treatment discontinuation, rescue treatment unblinding, 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 the components of the hematologic response components data are available within the 26 weeks period. CIF curves for TMA response will be generated for each treatment group. HR with 95% CI and p-value from Fine and Gray's sub-distribution hazard model stratified by randomization stratification factors will be presented for comparing the 2 treatment groups.

9.4.1.4.7. Hemoglobin Response

The criteria for hematologic response are presented in Table 7.

For participants who have rescue treatment trigger events observed, only data collected on and prior to the trigger events will be used to assess hemoglobin response.

Hemoglobin maintenance during the 26-week randomized Treatment Period will be summarized by treatment group 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.

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 postbaseline time point. This analysis will be conducted using 2 approaches described in Section 9.4.1.4.

9.4.1.4.8. Hematologic Parameters

Hematologic parameters (haptoglobin, hemoglobin, platelets, LDH, and schistocytes) will be summarized by treatment group at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline.

9.4.1.4.9. Platelet Response

The criteria for platelet response are presented in Table 7.

Platelet response during the 26-week randomized Treatment Period will be summarized by treatment group 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.

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 postbaseline time point. This analysis will be conducted using 2 different approaches described in Section 9.4.1.4.

9.4.1.4.10. Partial Response

Partial response (participant meets ≥ 1, but not all, criteria for TMA response (Table 7) during the 26-week Treatment Period will be summarized by treatment group 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. This will include separate presentations for participants with response to only 1 component, only 2 components, and at least 1, but not all components.

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 postbaseline time point. This analysis will be conducted using 2 approaches described in Section 9.4.1.4.

9.4.1.4.11. Modified TMA Response

Modified TMA response will be analyzed using the same methodology as for TMA Response.

9.4.1.4.12. Organ Dysfunction

Treatment effect on organ dysfunction will be evaluated in the following end organ systems: renal, cardiovascular, CNS, pulmonary, and GI, following treatment policy strategy.

A sensitivity analysis will be performed 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 in the FAS. The CIF estimates and 95% CI at fixed time points of interest will be provided for each organ dysfunction. Gray's test stratified by randomization stratification factors will be performed to obtain the p-value for comparing the 2 treatment groups.

Full details for organ dysfunction analyses will be described in the SAP.

Renal Dysfunction:

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

For participants who require dialysis, change from baseline in dialysis requirements will be summarized. An analysis will present the number and proportion of participants who require dialysis over time. A 2-sided 95% CI for the proportion will be provided. A participant will be considered as not requiring dialysis at a specific postbaseline time point if they have been dialysis free for at least 5 days prior to that time point.

Cardiopulmonary Involvement:

The presence of pulmonary hypertension, pleural effusion, pulmonary edema, and pericardial effusion will be summarized. An analysis will present over time the number and proportion of participants with any of these conditions. A 2-sided 95% CI for the proportion will be provided.

Additionally, use of any ventilatory or respiratory support will be summarized similarly.

Hypertension will be assessed by blood pressure measurement at every visit as part of vital signs collection, and analysis of concomitant medications to control the hypertension. Presence of hypertension will be summarized by presenting the number and proportion of participants who shift in their hypertensive status from baseline to postbaseline visits. Selected echocardiography parameters will be summarized over time.

CNS Involvement:

The presence of PRES will be summarized by presenting the number and proportion of participants with shifts in presence of PRES status from baseline to postbaseline visits.

GI Involvement:

Signs and symptoms of GI involvement such as diarrhea, vomiting, pain, and bleeding will be summarized. An analysis will present over time the number and proportion of participants with any of these conditions.

The frequency and estimated volume of GI bleeding will also be summarized.

9.4.1.4.13. TMA Relapse

Among participants who will have achieved TMA response, as defined in the secondary endpoint, TMA relapse will be summarized by treatment group by calculating the point estimate and a 95% CI for the proportion of participants with a TMA relapse. The CI will be based on exact confidence limits using the Clopper-Pearson method.

An analysis will summarize time to TMA relapse from the time of response. Participants who achieve TMA response will be censored at the last available assessment for TMA relapse, or death if they have not experienced a relapse. KM cumulative distribution curves will be

generated for each treatment group. A corresponding summary table will present the first quartile, median, and third quartile, along with corresponding 2-sided 95% CI, of time to TMA relapse.

9.4.1.4.14. Loss of Response/Duration of Response

Loss of response will be defined using composite endpoint strategy where loss of response will be assumed from the point of an intercurrent event onward. Participants who experience loss of response will be summarized by treatment group by calculating the point estimate and a 95% CI among TMA responders. The CI will be based on exact confidence limits using the Clopper-Pearson method.

Duration of response is the time interval from initial TMA response to first occurrence of loss of TMA response or TMA relapse. Responders who do not have any events defined as loss of TMA response are censored at the last day with TMA response. The duration of response will be assessed by KM analysis as a time-to-event variable for all participants in the FAS. Non-responders will be censored at the latest of last assessment on-study or death and will have a duration of response of zero. KM cumulative distribution curves will be generated for each treatment group. A corresponding summary table will present by treatment group the first quartile, median, and third quartile, along with corresponding 2-sided 95% CI, of time to loss of TMA response, and the KM estimates at fixed time points of interest. Additionally, a sensitivity analysis will be conducted using a similar approach for only the responders in the FAS.

9.4.1.5. Multiplicity Adjustment

For the primary analysis, the ravulizumab treatment group will be compared to the placebo treatment group based on the null and alternative hypotheses below. Hypothesis testing will be two-sided and performed at the 0.05 level of significance.

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 in the ravulizumab treatment group and $S(t)_{placebo}$ is the EFS in the placebo treatment group.

If the null hypothesis is rejected, key secondary endpoints will be tested for inequality using a hierarchical stepdown closed-testing procedure. The key secondary endpoints will be tested in the following order until a non-significant test is observed, at which point no further testing of subsequent endpoints will occur:

1. OS during the 26-week Treatment Period
2. OS 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

9.4.1.6. Analyses of Exploratory Endpoints

The analyses of exploratory endpoints will be based on treatment policy strategy. Sensitivity analyses may be performed by excluding the data after intercurrent events and will be detailed in the SAP.

9.4.1.6.1. Biomarkers

For exploratory biomarker analyses, summary statistics will be presented for observed values, change and percentage change from baseline.

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

9.4.1.6.2. Health-Related Quality of Life

Health-related quality of life will be evaluated using EQ-5D-5L, EQ-5D-5L Proxy (version 1), SF-12 and FACIT-Fatigue. For EQ-5D-5L, the visual assessment scale score will be obtained and the US composite time trade-off will be calculated based on this instrument and these 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. Summary scores from the SF-12 and FACIT-Fatigue will be treated as continuous variables. An MMRM with the fixed categorical effect of treatment group, visit, interaction between treatment and visit, and continuous effect of the specific test's baseline value as covariates, and unstructured covariance matrix may be fit to test whether changes differ between the 2 treatment groups at each time point. The analysis of summary scores from SF-12 will be conducted separately for adult and adolescent participants.

Consideration will be given due to expected missing responses at baseline for the participant-reported instruments, detailed in the SAP. All efforts will be made to mitigate missing responses (Coens, 2020). To assess participant-reported compliance, a form documenting reasons for missed responses will be completed by study staff at each assessment with planned participant-reported data collection. The assessments that are missed due to disease severity or similar, as confirmed on the compliance form, will be informative as opposed to missing for unknown reasons. Knowing reasons for missed responses allows for the application of statistical approaches that rely on fewer assumptions and will yield estimates that are considered to have less bias.

9.4.1.6.3. Global Impression of Disease Severity and Change

The global impression of disease severity and change of participant TMA symptoms will be evaluated by participants, caregivers, and clinicians. For the caregiver and participant global impression of severity and change outcomes, the observed number and proportion of respondents endorsing each category of the verbal rating scale will be presented for each assessment time point. Change from baseline on the prospective global severity anchors will be presented as the number and proportion of participants and caregivers at each level of categorical change from baseline at each postbaseline assessment.

For global impression of severity and change outcomes by clinicians, the observed number and proportion of respondents endorsing each category of the verbal rating scale will be presented for each assessment time point. Change from baseline on the prospective global severity anchors will be presented as the number and proportion of participants and caregivers at each level of categorical change from baseline at each postbaseline assessment.

9.4.1.6.4. Medical Resource Utilization

Hospitalizations will be summarized 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.

Transfusion requirements will be summarized by presenting 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 presenting the number and proportion of participants requiring physician or emergency room visits and the underlying reason.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Set and based on the treatment received. Participants who receive post-unblinding rescue treatment will have their placebo treatment and post-unblinding rescue treatment data summarized separately.

9.4.2.1. Adverse Events

The following definitions will be used for AEs:

- Pretreatment AEs: Any AE that starts after providing informed consent/assent, but before the first infusion of study intervention (ravulizumab or placebo).
- TEAE: Any AE that starts between the start of the first infusion of study intervention and up to 8 months after the last infusion of study intervention, inclusive.
- TESAE: A TEAE that is serious.
- Post-treatment AEs: Any AE that starts 8 months or later after the last dose of study drug.

The incidence of TEAEs, TEAEs leading to withdrawal from the study, TEAEs leading to study treatment discontinuation, drug-related TEAEs, TEAEs during ravulizumab administration, and SAEs will be summarized by treatment group. All AEs will be coded using the MedDRA Version 22 or higher and will be summarized by SOC and Preferred Term overall, by severity, and by relationship to treatment. Detailed by-participant listings of TEAEs, SAEs, related TEAEs, TEAEs during ravulizumab administration, TEAEs leading to withdrawal from the study, and TEAEs leading to study treatment discontinuation will be provided.

9.4.2.2. Physical Examination and Vital Signs

Adverse changes from baseline in physical examination findings will be classified as AEs and analyzed accordingly.

Vital signs will be summarized descriptively at baseline and postbaseline time points and for changes from baseline.

By-participant listings will be provided.

9.4.2.3. Clinical Laboratory Tests

Observed values and changes from baseline in clinical chemistry, hematology, 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 in classification will be summarized for all study visits.

9.4.2.4. Electrocardiograms

By-participant data listings of ECG parameters will be provided. ECGs will be evaluated and summarized as normal, abnormal not clinically significant, or abnormal clinically significant. Observed values and change from baseline in ECG intervals (PR, RR, QT, and QTc) will be summarized descriptively at baseline and each postbaseline time point. QT interval will be corrected for heart rate using QTcF.

9.4.2.5. Immunogenicity

The incidence and titers for ADAs to ravulizumab will be presented at each postbaseline time point in tabular format. Additionally, any confirmed ADA positive samples will be tested for antibody titer and the presence of neutralizing antibodies to ravulizumab.

9.4.3. Pharmacokinetic/Pharmacodynamic Analysis

Individual PK/PD data will be collected for all participants.

Graphs of mean serum ravulizumab concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual participants may also be provided. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate.

The PD effects of ravulizumab will be evaluated by assessing the absolute values and changes and percentage changes from baseline in serum free C5 and serum total C5 concentrations over time, as appropriate. Descriptive statistics will be calculated for the PD data at each sampling time, as appropriate.

9.5. Planned Analyses

9.5.1. Dose Confirmation Analysis

An early analysis of the PK/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 the minimum of 10 participants completing Visit- 5 at Day 21 as part of the dose confirmation analysis to support adjustments to the dosing regimen and/or the CCI supplemental dosing for participants ongoing in Stage 1. If necessary, additional participants may be enrolled into Stage 1 either prior to or during the

analysis (eg, 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.

9.5.2. Interim Analysis

An IA may be conducted at the discretion of Alexion when at least 80% of the expected events (53 out of 66 events) of clinical worsening or death have been observed through 26 weeks. Enrollment will not be paused during the IA. The purpose of the optional IA is to evaluate the study for stopping early for efficacy. If conducted, the primary endpoint will be evaluated using the Lan-DeMets approach with an O'Brien-Fleming spending function to control the Type I error rate at 5%. The IA for efficacy assessment will be considered positive if the primary endpoint is statistically significant per the pre-specified alpha spending method.

The IA will be conducted by an IDAC. The IDAC will provide a report of the IA outcome to the independent DMC. The DMC will review the IA report and provide appropriate recommendations to Alexion as described in the SAP and DMC charter. The recommendation of the DMC to Alexion will be non-binding. Alexion will make the ultimate decision for implementation of any suggestions. Details of the DMC's responsibilities and logistics will be outlined in the charter. Details on blinding/unblinding related review of DMC recommendations as part of the IA will be provided in the Blind Management Plan.

9.5.3. Primary Analysis

A primary endpoint analysis will be conducted when all participants in Stage 2 have completed or withdrawn from the 26-week Treatment Period of the study, and all participants in the 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 (SoA Table 2) or 66 clinical worsening events or deaths occurred during the 26 weeks, whichever is earlier. The SAP will describe the planned analysis in greater detail.

9.5.4. Final Analysis

The final study analysis will be conducted at the end of the study (Section 4.4). The SAP will describe the planned analysis in greater detail.

9.6. Data Monitoring Committee

An independent 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.

If an IA with stopping rules for early efficacy is conducted, the DMC will review the unblinded IA report and provide appropriate recommendation to Alexion.

Each member of the DMC will be required to sign a contract agreement, which includes a confidentiality and financial disclosure statement.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments (ie, modifications), ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated. If any of these documents also require regulatory/health authority approval per local regulations, Alexion will obtain such approval before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. If these documents also require regulatory/health authority approval per local regulations, Alexion will obtain such approval before implementation.
- The Investigator will notify the IRB/IEC of deviations from the study protocol or GCP as defined by applicable law as a serious breach or as required by IRB/IEC procedures.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU CTR 536/2014 for clinical studies (if applicable), and all other applicable local regulations
  - Promptly notifying Alexion of any (potential) serious breach of the protocol or regulations (including if a data breach compromises the integrity, confidentiality, or availability of the personal data of participants) so that legal and ethical obligations are met. A "serious breach" means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

- In certain regions/countries, Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - Alexion will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority (including data protection authorities and, if applicable, affected participants in case of a personal data breach), IRB/IEC, and Investigators. Under EU CTR 536/2014, Alexion is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
  - A "personal data breach" means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed.
- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach, including personal data breaches.
  - A (potential) serious breach is promptly reported to Alexion or delegated party, through the contacts (email address or telephone number) provided by Alexion.
- The Coordinating Investigator will be identified among the enrolling Investigators during the course of the study and will be responsible for reviewing the CSR and confirming that it accurately describes the conduct and results of the study.

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator to obtain signed (written or electronic signature) informed consent and assent from all study participants or their legally authorized representative prior to performing any study-related procedures including screening assessments.
- The Investigator or his/her representative will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed

consent or assent or a certified translation if applicable, that meets the requirements of 21 CFR 50, local regulations, EU GDPR, ICH GCP guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that signed (written or electronic) informed consent or assent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent or assent must also sign the informed consent or assent form(s).
- Participants must be reconsented or reassented to the most current version of the informed consent or assent form(s) during their participation in the study. Participants ≥ 12 to < 18 years of age at time of signing the assent during the Screening Period that turn 18 years of age while enrolled on-study should be re-consented when they turn 18 years of age.
- A copy of the signed (written or electronic) informed consent or assent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Signed (written or electronic) consent or assent forms must remain in each participant's study file and must be available for verification at any time.

Participants who are rescreened are required to sign a new ICF (see Section 5.4).

There will be a separate ICF that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant or their legally authorized representative the objectives of the exploratory research. Participants or their legally authorized representative will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Recruitment Strategy

Participants will be identified by a quality research staff. This may be done through a review of medical records, external referrals or using databases. Recruitment strategies may include referral letters where permitted by local regulations. All recruitment materials will be submitted to the local IRB/IEC as required, for review and approval for use.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by a Trusted Third Party contracted by Alexion or by a PI. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related and coded (pseudonymized) data will be used by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the participants who will be required to give consent for their data to be used as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Alexion and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- The EU GDPR defines pseudonymization as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.
- Appropriate safeguards will be implemented to protect coded data during and after the study that include:
  - Access to the coded data will be limited to specific individuals subject to confidentiality obligations (including the obligation to not attempt to re-identify individuals/decode the clinical data).
  - The coded data will be protected with security measures to avoid data alteration, loss, and unauthorized accesses and further de-identification techniques may be applied.
  - A data protection impact assessment, where required, will apply to identify, and mitigate privacy risks, if any, associated with each scientific research.
  - The coded data will not be shared for direct marketing purposes or other purposes that are not legal duties or are not considered scientific research according to the applicable data protection legislation. In particular, they will not be used to make decisions about future services available to the participant, such as insurance.

- In addition to having the participants' data and biosamples coded, the data are also protected by high-standard technical security means, such as strong access control and encryption.
- Participants are also protected legally by the following means if the level of disclosure of the coded data includes sharing of the latter with other third parties, as the participants will be explained in the ICF:
  - The participants' coded data are protected by contractual arrangements, Codes of Conduct, or certifications that set the rules for personal information protection to those available in European countries or other alternatives set forth in the law, as well as any supplementary technical and organizational measures that may results out of conducted transfer impact assessments.

10.1.6. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on CRFs unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion. Clinical study documents and records required as part of the TMF are archived and stored by Alexion for at least 30 years.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Source documents are filed at the Investigator's site.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the first participant is consented or assented.

Alexion reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the EoS or ED Visit, all data have been collected and entered into the EDC system, all required documents and study supplies have been collected, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion's procedures, or GCP guidelines
- Inadequate or no recruitment of participants by the Investigator
- Discontinuation of further study intervention development

Alexion or regulatory authority may terminate the study for reasonable cause. Conditions that may warrant termination of the study include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk of the study drug to participants enrolled or continuing in the study.
- Alexion decision to suspend or discontinue testing, evaluation, or development of the study intervention for the HSCT-TMA indication.

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 6 months of the primary evaluation date or EoS, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and to provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.
- In general, primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.
  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.
- Alexion will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.

10.2. Mapping Objectives to Estimands

Table 15: Mapping Objectives to Estimands

Objective	Estimand
Primary	
To assess the efficacy of ravulizumab versus placebo in the treatment of adult and adolescent participants with HSCT-TMA	• Population: Participants in the FAS population (defined in Section 9.3) • Variable: EFS during the 26-week randomized Treatment Period • Treatments: Ravulizumab vs placebo • IE: o Additional HSCT Follow up post-additional HSCT will be censored • Summary measure: HR between treatment groups
Key Secondary	
To assess OS	• Population: Participants in the FAS population (defined in Section 9.3) • Variable: OS during the 26-week randomized Treatment Period and during 100 days post-randomization. • Treatments: Ravulizumab vs placebo • IE: o Additional HSCT Follow up post-additional HSCT will be censored • Summary measure: HR between treatment groups
To assess non-relapse mortality	• Population: Participants in the FAS population (defined in Section 9.3) • Variable: Non-relapse mortality during the 26-week randomized Treatment Period • Treatments: Ravulizumab vs placebo • IE: o Additional HSCT Follow up post-additional HSCT will be censored • Summary measure: Hazard ratio between treatment groups
To characterize TMA response after treatment with ravulizumab	• Population: Participants in the FAS population (defined in Section 9.3) • Variable: Number of TMA response criteria met during the 26-week randomized Treatment Period • Treatments: Ravulizumab vs placebo • IE:

Table 15: Mapping Objectives to Estimands

Objective	Estimand
	○ Treatment discontinuation ○ Rescue treatment unblinding ○ Additional HSCT ○ Death All data after an IE will be censored. • Summary measure: Difference in number of TMA response criteria met between treatment groups
To characterize TMA response after treatment with ravulizumab	• Population: Participants in the FAS population (defined in Section 9.3) • Variable: Hematologic response (Section 3.2) during the 26-week randomized Treatment Period • Treatments: Ravulizumab vs placebo • IE: ○ Treatment discontinuation ○ Rescue treatment unblinding ○ Additional HSCT ○ Death All participants who do not have an observed hematologic response prior to experiencing an IE will be considered non-responders. • Summary measure: Difference in proportion of participants achieving hematologic response
To assess improvement in organ dysfunction	• Population: Participants in the FAS population (defined in Section 9.3) • Variable: Change from baseline in eGFR at Week 26 • Treatments: Ravulizumab vs placebo • IE: ○ Treatment discontinuation ○ Rescue treatment unblinding ○ Death ○ Additional HSCT All data after the IE will be considered missing. • Summary measure: Difference between treatment groups in the mean change from baseline

Note: Key secondary endpoints are presented in order of inclusion in the hierarchical stepdown closed-testing procedure.

10.3. Clinical Laboratory Tests

- The tests detailed in Table 16 will be performed by the study central laboratory unless otherwise noted. Please refer to the Laboratory Manual for specific testing schedules and details.
- As described in Section 5, 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. If any laboratory results are not available ≤ 14 days prior to the start of the Screening Period, these assessments must be conducted during the Screening Period. 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. In the UK, if a local laboratory result for ST-HUS is used to confirm eligibility prior to enrollment, the ST-HUS test must still be repeated at the central laboratory; however, these results are not required prior to enrollment.
- After the Screening Period, local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: WOCBPs should only be enrolled after a negative serum pregnancy test result at Screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB/IEC and should be performed per the time points specified in the SoA (Section 1.3).
- Investigators must document their review of each laboratory safety report.
- The names and the locations of the central laboratories that will be operating in China, including vendors involved in sample disposal and transport activities, have been included in Section 10.16.1.1.

Table 16: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Platelet count • Immature platelet fraction • RBC count • Hemoglobin (including free hemoglobin) • Hematocrit • RBC indices (mean corpuscular volume, mean corpuscular hemoglobin,) • Percentage of reticulocytes • Absolute reticulocyte count • RBC distribution width • White blood cell count with differential (including early progenitors) • Haptoglobin • RBC morphology (peripheral blood smear); particularly the presence of schistocytes
Coagulation Panel (Screening only)	• INR • PT • APTT • D-Dimer • Fibrinogen

Clinical Chemistry[a]	• Liver function tests:
	  ○ ALT
	  ○ AST
	  ○ ALP
	  ○ Albumin
	  ○ total protein
	  ○ A/G ratio (albumin/globulin ratio)
	  ○ Bilirubin (total, direct and indirect)
	  ○ GGT
	  ○ Glucose (non-fasting)
	  ○ LDH
	• Renal function:
	  ○ Anion gap
	  ○ Bicarbonate
	  ○ Blood urea nitrogen
	  ○ Calcium
	  ○ Chloride
	  ○ Creatinine
	  ○ Magnesium
	  ○ Phosphorus

Table 16: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
	○ Potassium ○ Sodium ○ Uric acid • Other clinical chemistry parameters: ○ C-reactive protein
Routine Urinalysis/Urine Chemistry	• Bilirubin • Blood • Color • Creatinine • Glucose • Ketones • Nitrite • pH • Protein • Specific gravity • Urobilinogen
Other Screening Tests	• Serum follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine human chorionic gonadotropin pregnancy test (as needed for WOCBP)[a] • HIV antibody (HIV-1and HIV-2) • ADAMTS13 activity • ST-HUS screen (eg, Shiga toxin enzyme immunoassay/PCR in stool/stool culture/rectal swab) • Coombs test, direct
Other Study-specific Tests	• Immunogenicity (ADA) • Serum PK • Serum PD (total and free C5) • CCI [redacted] • Genetic testing (whole blood and buccal swab)[b] • Exploratory biomarkers[b]

[a] Serum pregnancy test at Screening and End of Study Visit/Early Discontinuation Visit, and local urine pregnancy test at all other times as specified in the SoA.
[b] Samples will be collected only in countries where the applicable regulatory authorities permit exportation of biologic samples for this purpose.

The following procedures for blood collection in participants from 12-17 years of age should be adhered to:

1. Number of attempts: The number of attempts for sampling blood is limited to 3 times per day. This means that, after 3 punctures for collection of blood have been performed and

no or insufficient blood could be collected, no other puncture will be done on the same day.

2. Volume of blood samples: Per study participant, the study-related blood loss (including any losses in the collection procedure) should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight. Three percent (3%) is 2.4 mL blood per kg of body weight. If an Investigator decides to deviate from these limits, the deviation must be fully documented, and the Investigator should provide justification for the deviation. If the required blood volume cannot be obtained, due to the above-mentioned safety limits, sample collection for certain assessments will be prioritized. Guidance for prioritization of assessments will be provided to the Investigator in a separate document.
3. EMLA cream/plaster: To minimize the possible pain and discomfort due to collection of blood, the Investigator should apply an EMLA cream/plaster at the puncture site.

Reference: (European-Commission, 2008).

10.4. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
  - Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events Not Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error.

Events Not Meeting the AE Definition
• Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.4.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may

An SAE is defined as any untoward medical occurrence that, at any dose:
require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An SUSAR is defined as:
A serious event that is not listed in the IB and that the Investigator identifies as related to investigational product or procedure. United States Title 21 CFR 312.32 and EU CTR 536/2014 and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. Alexion has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance. SUSARs will be reported to the national competent authority and IRBs/IECs where applicable.

10.4.3. Recording and Follow-up of AE and/or SAE

Recording of AE and/or SAE
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the CRF. • It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
• An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe. The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017: • Grade 1: Mild (awareness of sign or symptom, but easily tolerated) • Grade 2: Moderate (discomfort sufficient to cause interference with normal activities) • Grade 3: Severe (incapacitating, with inability to perform normal activities) • Grade 4: Life-threatening • Grade 5: Fatal

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the CRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study intervention caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study intervention.
  - Related: There is a reasonable possibility the study intervention caused the AE.
    - The AE has a temporal relationship to the administration of the study intervention.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study intervention.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized Follow-up Period, the Investigator will provide Alexion with a copy of any post-mortem findings including histopathology.

Follow-up of AEs and SAEs

- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.4.4. Reporting of SAEs

SAE Reporting to Alexion via an Electronic Data Collection Tool

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours of awareness.
- The primary mechanism for reporting an SAE to Alexion will be the electronic data collection tool.
- If the electronic system is unavailable at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE reporting via fax or email. Facsimile transmission or email may be used in the event of electronic submission failure.
  - Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347
- The site will enter the SAE data into the EDC system as soon as it becomes available.
- When further information becomes available, the EDC should be updated within 24 hours with the new information and an updated SAE report should be submitted to Alexion GDS.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next paragraph).

SAE Reporting to Alexion via Paper Safety Reporting Form

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours awareness.
- SAEs will be reported using the Safety Reporting Form and submitted to Alexion GDS. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below:
  - Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347
- Additional follow-up information, if required or available, should be entered into the CRF and sent to Alexion GDS within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above.
- For all SAEs, the Investigator must provide the following:
  - Appropriate and requested follow-up information in the time frame detailed above
  - Causality of the SAE(s)
  - Treatment of/intervention for the SAE(s)
  - Outcome of the SAE(s)
  - Medical records and laboratory/diagnostic information
- All paper forms and follow-up information submitted to Alexion GDS **must** be accompanied by a cover page signed by the Investigator.

SAE Reporting to Alexion via Paper Safety Reporting Form
• Paper source documents and/or reports should be kept in the appropriate section of the study file.

10.4.5. Unexpected Events

Apart from the reporting of SUSARs, there may be other events which are relevant in terms of benefit-risk balance, and which should be reported in a timely manner according to regional and national requirements (eg, EU CTR 536/2014 [48]). It is important for participant safety that, in addition to SAEs and reactions, all unexpected events that might materially influence the benefit-risk assessment of the study intervention or that would lead to changes in the administration of the study intervention or in overall conduct of a clinical study should be reported. Examples of such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as carcinogenicity).

Under the EU CTR 536/2014 (49), where unexpected events require an urgent modification of a clinical trial, it should be possible for Alexion and the Investigator to take urgent safety measures without awaiting prior authorization. If such measures constitute a temporary halt of the clinical trial, Alexion should apply for a substantial modification before restarting the clinical trial.

10.5. Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP that either causes harm to the participant or has the potential to cause harm to the participant.

Any events of medication error, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Medication Error Report Form.

A medication error is not lack of efficacy of the study intervention, but rather a human or process related failure while the intervention is under the control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred.
- Was identified and intercepted before the participant received the drug.
- Did not occur, but circumstances were recognized that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion.
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, eg, wrong route or wrong site of administration.
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature.
- Wrong participant received the medication (excluding IRT/RTSM errors).
- Wrong drug administered to participant (excluding IRT/RTSM errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error.
- Participant accidentally missed drug dose(s), eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose [refer to Section 8.5 for information on overdose]).
- Participant failed to return unused medication or empty packaging.

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, nontherapeutic excessive use of IMP for a perceived reward or desired nontherapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study).
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use of IMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person.
- The drug is sold to other people for recreational purposes.
- The drug is used to facilitate assault in another person.
- The drug is deliberately administered by the wrong route.
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole.
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose.
- Someone who is not enrolled in the study intentionally takes the drug.

10.6. Management of Potential Infusion-Associated Adverse Events During Study Intervention Administration

IV and infusion-associated reactions are a potential risk with the use of monoclonal antibodies; these reactions can be nonimmune or immune mediated (eg, hypersensitivity reactions). Signs and symptoms may include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Signs and symptoms of hypersensitivity or allergic reactions may include hives, swollen face, eyelids, lips, or tongue, or trouble with breathing.

All administration-, IV-, and infusion-associated reactions will be reported to the Investigator and qualified designee. The Investigator and qualified designee are responsible for detecting, documenting, and recording events that meet the definition of AE or SAE and remain responsible for following up events that are serious, considered related to the study drug, or study procedures; or that caused the participant to discontinue study intervention (Section 7).

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.4.

Participants who experience a reaction during the administration of study intervention should be treated according to institutional guidelines.

Participants who experience a severe reaction during administration of study intervention resulting in discontinuation of study intervention should undergo all scheduled safety, PK, and PD evaluations required by the protocol. Alexion must be notified within 24 hours of any infusion reaction requiring interruption or discontinuation of study intervention. All AEs that may indicate an infusion related response will be graded according to the CTCAE v5.0 or higher.

If anaphylaxis occurs according to the criteria listed in Table 17, then administration of subcutaneous epinephrine (1/1000, 0.3 mL to 0.5 mL, or equivalent) should be considered. In the case of bronchospasm, treatment with an inhaled beta agonist also should be considered. Participants administered an antihistamine for the treatment or prevention of an infusion reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

Table 17: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
• Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least 1 of the following: o Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) o Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
• Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours): o Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips/tongue/uvula) o Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) o Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) o Persistent GI symptoms (eg, crampy abdominal pain, vomiting)
• Reduced blood pressure after exposure to known allergen for that participant (minutes to several hours): o Systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that participant's baseline

Source: (Sampson, 2006)

10.7. COVID-19 Risk Assessment

If untreated, HSCT-TMA can cause irreversible morbidity and even mortality. As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining an investigational study with a therapeutic treatment is potentially significant. Given that treatment for this condition does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in participants not receiving immunosuppressants. However, there are no specific data for HSCT-TMA to further inform on this risk. Apart from the predictable risk of infection with *Neisseria* species, which is well-known and directly related to the mechanism of action of ravulizumab, the mechanism which might lead to other serious infections including viral infections in patients treated with ravulizumab remains unclear. The site Investigator will therefore balance the risk/benefit considerations in the study participant taking these factors into account.

The potential risks identified, and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 18.

Table 18: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Potentially higher risk population for COVID -19 infection	Participants in this study will receive background therapy that may include immunosuppressants. Participants in this study may receive meningococcal vaccination and prophylactic antibiotics prior to treatment with a C5 inhibitor. It is unknown how this may impact their risk for COVID-19 infection.	During the time that the COVID-19 pandemic is active, Alexion will recommend that sites in a position to start the study and enroll participants follow the national and institutional guidance regarding prevention of COVID -19 infection. Additionally, during that period, it is expected that Investigators and their staff will take all possible precautions in order to minimize a participant's potential exposure to COVID-19 infection. Depending on the site, this will consist of measures such as social distancing, temperature screening, enhanced cleaning, and use of personal protective equipment for participants, staff, and caregivers, as necessary.

Table 18: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Healthcare institution availability for non-COVID-19 related activities	The COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new participants at sites unless the sites have the resources and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring of investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, participants' eligibility as well as site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to Screening. Each site will also be evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the CRF that explains the reason the data are missing (eg, missed study visits or participant study discontinuations due to COVID-19).

10.8. COVID-19 Vaccine Risk Assessment

Following a review of the available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished with concomitant ravulizumab administration, based on ravulizumab's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ravulizumab.

Vaccination may further activate complement. As a result, participants with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, participants should be closely monitored for disease symptoms after recommended vaccination.

Because vaccines may activate complement, if possible, consider vaccination when the underlying complement mediated disease is clinically controlled and when systemic C5 inhibitor concentration (and subsequent complement blockade) is relatively high, shortly after administration.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination. The potential risks identified, and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 19.

Table 19: Potential Risks and Mitigation Measures due to COVID-19 Vaccine

Risks Category	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risks		
Data quality and integrity	Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules and increase missed visits and/or participant study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures).	Capture specific information in the CRF that explains the reason for missing data (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine).

10.9. Contraceptive Guidance and Collection of Pregnancy Information

10.9.1. Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     – A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.9.2. Contraception Guidance

10.9.2.1. Guidance for Female Participants

Female participants of non-childbearing potential are exempt from contraception requirements. Non-childbearing potential for female participants is defined as any of the following:

1. Prior to first menses
2. Postmenopausal, as documented by amenorrhea for at least 1 year prior to the Day 1 Visit and FSH serum concentration consistent with postmenopausal status
3. Permanent sterilization at least 6 weeks prior to the Day 1 Visit:
4. Hysteroscopic sterilization
5. Bilateral tubal ligation or bilateral salpingectomy
6. Hysterectomy
7. Bilateral oophorectomy

Female participants of child-bearing potential must use a highly effective or acceptable method of contraception (for participants in the UK, only highly effective methods of contraception can be utilized), including at least one of the following until at least 8 months (generally 5.5 terminal half-lives) after the final dose of study drug.

Highly effective methods are:

1. Intrauterine device in place for at least 6 weeks prior to study intervention.
2. Progestogen-only hormonal contraception (either oral, injectable, or implantable) for at least 6 weeks prior to study intervention.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to study intervention.
4. Bilateral tubal occlusion for at least 6 weeks prior to study intervention.
5. Combined (estrogen- and progestogen containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to study intervention.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within the prior 6 months).
7. Sexual abstinence for female participants:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent female participants who wish to initiate a highly effective method of contraception during the study must refrain from heterosexual intercourse for at least one menstrual cycle.
        – Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods) is not considered a highly effective method of contraception for female participants.

Other methods of contraception that are not considered highly effective for female participants but are acceptable birth control methods that result in a failure rate of more than 1% per year include (note, for participants in the UK only highly effective methods of contraception can be utilized):

1. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
2. Male or female condom with or without spermicide.

3. Cervical cap, diaphragm, or sponge with spermicide.
4. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods; if locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action).

Female participants must not donate ova from the Day 1 Visit at least until 8 months after their final dose of study intervention.

The following methods of contraception are considered unacceptable in this study:

- Periodic abstinence (calendar, symptothermal or post ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Female condom and male condom should not be used together (due to risk of failure from friction).

10.9.2.2. Guidance for Male Participants

Contraception is the responsibility of the heterosexually active male participant, regardless of his female partner's method of contraception.

Male participants who have had a vasectomy > 6 months prior to Screening must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to Screening must use a condom and spermicide during heterosexual intercourse.

Male participants who have not had a vasectomy must use a condom and spermicide during heterosexual intercourse.

10.9.2.2.1. Sexual Abstinence for Male Participants

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participants' s preferred and usual lifestyle. Abstinent male participants who become heterosexually active must use a condom and spermicide during intercourse.

Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods for a female partner) is not considered a highly effective method of contraception for male participants.

Male participants must not donate sperm from the Day 1 Visit until 8 months after the final dose of study intervention.

10.9.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study intervention via semen following paternal exposure. If a female participant or a male participant's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy

Reporting and Outcome/Breastfeeding" form to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to study intervention during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding") and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

Any female participant who becomes pregnant while participating in the study will be discontinued from study intervention.

10.9.3.1. Male Participants With Partners who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate Pregnancy Outcome/Breastfeeding form and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.9.3.2. Female Participants who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- The participant will be followed-up to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks

gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.10. Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact study intervention absorption, distribution, metabolism, and excretion; mechanism of action of the study intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood and buccal swab samples will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to ravulizumab or HSCT-TMA and related diseases. They may also be used to develop tests/assays including diagnostic tests related to ravulizumab and HSCT-TMA and related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to ravulizumab or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- Alexion or designee will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on ravulizumab continues but no longer than 15 years or other period as per local requirements.

10.11. Biomarkers

- Blood and urine samples will be collected for biomarker analyses and the data will be used for research (eg, exploratory) related to ravulizumab or HSCT-TMA and related diseases. These samples may also be used to develop methods, assays, prognostics and/or companion diagnostics related to the study intervention target, disease process, pathways associated with disease state, and/or mechanism of action of ravulizumab.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to ravulizumab to understand study disease or related conditions.
- The results of biomarker analyses may be reported in the CSR or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a facility selected by Alexion that has adequate measures to protect confidentiality.
- The samples will be retained no longer than 5 years from the date Alexion approves the CSR or other period as per local requirements.

10.12. Clinical Outcomes Assessments

10.12.1. Global Impression Scales

10.12.1.1. Clinician Global Impression of Severity

HSCT-TMA Clinician Global Measures
(Clinician Global Impression of Severity)

You have diagnosed the patient with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplant (HSCT) [HSCT-TMA]. TMA is a complication of HSCT in which small blood vessels inside many of the patient's body's vital organs do not function normally with serious consequences involving multiple organ systems.

The following question refers to the patient's overall HSCT thrombotic microangiopathy (TMA) symptoms.

Clinician Global Impression of Severity in TMA Symptoms

Please choose the response that best describes the overall severity of the patient's TMA symptoms in the past 7 days (week). (Select one response)

- ☐ Normal, no symptoms at all
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

Clinician Global Impression of Severity (CGI-S)_v1.0_14Oct2020

10.12.1.2. Clinician Global Impression of Change

HSCT-TMA Clinician Global Measures
(Clinician Global Impression of Change)

You have diagnosed the patient with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplant (HSCT) [HSCT-TMA]. TMA is a complication of HSCT in which small blood vessels inside many of the patient's body's vital organs do not function normally with serious consequences involving multiple organ systems.

The following question refers to the patient's overall HSCT thrombotic microangiopathy (TMA) symptoms.

Clinician Global Impression of Change in TMA Symptoms

Please select the appropriate box to reflect the magnitude and direction of the change in the patient's TMA symptoms since the baseline visit, based upon your clinical judgment. Compared with how the patient's TMA symptoms were prior to participating in the clinical study, how would you rate their current TMA symptoms:

- ☐ Very Much Worse
- ☐ Much Worse
- ☐ Minimally Worse
- ☐ No Change
- ☐ Minimally Better
- ☐ Much Better
- ☐ Very Much Better

Clinician Global Impression of Change (CGI-C)_v1.0_14Oct2020

10.12.1.3. Patient Global Impression of Severity

HSCT TMA Patient Global Measures
(Patient Global Impression of Severity)

You have been diagnosed by your doctor with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplant (HSCT) [HSCT-TMA]. TMA is a complication of HSCT in which small blood vessels inside many of your body's vital organs do not function normally with serious consequences involving multiple organ systems.

The following question refers to your overall HSCT thrombotic microangiopathy (TMA) symptoms.

Patient Global Impression of Severity in TMA Symptoms

Please choose the response that best describes the overall severity of your TMA symptoms in the past 7 days (week). (Select one response)

- ☐ Normal, no symptoms at all
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

Patient Global Impression of Severity (PGI-S)_v1.0_14Oct2020

10.12.1.4. Patient Global Impression of Change

HSCT TMA Patient Global Measures
(Patient Global Impression of Change)

You have been diagnosed by your doctor with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplant (HSCT) [HSCT-TMA]. TMA is a complication of HSCT in which small blood vessels inside many of your body's vital organs do not function normally with serious consequences involving multiple organ systems.

The following question refers to your overall HSCT thrombotic microangiopathy (TMA) symptoms.

Patient Global Impression of Change in TMA Symptoms

Please think about the overall severity of your TMA symptoms at the start of the clinical study. Compared with how your TMA symptoms were prior to participating in the clinical study, how would you rate your current TMA symptoms: (Select one response)

- ☐ Very Much Worse
- ☐ Much Worse
- ☐ Minimally Worse
- ☐ No Change
- ☐ Minimally Better
- ☐ Much Better
- ☐ Very Much Better

Patient Global Impression of Change (PGI-C)_v1.0_14Oct2020

10.12.1.5. Caregivers Global Impression of Severity

HSCT-TMA Caregiver Global Measures
(Caregiver Global Impression of Severity)

The patient has been diagnosed with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplant (HSCT) [HSCT-TMA]. TMA is a complication of HSCT in which small blood vessels inside many of your body's vital organs do not function normally with serious consequences involving multiple organ systems.

The following question refers to the patient's overall HSCT thrombotic microangiopathy (TMA) symptoms.

Caregiver Global Impression of Severity in TMA Symptoms

Please choose the response that best describes the overall severity of the patient's TMA symptoms in the past 7 days (week). (Select one response)

- ☐ Normal, no symptoms at all
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

Caregiver Global Impression of Severity (CaGI-S)_v1.0_14Oct2020

10.12.1.6. Caregivers Global Impression of Change

HSCT-TMA Caregiver Global Measures
(Caregiver Global Impression of Change)

The patient has been diagnosed with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplant (HSCT) [HSCT-TMA]. TMA is a complication of HSCT in which small blood vessels inside many of your body's vital organs do not function normally with serious consequences involving multiple organ systems.

The following question refers to the patient's overall HSCT thrombotic microangiopathy (TMA) symptoms.

Caregiver Global Impression of Change in TMA Symptoms

Please think about the overall severity of the patient's TMA symptoms at the start of the clinical study. Compared with how the patient's TMA symptoms were prior to participating in the clinical study, how would you rate their current TMA symptoms: (Select one response)

- ☐ Very Much Worse
- ☐ Much Worse
- ☐ Minimally Worse
- ☐ No Change
- ☐ Minimally Better
- ☐ Much Better
- ☐ Very Much Better

Caregiver Global Impression of Change (CaGI-C)_v1.0_14Oct2020

10.12.2. EuroQoL 5-Dimensions 5-Level

10.12.2.1. Participant-Reported



Header to be completed by Study Site	
Study Number: ALXN1210-TMA-313	Subject ID: _____
Date Completed: _____	Time Completed: _____
Completed by: ☐ Patient	

Health Questionnaire

English version for the USA

SAMPLE

USA (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

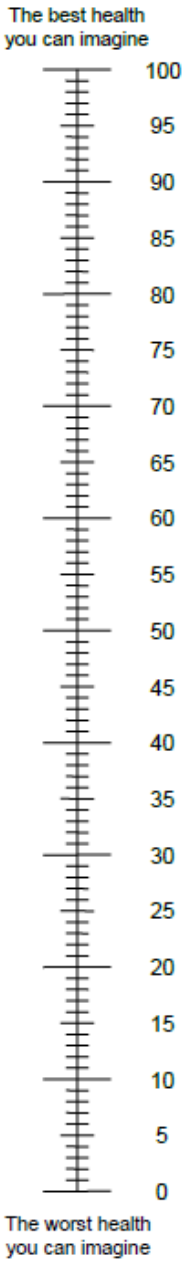
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

SAMPLE

USA (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



SAMPLE

3

USA (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

10.12.2.2. EQ-5D-5L Proxy (version 1)



Health Questionnaire

English version for the USA

Proxy version of the EQ-5D-5L: 1
Asking the proxy to rate how he or she (i.e. the proxy) would rate the subject's health.

© 2015 EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation. USA (English) v1.1

Under each heading, please check the ONE box that best describes (*insert name of person whose health is being assessed, e.g. Mr Smith's or Jane's)* health TODAY.

MOBILITY

No problems walking	❑
Slight problems walking	❑
Moderate problems walking	❑
Severe problems walking	❑
Unable to walk	❑

SELF-CARE

No problems washing or dressing him/herself	❑
Slight problems washing or dressing him/herself	❑
Moderate problems washing or dressing him/herself	❑
Severe problems washing or dressing him/herself	❑
Unable to wash or dress him/herself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

No problems doing his/her usual activities	❑
Slight problems doing his/her usual activities	❑
Moderate problems doing his/her usual activities	❑
Severe problems doing his/her usual activities	❑
Unable to do his/her usual activities	❑

PAIN / DISCOMFORT

No pain or discomfort	❑
Slight pain or discomfort	❑
Moderate pain or discomfort	❑
Severe pain or discomfort	❑
Extreme pain or discomfort	❑

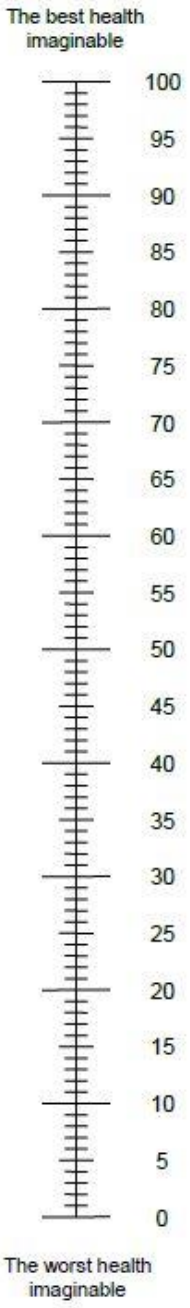
ANXIETY / DEPRESSION

Not anxious or depressed	❑
Slightly anxious or depressed	❑
Moderately anxious or depressed	❑
Severely anxious or depressed	❑
Extremely anxious or depressed	❑

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- We would like to know how good or bad you think the subject's (*insert name of person whose health is being assessed, e.g. Mr Smith's or Jane's*) health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health imaginable.
  0 means the worst health imaginable.
- Mark an X on the scale to indicate how good or bad you think the subject's (*insert name of person whose health is being assessed, e.g. Mr Smith's or Jane's*) health is TODAY.
- Now, please write the number you marked on the scale in the box below.

THE SUBJECT'S HEALTH TODAY = ☐



3

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10.12.3. Short-Form Health Survey 12 Item

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

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3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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6. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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10.12.4. Functional Assessment of Chronic Illness Therapy-Fatigue

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

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10.13. The International Society on Thrombosis and Haemostasis Criteria for Disseminated Intravascular Coagulation

The ISTH Criteria for DIC (Taylor, 2001) will be used for DIC diagnosis in this study.

INSTRUCTIONS Use only in participants with clinical suspicion for DIC (eg, excessive bleeding in the setting of malignancy, severe infection or sepsis, obstetric complications, trauma).

Diagnostic criteria for overt DIC (participant has to have an underlying disorder known to be associated with overt DIC to use this algorithm):

Variable		**Points**
Platelet count, cells × 10^9/L	≥ 100	0
	50 to < 100	1
	< 50	2
Elevated levels of a fibrin-related marker [a] (eg, D-dimer, fibrin degradation products)	No increase	0
	Moderate increase	2
	Severe increase	3
Prolonged PT, seconds	< 3	0
	3 to < 6	1
	≥ 6	2
Fibrinogen level, g/L	≥ 1	0
	< 1	1

[a] Use laboratory-specific cutoff values.

Interpretation

Score	**Diagnosis**
< 5	Not suggestive of overt DIC, may be non-overt DIC; repeat within next 1 to 2 days and manage clinically as appropriate
≥ 5	Compatible with overt DIC; treat for DIC as appropriate and repeat scoring daily

10.14. European Society for Blood and Bone Marrow Transplantation Criteria for Veno-Occlusive Disease

10.14.1. EBMT Criteria for VOD in Children

The EBMT criteria for hepatic SOS/VOD in children (Corbacioglu, 2018) will be used for VOD diagnosis in this study.

- No limitation for time of onset of SOS/VOD.
- The presence of 2 or more of the following (with the exclusion of other potential differential diagnoses):
  - Unexplained consumptive and transfusion-refractory thrombocytopenia (≥ 1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines).
  - Otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics, or a weight gain > 5% above baseline value.
  - Hepatomegaly (best if confirmed by imaging [suggested imaging: ultrasonography, CT, or MRI]) above baseline value.
  - Ascites (best if confirmed by imaging [suggested imaging: ultrasonography, CT, or MRI]) above baseline value.
  - Rising bilirubin from a baseline value on 3 consecutive days, or bilirubin ≥ 2 mg/dL within 72 hours.

10.14.2. EBMT Criteria for VOD in Adults

The EBMT criteria for hepatic SOS/VOD in adults (Mohty, 2016) will be used for VOD diagnosis in this study.

Classical SOS/VOD **In the first 21 days after HSCT**	**Late onset SOS/VOD** **> 21 Days after HSCT**
Bilirubin ≥ 2 mg/dL and two of the following criteria must be present: Painful hepatomegaly Weight gain > 5% Ascites	Classical VOD/SOS beyond Day 21 OR Histologically proven SOS/VOD OR Two or more of the following criteria must be present: Bilirubin ≥ 2 mg/dL (or 34 µmol/L) Painful hepatomegaly Weight gain > 5%

Classical SOS/VOD **In the first 21 days after HSCT**	**Late onset SOS/VOD** **> 21 Days after HSCT**
	Ascites AND Hemodynamical or/and ultrasound evidence of SOS/VOD

These symptoms/signs should not be attributable to other causes.

10.15. Graft Versus Host Disease Grading

The criteria outlined by EBMT, NIH, and the CIBMTR (Schoemans, 2018) will be used for assessing acute GVHD grade in this study. Patients 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.

Grade	Description
I	Rash on ≤ 50% of skin, no liver or gut involvement
II	Rash on > 50% of skin, bilirubin 2-3 mg/dL, or diarrhea 500-1000 mL/day, or persistent nausea
III	Bilirubin 3-15 mg/dL, or gut stage 2-4, diarrhea > 1000 mL/day, or severe abdominal pain with or without ileus
IV	Generalized erythroderma with bullous formation, or bilirubin > 15 mg/dL
Not applicable	Acute GVHD present but cannot be graded

10.16. Country-specific Requirements

10.16.1. China

10.16.1.1. Name and Locations of the Central Laboratories Operating in China

As required by the CBDC, below are the names and the locations of the central laboratories that will be operating in China and could be in contact with "whole blood" samples for this study including vendors involved on sample disposal and transport activities.

Table 20: Name and Locations of the Central Laboratories Operating in China

Company	Address
Central laboratories	• PPD Laboratories (SUZHOU) Co., Ltd. Bld 6, 19 Yong'an Road Xushuguan Town SND, Suzhou, Jiangsu 215151 China • Guangzhou Kingmed Center for Clinical Laboratory Co., Ltd. No.10 Luoxuan 3rd Road Guangzhou International Biotech Island, Guangdong 510005 China
Sample destruction vendor	• Zhangjiagang Huarui Hazard Waste Disposal Center Ranzheng Industry District, Leyu Town, Zhangjiagang, Jiangsu 215621 China
Sample transit vendor	• Federal Express (China) China Limited No.27-37 Axls and Mezzanine, No.1 Warehouse, Aire Cargo Express Centre of Capital Airport, Shunyi District, Beijing 101300 China

Involved Sample:

Type of Sample	Test Content	Test Site	Disposal Plan of Remain Samples
Whole blood	Direct Coombs	Guangzhou Kingmed Center for Clinical Laboratory Co., Ltd.	Collect whole blood from various medical institutions and transport to PPD Laboratories (SUZHOU) Co., Ltd. and then to Guangzhou Kingmed Center for Clinical Laboratory Co., Ltd. for testing by Federal Express (China) China Limited, the remaining samples will be returned to PPD Laboratories (SUZHOU) Co., Ltd. within 1 month by Federal Express (China) China Limited

Type of Sample	Test Content	Test Site	Disposal Plan of Remain Samples
			after testing is completed. The returned samples will be stored at PPD Laboratories (SUZHOU) Co., Ltd. for 14 days, post which they will be destroyed by Zhangjiagang Huarui Hazard Waste Disposal Center.
Whole blood	Hematology	PPD Laboratories (SUZHOU) Co., Ltd	Collect whole blood from various medical institutions and transport it to PPD Laboratories (SUZHOU) Co., Ltd. for testing by Federal Express (China) China Limited. The remaining samples will be stored at PPD Laboratories (SUZHOU) Co., Ltd. for 14 days after testing is completed, then they will be destroyed by Zhangjiagang Huarui Hazard Waste Disposal Center.

10.17. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 5	Global	28 Mar 2024	This substantial amendment incorporated new secondary endpoints of modified TMA response, OS by Day 100, and non-relapse mortality by Day 100.
Amendment 4.1	EU	05 Dec 2023	This non-substantial amendment addressed the requirements for transitioning a clinical study under the EU CTR. Further modifications included non-substantial changes, minor corrections, and harmonized terminology.
Amendment 4	Global	28 Mar 2023	This amendment incorporated a reduction in the study sample size with the possibility of an SSR based on a planned interim analysis (when approximately 50% of participants would complete or would withdraw from the 26-week Treatment Period).
Amendment 3.2	UK	20 Apr 2022	The revisions were made upon MHRA request to remove the option for Investigators in the UK to enroll patients prior to availability of local or central laboratory results from the ST-HUS screen and ADAMTS13 test and update the requirements for pregnancy exposure/lactation mitigations.
Amendment 3.1 (Not implemented)	UK	04 Mar 2022	To include changes to the dosing schedules and instructions for supplemental dosing and remove the requirement for supplemental dosing after CCI [redacted] as done in Protocol Amendment 3, but remove any changes in Protocol Amendment 3 that were not related to the supplemental dosing regimen

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 3	Global	03 Dec 2021	To allow for participants to be enrolled based on local laboratory assessments to align with current practice patterns for management of TMA patients, update eligibility criteria, and modify the supplemental dosing regimen and requirements.
Amendment 2.1	UK	03 Jun 2021	To include COVID-19 risk assessment and COVID-19 vaccine risk assessment language.
Amendment 2	Global	19 Nov 2020	To implement regulatory guidance to change the protocol from an open-label to a double-blind, placebo-controlled study.
Amendment 1.1	Italy	23 Oct 2020	To conform with requests made by the Italian Medicines Agency (AIFA).
Amendment 1	Global	25 Mar 2020	To refine the criteria for TMA response and to remove ravulizumab dose administration on Day 183.
Original protocol	Not applicable	20 Feb 2020	Not applicable.

10.18. 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
aHUS	atypical hemolytic uremic syndrome
ALP	alkaline phosphatase
ALT	alkaline aminotransferase
AST	aspartate transaminase
APTT	activated partial thromboplastin time
AxMP	auxiliary medicinal product
BiPAP	bilevel positive airway pressure
BSC	best supportive care
C5	complement component 5
C5i	complement component 5 inhibitor
CCI [redacted]	
CaGI-C	Caregiver Global Impression of Change
CaGI-S	Caregiver Global Impression of Severity
CBDC	China Biological Development Center
CGI-C	Clinician Global Impression of Change
CGI-S	Clinician Global Impression of Severity
CGT	gamma-glutamyltransferase
CFR	Code of Federal Regulations
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CIF	cumulative incidence function
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
CNI	calcineurin inhibitor
CNS	central nervous system
COA	clinical outcomes assessment

Abbreviation	Definition
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
(e)CRF	(electronic) case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTIS	Clinical Trial Information System
D	day
DIC	disseminated intravascular coagulation
DMC	Data Monitoring Committee
EBMT	European Society for Blood and Bone Marrow Transplantation
ECG	electrocardiogram
ED	early discontinuation
EDC	electronic data capture
EFS	event-free survival
eGFR	estimated glomerular filtration rate
EMLA	eutectic mixture of local anesthetics
EoS	End of Study
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FSH	follicle stimulating hormone
gMG	myasthenia gravis
GI	gastrointestinal
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	global drug safety
GVHD	graft versus host disease
Hib	*Haemophilus influenzae type b*
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HIV	human immunodeficiency virus
HPF	high power field
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormonal replacement therapy
HSCT	hematopoietic stem cell transplant
HSCT-TMA	hematopoietic stem cell transplant-associated thrombotic microangiopathy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDAC	independent data analysis center
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISTH	International Society of Thrombosis and Haemostasis
ITT	intention-to-treat
IV	intravenous(ly)
JAPC	Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MAR	missing-at-random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
MRI	magnetic resonance imaging
N meningitidis	*Neisseria meningitidis*
NIH	National Institutes of Health
NIMP	non-investigational product

Abbreviation	Definition
NMOSD	neuromyelitis optica spectrum disorder
NRI	non-responder imputation
OS	overall survival
P	peak [ie, at the end of IV infusion of dose]
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	Principal Investigator
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PP	Per Protocol
PRES	posterior reversible encephalopathy syndrome
PT	prothrombin time
q8w	every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SF-12	12-Item Short Form Survey
SoA	schedule of activities
SOC	System Organ Class
SOS	sinusoidal obstruction syndrome
SP	Screening Period
SSR	sample size re-estimation
ST-HUS	Shiga toxin-related hemolytic uremic syndrome
SUSAR	suspected unexpected serious adverse reaction
T	trough [ie, predose])
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMA	thrombotic microangiopathy

Abbreviation	Definition
TMF	trial master file
TPE	therapeutic plasma exchange
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
V	visit
VOD	veno-occlusive disease
WOCBP	woman of childbearing potential

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