TITLE PAGE

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

Protocol Number: ALXN1210-TMA-314

AstraZeneca D Code: D9284C00002

Amendment Number: Protocol Amendment 4

Compound: Ravulizumab (Sponsor code ALXN1210)

Study Phase: Phase 3

Brief Title: Ravulizumab in Pediatric Participants with TMA after HSCT

Sponsor Name: Alexion Pharmaceuticals, Inc.

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

Regulatory Agency Identifier Number(s)

IND: 128367

EudraCT: 2020-000761-16

EU CT Number: 2023-507850-33-00

Approval Date: 02 Sep 2024

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

PPD PPD

Alexion Pharmaceuticals, Inc.

Date

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 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 4 (02 Sep 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 incorporates new secondary endpoints of CCI [redacted] overall survival by Day 100, and non-relapse mortality by Day 100. These endpoints were added based on feedback from the healthcare providers as these data are considered clinically meaningful in this patient population and will support the assessment of the efficacy of ravulizumab in participants with HSCT-TMA.

Other updates in this amendment include:

- Modifications from non-substantial Protocol Amendment 3.1, dated 27 Sep 2023 which was released to sites within the EU to address the requirements for transitioning a clinical study under the EU CTR. These changes were also communicated to non-EU sites through Administrative Change Letter 9 (dated 29 Feb 2024).
- Updates from Administrative Change Letters 7, 8, and 10 (dated 04 May 2023, 08 Jun 2023, and 21 May 2024, respectively), which were released after the Protocol Amendment 3.
- Clarifications on other protocol requirements, including but not limited to assessment of acute GVHD status, pregnancy testing, handling of participants with subsequent HSCT.
- Addition of text and medical literature references to support the statement that patients with HSCT-TMA were anticipated to experience more bleeding events and require more CCI [redacted] than patients with other approved indications for ravulizumab, with respect to the dose confirmation analysis.
- The option to perform an interim analysis was introduced. This interim analysis will not impact the progression of the study.

Lastly, minor editorial, grammatical, and formatting changes were made for consistency and clarity. Cross referencing to tables and sections were also corrected throughout the protocol, where necessary.

See the table below for all the updates included in this amendment. The new/updated text is presented in bold:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 3.1 Overview of Objectives and Endpoints	Added secondary endpoint: CCI [redacted] **during the 26-week Treatment Period**	CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
Section 3.2 Definitions of Endpoints Global/as appropriate details regarding these endpoints have been included throughout the protocol.		CCI [redacted]
	Overall survival by Day 100 and non-relapse mortality by Day 100 were added as secondary endpoints.	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.
Global, clarification on "acute" GVHD	All references to grading of GVHD within the protocol have been updated to **acute** GVHD.	Clarification of current protocol requirements that assessment of GVHD refers to acute GVHD and not chronic GVHD.
Section 1.3 SoA, Table 1, and Table 2 Section 5.1 Inclusion Criteria Section 10.2 Clinical Laboratory Tests	Text added in Section 5.1, Inclusion Criterion #6, SoA tables, and Laboratory Assessments Table 8: **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.**	Clarification of current protocol requirements that at timepoints where urine pregnancy tests are needed, a serum pregnancy test can be used instead.
Section 2.3.1 Risk Assessment	Revised language for the potential risk of immunogenicity and mitigation strategy: Potential clinical consequences may include **hypersensitivity, anaphylaxis or related type of reactions, or loss of efficacy**. **Stop medication in the event of any drug-related severe adverse events like systemic hypersensitivity or anaphylaxis.**	Updated language to clarify risk mitigation strategy for the potential risk of immunogenicity.
Section 3.2 Definitions of Endpoints	Footnote added to Table 4: **Schistocytes of ≤ 1% or a result of "none" should be considered the "absence of schistocytes" in alignment with the International Council for Standardization in Hematology recommendations for schistocyte**	Clarification to provide the specific threshold for presence/absence of schistocytes.

Section # and Name	Description of Change	Brief Rationale
	counting (Zini, 2021).	
	CCI [redacted]	CCI [redacted]
Section 4.2.4 CCI [redacted]	New section added: CCI [redacted] **revises the hemolysis criteria to** CCI [redacted] **since, in the clinical setting, LDH is often elevated for other reasons such as infections, malignancy, muscle injury, hepatic or renal disease, heart attack, etc. (Farhana and Lappin, 2024; Merck-Manual, 2024). The threshold of '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.**	CCI [redacted]
Section 4.3.1 Ravulizumab	Text added: ….**as well** as more frequent **bleeding events necessitating** CCI [redacted] **and resulting in faster eculizumab clearance (Jodele, 2014b; Jodele, 2015; Yamada, 2020).**	Added for completeness, in response to a request from the South Korean health authorities following the dose confirmation analysis to provide reference information on the relationship between bleeding events and faster drug clearance.
Section 6.5.2 Hematopoietic Stem Cell Transplant Following Day 1 Section 8.1.6 Hematopoietic Stem Cell Transplant Information	Newly added section to provide guidance on procedures to be followed for participants undergoing one or more additional HSCT procedures following Day 1, including best care options, reporting of AEs and SAEs, handling of vaccinations/antibiotic prophylaxis, and temporary pause in the study intervention. Text added in Section 8.1.6: **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,**	Subsequent HSCT during the study may be required as part of standard of care or in response to a participant's condition. Clarification added that participants can remain in the study at the Investigator's discretion. Efficacy data starting with the date of new HSCT would not be evaluated as part of the primary endpoint analysis due to the impact of transplant conditioning regimens on the laboratory

Section # and Name	Description of Change	Brief Rationale
	and conditioning regimen.	test values of the participant as mentioned in Section 9.4.
Section 6.7 Intervention After the End of the Study	Text updated: Participants will not receive any additional treatment with ravulizumab as part of the protocol after completion of the study or withdrawal from the study, **unless required by local regulations**.	Clarification to comply with local regulations regarding post-study drug access.
Section 7.1 Temporary Interruption of Study Intervention Administration	Added a new section to include guidance on criteria for temporary interruption of study intervention administration.	Clarification added on the procedure for temporary interruption of study intervention as it was not specified in the previous version of the protocol.
Section 7.2 Permanent Discontinuation of Study Intervention	Text added: **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 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. Additional visits after the Safety Follow-up phone call are not required.**	Clarification of current protocol requirements that any enrolled participant later found not to meet eligibility based on laboratory results for the ST-HUS screen and ADAMTS13 activity test must be discontinued and will undergo safety follow-up. This clarification was previously requested by the US FDA.
Section 7.3 Participant Discontinuation/ Withdrawal from the Study	Language was revised to clarify that: • Safety Follow-up call at 8 weeks will only be performed if the participant agrees. • Information on survival status will be collected if allowed by local regulations.	Clarification of current protocol requirement.
Section 8.1.7 Study Intervention Administration	Text added: **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.**	Clarification of current protocol requirements.
	Updated description of analyses sets to clarify that all participants who sign the informed consent will be included in the respective	Clarification of current protocol requirements.

Section # and Name	Description of Change	Brief Rationale
Section 9.3 Populations for Analyses	analysis sets.	
	Justification added for the exclusion criteria of ST-HUS or ADAMTS13 positive test results in this study.	Clarification of current protocol requirements that any enrolled participant later found not to meet eligibility based on laboratory results for the ST-HUS screening and ADAMTS13 activity test must be discontinued and will undergo safety follow-up. This clarification was previously requested by the US FDA.
Section 9.4.1.1 Analyses of Primary Efficacy Endpoint	Language regarding intercurrent event of treatment discontinuation was revised for consistency. Text added: **Sensitivity analyses of TMA response as well as TMA response parameters will be performed using local laboratories, where available, when central laboratories are missing**.	Text updated for consistency of presentation with the adult study (ALXN1210-TMA-313). The details of the analyses will be described in the SAP. Sensitivity analyses added to support the assessment of efficacy of ravulizumab in this population by also using local laboratory data for these common tests which are routinely performed by accredited local laboratories.
Section 9.4.1.2.10 CCI [redacted]	Text added: CCI [redacted] **will be analyzed using the** CCI [redacted] CCI [redacted]	CCI [redacted]
Section 9.5.3 Interim Analysis For Follow-Up Period	Newly added section. Text added: **An interim analysis may be performed to provide interim descriptive analyses, after all participants have completed or withdrawn from the 26-week Treatment Period, prior to the final analysis, for regulatory purposes. The SAP will describe the planned analyses.**	To allow the option to perform an interim analysis.

Section # and Name	Description of Change	Brief Rationale
Global	Minor editorial, grammatical, and formatting changes were made for consistency and clarity. Expansions of abbreviations were deleted in the text and all abbreviations defined in the List of Abbreviations. 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 and adherence to Alexion's style guide.
Updates from Protocol Amendment 3.1 (dated 27 Sep 2023) and Administrative Change Letter 9 (dated 29 Feb 2024)		
TITLE PAGE and Section 1.1 Synopsis	Added regulatory agency identifier numbers. Changed Short Title to **Brief** Title.	To provide information required under EU CTR.
Section 4.4 End of Study Definition	Rephrased the definition of end of study.	To align with EU CTR requirements.
Section 6.2 Preparation/Handling/Storage/ Accountability	Added details on study intervention accountability.	To align with EU CTR requirements.
Section 8.4.4 Regulatory Reporting Requirements for SAEs Section 10.3.5 Unexpected Events	Described reporting requirements and provided definition of unexpected events, respectively.	To align with EU CTR requirements.
Section 1.3 Schedules of Activities Section 8.4.5 and Section 10.4, Medication Error, Drug Abuse, and Drug Misuse	Added rows for continuous monitoring of medication error, drug abuse and misuse to Tables 1 and 2 in the SoA. Provided definition and examples of medication error, drug abuse, and drug misuse and described reporting requirements.	To align with EU CTR requirements.
Section 8.5 Treatment of Overdose	Described reporting requirements.	To align with EU CTR requirements.
Section 10.1.1 Regulatory and Ethical Considerations	Added details on serious breach (including personal data breach) prevention, identification, notification, and impact mitigation.	To align with EU CTR requirements.

Section # and Name	Description of Change	Brief Rationale
Section 10.1.4 Recruitment Strategy	Added new section to describe recruitment strategy for the study.	Updated in accordance with EU CTR.
Section 10.1.5 Data Protection	Described data protection measures to ensure patient identity remains secure	To align with EU CTR requirements.
Section 10.1.7 Data Quality Assurance	Specified document retention period by Investigator to be at least 25 years after study completion and by Alexion to be at least 30 years.	To align with EU CTR requirements.
Updates from Administrative Change Letters 7 (dated 04 May 2023), 8 (08 Jun 2023), and 10 (21 May 2024)		
Section 6.5.1.2 Other Allowed Medication and Therapies	Text added: **For any participant who undergoes one or more additional HSCT procedures following Day 1, the Investigator should contact the Alexion Medical Monitor to discuss best care options for the individual participant and next steps.**	This update was included in the Administrative Change Letter 10, dated 21 May 2024. This change does not affect patient safety, the scope of the investigation or scientific quality of the study. The purpose of this change was to add clarification on the steps to be taken in case subsequent HSCT during the study may be required as part of standard of care or in response to a participant's condition.
Section 2.3.1 Risk Assessment Section 5.1 Inclusion Criteria Section 10.8.2.1 Guidance for Female Participants	Mitigation Strategy section updated for the potential risk of pregnancy exposure/lactation: Added clarification that only highly effective methods of contraception can be utilized for participants in South Korea. Inclusion criterion 6 updated to capture the change that only highly effective methods of contraception can be utilized for participants in South Korea. Updated following statements: Female participants of childbearing potential… (for participants in the UK **and South Korea**, only highly effective methods of contraception	This update was included in the Administrative Change Letter 8, dated 08 Jun 2023. This change does not affect patient safety, the scope of the investigation or scientific quality of the study. The purpose of this change is to clarify contraceptive methods requirements for participants in South Korea that comply with local regulations.

Section # and Name	Description of Change	Brief Rationale
	can be utilized)… Other methods of contraception…… (note, for participants in the UK **and South Korea** only highly effective methods of contraception can be utilized).	
Section 2.3.1 Risk Assessment Section 5.1 Inclusion Criteria Section 8.1.9 Vaccination and Antibiotic Prophylaxis	Mitigation Strategy section updated for the identified risk of meningococcal infection: Participants must be vaccinated …… feasible according to the **national guidelines and recommendations for** immune reconstitution and **vaccination** for HSCT-TMA patients …... **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. Inclusion Criterion 7 updated: 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)**. 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…... **Participants must be administered prophylactic antibiotics for meningococcal infection until at least 2 weeks after vaccination. 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**	This update was included in the Administrative Change Letter 7, dated 04 May 2023.This change does not affect patient safety, the scope of the investigation or scientific quality of the study. The purpose of this change is to revise the language for more clarity on vaccination requirements and the use of prophylaxis against meningococcal infection. In addition, previous language was unclear as the term "institutional" was intended to encompass national as well as local guidelines. To ensure consistency across centers this language clarifies that national guidelines should take precedence over international or local guidelines.

Section # and Name	Description of Change	Brief Rationale
	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*. ….**Sites must** follow the relevant immune reconstitution guidelines…... Vaccination may not be sufficient to prevent meningococcal infection; **therefore, consideration** should be given per **national** guidance…. All participants **mus**t be monitored…….. **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*.** ...***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**.	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

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

Brief Title: Ravulizumab in Pediatric Participants with TMA after HSCT

Regulatory Agency Identifier Number(s):

Registry	Identification
IND	128367
EudraCT	2020-000761-16
EU CT Number	2023-507850-33-00

Rationale:

TMA is a rare, severe, and potentially fatal post-transplant complication of HSCT that presents via endothelial injury and affects the kidney and other organs (Dvorak, 2019; Jodele, 2015; Seaby and Gilbert, 2018). 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 pediatric participants (from ≥ 28 days to < 18 years of age) with HSCT-TMA.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of ravulizumab plus BSC in the treatment of pediatric participants with HSCT-TMA	• TMA response during the 26-week Treatment Period
Secondary	

To characterize TMA response after treatment with ravulizumab	• Time to TMA response during the 26-week Treatment Period
	• TMA response and time to response for each individual component of TMA response during the 26-week Treatment Period
	• Hematologic response during the 26-week Treatment Period
	• Time to hematologic response during the 26-week Treatment Period
	• Hemoglobin response during the 26-week Treatment Period
	• Platelet response during the 26-week Treatment Period
	• Partial response during the 26-week Treatment Period
	• Loss of TMA response during the 26-week Treatment Period
	• Duration of TMA response during the 26-week Treatment Period and through 52 weeks
	• Changes from baseline during the 26-week Treatment Period and through 52 weeks in the following:
	  ○ Haptoglobin
	  ○ Platelets
	  ○ LDH
	  ○ Hemoglobin
	• CCI [redacted] during the 26-week Treatment Period

To assess improvement in organ dysfunction	• Change from baseline in TMA-associated organ dysfunction in renal system, cardiovascular system, pulmonary system, CNS, and GI system through 26 weeks and 52 weeks
To assess TMA relapse	• TMA relapse during the Follow-up Period
To assess overall survival	• Overall survival by Day 100, 26 weeks, and 52 weeks
To assess non-relapse mortality	• Non-relapse mortality by Day 100, during the 26-week Treatment Period and through 52 weeks

Objectives	Endpoints
Pharmacokinetics and Pharmacodynamics	
To assess PK/PD of ravulizumab in pediatric participants with HSCT-TMA	• Serum concentrations of ravulizumab over time • Changes in serum free C5 concentrations over time • Changes in serum total C5 concentrations over time
Safety	
To characterize the safety profile of ravulizumab plus BSC in pediatric participants with HSCT-TMA	• Incidence of treatment-emergent AEs and treatment-emergent SAEs • Changes from baseline in vital signs and laboratory parameters • Incidence of ADAs and assessment of immunogenicity

Overall Design Synopsis:

This study will be an open-label, single-arm, multicenter study to evaluate the safety, efficacy, PK, and PD of ravulizumab administered by IV infusion to pediatric participants, from ≥ 28 days to < 18 years of age, with HSCT-TMA. Eligible participants are those who received HSCT within 12 months prior to Screening and subsequently developed TMA that does not resolve within 72 hours after withdrawal or adjustment of any TMA-associated medication and/or treatment of any associated underlying triggering condition.

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

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

Weight[a]	Loading Phase Doses			Maintenance Doses
	Day 1	Day 5	Day 10	Starting Day 15
5 to < 10 kg	600 mg	300 mg	300 mg	400 mg q4w
10 to < 20 kg	600 mg	300 mg	300 mg	800 mg q4w
20 to < 30 kg	900 mg	300 mg	300 mg	2100 mg q8w
30 to < 40 kg	1200 mg	300 mg	300 mg	2700 mg q8w
40 to < 60 kg	2400 mg	600 mg	600 mg	3000 mg q8w
60 to < 100 kg	2700 mg	900 mg	900 mg	3300 mg q8w

Weight[a]	Loading Phase Doses			Maintenance Doses
	Day 1	Day 5	Day 10	Starting Day 15
≥ 100 kg	3000 mg	900 mg	900 mg	3600 mg q8w
CCI [redacted]				

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

For all participants, the need for a supplemental dose of ravulizumab following CCI [redacted] (ie, CCI [redacted] supplemental dosing) will be assessed when the participant reaches CC CCI [redacted]; the specific study days when these assessments must be made are described in Section 8.1.7.2.1.1 (see also Table 1). For participants with body weight CCI [redacted] kg, a CCI [redacted] supplemental dose must be administered if the participant CCI [redacted] since the last maintenance dose. For participants with body weight CCI [redacted] kg or with body weight CCI [redacted] kg, a clinical algorithm must be followed to assess the need for CCI [redacted] supplemental dosing (see Section 8.1.7.2.1.2).

In addition, for all participants, supplemental doses of ravulizumab will be allowed on an individual case basis for demonstrated clinical worsening (assessed and agreed upon by the Investigator and Alexion Medical Monitor).

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

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

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

Disclosure Statement: This is an open-label study with 1 treatment group.

Number of Participants:

Approximately 40 participants will be enrolled and treated in the study. A minimum of 5 participants ≥ 28 days to < 2 years of age, 10 participants ≥ 2 years to < 12 years of age, and 10 participants ≥ 12 years to < 18 years of age are planned to be enrolled.

Intervention Groups and Duration:

All participants will receive ravulizumab in addition to BSC.

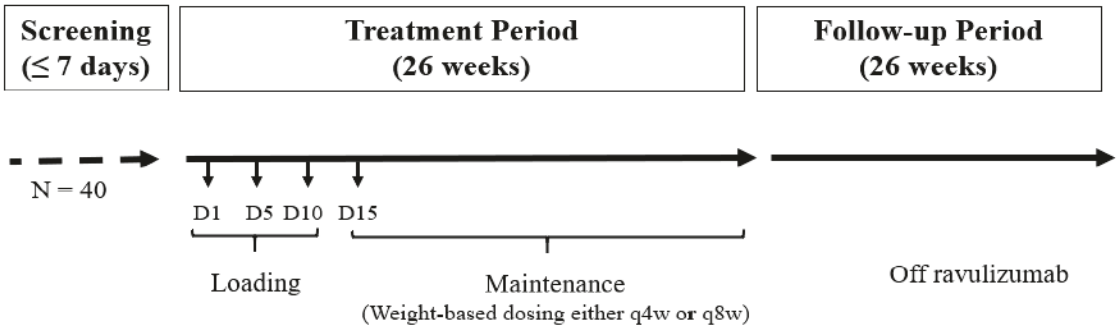
For each participant, the expected duration of study participation will be up to 53 weeks. This includes the Screening Period (up to 1 week), the Treatment Period (26 weeks), and the

Follow-up Period (26 weeks). For participants who discontinue study early, a Safety Follow-up phone call will be performed 8 weeks after the last dose of ravulizumab.

Data Monitoring Committee: Yes

1.2. Schema

Figure 1: Study Design Schematic



	Loading			Maintenance
5 to < 10 kg	D1 = 600 mg	D5 = 300 mg	D10 = 300 mg	400 mg q4w
10 to < 20 kg	D1 = 600 mg	D5 = 300 mg	D10 = 300 mg	800 mg q4w
20 to < 30 kg	D1 = 900 mg	D5 = 300 mg	D10 = 300 mg	2100 mg q8w
30 to < 40 kg	D1 = 1200 mg	D5 = 300 mg	D10 = 300 mg	2700 mg q8w
40 to < 60 kg	D1 = 2400 mg	D5 = 600 mg	D10 = 600 mg	3000 mg q8w
60 to < 100 kg	D1 = 2700 mg	D5 = 900 mg	D10 = 900 mg	3300 mg q8w
≥ 100 kg	D1 = 3000 mg	D5 = 900 mg	D10 = 900 mg	3600 mg q8w

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.

1.3. Schedules of Activities

The schedule of study visits and assessments from Screening through completion of the 26-week Treatment Period is presented in Table 1. The schedule of study visits and assessments for the Follow-up Period is presented in Table 2.

Table 1: Schedule of Activities – Screening and Treatment Period

	SP	Treatment Period													Note
Visit		**V 1**	**V 2**	**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 study early. After ED, if the participant agrees, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab to collect AEs and concomitant medication information.**
Days	**≤7 days**	**D 1**	**D 5**	**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															
Inclusion/ Exclusion criteria	X															Confirm eligibility prior to 1st dose of ravulizumab[a]
Medical history	X															
HSCT information	X															
Transfusion history	X															Section 8.1.8
Demographics	X															
Weight and height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV-1and HIV-2 Test	X															Test at Screening or documented negative test within 6 months before Screening
ADAMTS13[a, b]	X															
ST-HUS screen[a, b]	X															

Table 1: Schedule of Activities – Screening and Treatment Period

	SP	Treatment Period													Note
Visit		**V 1**	**V 2**	**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 study early. After ED, if the participant agrees, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab to collect AEs and concomitant medication information.**
Days	**≤7 days**	**D 1**	**D 5**	**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**	
Coombs test, direct	X															
Pregnancy test (WOCBP only)	X	X	X	X	X					X			X		X	Serum pregnancy test at Screening and EoS/ED Visit. Urine pregnancy test at all other timepoints. Additional urine testing when deemed necessary by the Investigator[c]
Acute GVHD status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 10.14
PedsQL	X						X					X			X	For participants ≥ 2 years of age
Dispense participant safety card	X															Instruct participants to carry safety card at all times and bring it to scheduled visits
Review participant safety card		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
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Perform complete physical examination at Screening and Day 183; abbreviated physical examination at all other visits
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	2 consecutive blood pressure measurements obtained one minute apart are required at Screening; one measurement at all other visits.

Table 1: Schedule of Activities – Screening and Treatment Period

	SP	Treatment Period													Note
Visit		**V 1**	**V 2**	**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 study early. After ED, if the participant agrees, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab to collect AEs and concomitant medication information.**
Days	**≤7 days**	**D 1**	**D 5**	**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**	
																Vital signs will be collected predose and postdose at ravulizumab dosing visits.
ECG	X														X	
Chest X-ray or CT-Chest	X														X	Section 8.3.4
Echocardiogram	X														X	
Clinical laboratory tests[c, d]	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 10.2
Prior medications and procedures	X															
Prophylactic antibiotic treatment	Continuous coverage															Refer to Section 8.1.9 for recommendations on prophylactic antibiotics and vaccinations
Concomitant medications and procedures	Continuous monitoring															
Transfusion requirements	Continuous monitoring															Refer to Section 8.1.8 for instruction

Table 1: Schedule of Activities – Screening and Treatment Period

	SP	Treatment Period													Note
Visit		**V 1**	**V 2**	**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 study early. After ED, if the participant agrees, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab to collect AEs and concomitant medication information.**
Days	**≤7 days**	**D 1**	**D 5**	**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**	
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																
CCI	CCI															CCI CCI Refer to Section 8.6.1 for detailed instruction.
CCI	CCI															

Table 1: Schedule of Activities – Screening and Treatment Period

	SP	Treatment Period													Note
Visit		V 1	V 2	V3	V4	V5	V6	V7	V8	V9	V1 0	V1 1	V12	V13	V14	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if participants discontinue study early. After ED, if the participant agrees, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab to collect AEs and concomitant medication information.**
Days	≤7 days	D 1	D 5	D1 0	D1 5	D2 1	D2 9	D4 3	D5 7	D7 1	D8 5	D9 9	D12 7	D15 5	D18 3	
Window (days)			-1	-1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	
CCI	CCI															CCI
CCI	CCI															
Biomarker/Future Biomarker Research																
Plasma and urine[c] samples for CCI	CCI															CCI
Plasma and urine [c] samples for CCI	CCI															

Table 1: Schedule of Activities – Screening and Treatment Period

	SP	Treatment Period													Note
Visit		**V 1**	**V 2**	**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 study early. After ED, if the participant agrees, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab to collect AEs and concomitant medication information.**
Days	**≤7 days**	**D 1**	**D 5**	**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**	
Blood and urine[c] samples for exploratory biomarker analysis CCI	CCI															CCI
Blood and urine[c] samples for exploratory biomarker analysis CCI	CCI															
Blood and buccal swab sample for genetics analysis[g]	CCI															One blood and one buccal swab sample are to be collected at any visit.
Administration of Study Intervention																
Ravulizumab CCI	CCI															Administer after all other required tests/procedures have been completed, except postdose sample collections.

Table 1: Schedule of Activities – Screening and Treatment Period

	SP	Treatment Period													Note
Visit		**V 1**	**V 2**	**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 study early. After ED, if the participant agrees, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab to collect AEs and concomitant medication information.**
Days	**≤7 days**	**D 1**	**D 5**	**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**	
Ravulizumab CCI	CCI															
Supplemental dosing of ravulizumab CCI	CCI															The need for CCI supplemental dosing must be assessed per criteria in Section 8.1.7.2.1.2 at CCI CCI CCI The supplemental dose must be administered within the same window noted above. 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.
Supplemental dosing of ravulizumab CCI	CCI															The need for CCI supplemental dosing must be assessed per criteria in Section 8.1.7.2.1.2 at CCI CCI The supplemental dose must be administered within the same window noted above. 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

Table 1: Schedule of Activities – Screening and Treatment Period

	SP	Treatment Period													Note
Visit		**V 1**	**V 2**	**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 study early. After ED, if the participant agrees, a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab to collect AEs and concomitant medication information.**
Days	**≤7 days**	**D 1**	**D 5**	**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**	
																these visits, as displayed within the SoA, will remain unchanged.
Supplemental dosing of ravulizumab CCI	CCI															The need for CCI supplemental dosing must be assessed per criteria in Section 8.1.7.2.1.2 at CCI CCI The supplemental dose must be administered within the same window noted above. 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] 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] 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.

[c] For participants unable to produce sufficient amounts of urine, urine samples may be collected using a catheter. 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.

[d] Clinical laboratory samples should be taken predose during dosing days.

Table 1: Schedule of Activities – Screening and Treatment Period

[e] In the event a supplemental dose is administered at a non-dosing visit, pre- (T) and post- (P) dose samples should be collected instead of the any time (X) sample.
[f] It is acceptable to collect postdose urine samples for biomarkers evaluation provided that the exact postdose timing of sample collection is recorded.
[g] These samples are optional. It should only be collected from participants who consent to DNA collection.
[h] CCI [redacted]
[i] For participants with body weight CCI kg, additional unscheduled visits may be required for supplemental dosing administration required after CCI

Table 2: Schedule of Activities – Follow-up Period

	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.**
Days (Window ± 7 days)	**D239**	**D295**	**D365 (EoS)/ED[a]**	
General Assessments/Procedures				
Weight and height	X	X	X	
Pregnancy Test (WOCBP only)			X	Serum test at EoS/ED. Additional urine testing when deemed necessary by the Investigator[b]
Acute GVHD status	X	X	X	Section 10.14
PedsQL	X		X	For participants ≥ 2 years of age
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		X	
Chest X-ray or CT-chest			X	Section 8.3.4
Echocardiogram			X	
Clinical laboratory tests	X	X	X	Hematology, chemistry, and urinalysis/urine chemistry as described in Section 10.2[b]
Review 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
Survival status	Continuous monitoring			
Monitor for PRES	Continuous monitoring			Monitor at every visit for the development of seizures, headache, altered mental status and/or visual loss

Table 2: Schedule of Activities – Follow-up Period

	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.**
Days (Window ± 7 days)	**D239**	**D295**	**D365 (EoS)/ED[a]**	
Prophylactic antibiotics treatment	Continuous coverage			Refer to Section 8.1.9 for recommendations on prophylactic antibiotics and vaccinations
Concomitant medications and procedures	Continuous monitoring			
Transfusion requirements	Continuous monitoring			Refer to Section 8.1.8 for instruction
AE	Continuous monitoring			
Medication error, drug abuse and misuse	Continuous monitoring			
Medical resource utilization	Continuous monitoring			
Pharmacokinetic and Pharmacodynamic Assessments				
CCI				CCI Refer to Section 8.6.1 for detailed instruction
CCI				
Biomarker/Future Biomarker Research				
CCI				
CCI				

[a] If necessary (for requirements see Section 4.1), a Safety Follow-up phone call will be performed 8 weeks after administration of the last dose of ravulizumab to collect AEs and concomitant medication information.

[b] For participants unable to produce sufficient amounts of urine, urine samples may be collected using a catheter. 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.

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 pediatric patients with HSCT-TMA.

Complement has been shown to play 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 pediatric 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 rare, severe, and potentially fatal post-transplant complication of HSCT that may affect 10% to 35% of HSCT recipients (Dvorak, 2019; Jodele, 2015; Seaby and Gilbert, 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% overall survival 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).

In pediatric patients, HSCT-TMA typically occurs early post allogeneic HSCT, with a median diagnosis at 35 to 47 days post-HSCT, and 88% to 92% occurring before Day +100. However, cases have been reported up to 2 years post-HSCT. Autologous recipients may develop HSCT-TMA even earlier, with a median of 18 days post-HSCT (Dvorak, 2019).

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 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 and Gilbert, 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 CCI 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 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 terminal complement complex via CCI 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 q8w. Ravulizumab, at a weight-based dosing regimen, is approved in multiple global regions for treatment of adult patients with PNH and adult and pediatric patients with aHUS. A detailed description of the chemistry, pharmacology, efficacy, and safety of ravulizumab is provided in the IB.

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 *Neisseria meningitidis*. Specific risk mitigation measures available to support the safe use of ravulizumab in participants in this study are described in Table 3.

As with any therapeutic protein, administration of ravulizumab may lead to the development of 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 10.5.

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. COVID-19 risk assessment is described in Section 10.6 and vaccination risk 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 IB or local product labeling.

Table 3: 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 *Neisseria 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 related to the mechanism of action	Increased awareness of healthcare professionals and participants about the potential risk of serious infection. Monitoring for signs and symptoms of

Table 3: Potential Risks and Mitigation Strategies

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	of ravulizumab, the mechanism that may lead to other serious infection in participants treated with ravulizumab remains unclear.	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 and South Korea) for a period of 8 months following the final dose of ravulizumab; for participants in the UK and South Korea, 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 pediatric or adult patients with HSCT-TMA, it represents an appropriate candidate for investigation due to the reported effectiveness of complement inhibition with eculizumab in 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.

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 Objective and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of ravulizumab plus BSC in the treatment of pediatric participants with HSCT-TMA	• TMA response during the 26-week Treatment Period
Secondary	

To characterize TMA response after treatment with ravulizumab	• Time to TMA response during the 26-week Treatment Period
	• TMA response and time to response for each individual component of TMA response during the 26-week Treatment Period
	• Hematologic response during the 26-week Treatment Period
	• Time to hematologic response during the 26-week Treatment Period
	• Hemoglobin response during the 26-week Treatment Period
	• Platelet response during the 26-week Treatment Period
	• Partial response during the 26-week Treatment Period
	• Loss of TMA response during the 26-week Treatment Period
	• Duration of TMA response during the 26-week Treatment Period and through 52 weeks
	• Changes from baseline during the 26-week Treatment Period and through 52 weeks in the following:
	  ○ Haptoglobin
	  ○ Platelets
	  ○ LDH
	  ○ Hemoglobin
	• CCI [redacted] during the 26-week Treatment Period

To assess improvement in organ dysfunction	• Change from baseline in TMA-associated organ dysfunction[a] in renal system, cardiovascular system, pulmonary system, CNS, and GI system through 26 weeks and 52 weeks
To assess TMA relapse	• TMA relapse during the Follow-up Period

Objectives	Endpoints
To assess overall survival	• Overall survival by Day 100, 26 weeks, and 52 weeks
To assess non-relapse mortality	• Non-relapse mortality by Day 100, during the 26-week Treatment Period and through 52 weeks
Pharmacokinetics and Pharmacodynamics	
To assess PK/PD of ravulizumab in pediatric participants with HSCT-TMA	• Serum concentrations of ravulizumab over time • Changes in serum free C5 concentrations over time • Changes in serum total C5 concentrations over time
Safety	
To characterize the safety profile of ravulizumab plus BSC in pediatric participants with HSCT-TMA	• Incidence of treatment-emergent AEs and treatment-emergent SAEs • Changes from baseline in vital signs and laboratory parameters • Incidence of ADAs and assessment of immunogenicity
Exploratory	
To assess biomarkers in pediatric 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]
To assess improvement in QoL patient-reported outcomes in pediatric participants with HSCT-TMA	• Change from baseline in QoL as measured by PedsQL
To describe health resource utilization in pediatric participants with HSCT-TMA	• Number, reason, and duration of hospitalizations (including stays in intensive care unit) • CCI [redacted] • Number of outpatient medical encounters (including physician or emergency room visits) and the underlying reason
To assess complement pathway genetic mutations in pediatric participants with HSCT-TMA	• Incidence of specific complement dysregulation-related mutations

[a] Organ dysfunction is defined in Section 8.2.2.4.

3.2. Definitions of Endpoints

TMA Response

For TMA response (defined in Table 4), 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 (details provided in the SAP).

Table 4: Overview of Thrombotic Microangiopathy Response

		TMA Response Parameter
TMA response	Hematologic response	If baseline platelet count ≤ 50000/mm^3, all of 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, all of 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

[a] Schistocytes of ≤ 1% or a result of "none" should be considered the "absence of schistocytes" in alignment with the International Council for Standardization in Hematology recommendations for schistocyte counting (Zini, 2021).

CCI

CCI (defined in Table 5), participants must CCI response criterion, CCI at 2 separate assessments obtained at least 24 hours apart, and any measurement in between (details provided in the SAP).

Table 5: Overview of CCI

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

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

Hematologic Response

The predetermined criteria for hematologic response are provided in Table 4.

Hemoglobin Response

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

Platelet Response

Platelet response is defined as follows (see also Table 4):

If baseline platelet count ≤ 50000/mm^3, all of 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, all of the following criteria must be met:

- ≥ 50% increase in platelet count compared to baseline value without platelet transfusion support during the prior 7 days

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.

Partial Response

Partial response is when the participant meets ≥ 1, but not all, criteria for TMA response as defined in Table 4.

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 that 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 will be an open-label, single-arm, multicenter study to evaluate the safety, efficacy, PK, and PD of ravulizumab administered by IV infusion to pediatric participants, from ≥ 28 days to < 18 years of age, with HSCT-TMA. Eligible participants are those who received HSCT within 12 months prior to Screening and subsequently developed TMA that does not resolve within 72 hours after withdrawal or adjustment of any TMA-associated medication and/or treatment of any associated underlying triggering condition. The study plans to enroll approximately 40 participants, with at least 35 participants evaluable for the primary analysis. A minimum of 5 participants ≥ 28 days to < 2 years of age, 10 participants ≥ 2 years to < 12 years of age, and 10 participants ≥ 12 years to < 18 years of age are planned to be enrolled.

The study will consist of 3 periods:

- A Screening Period of up to 7 days
- A 26-week Treatment Period
- A 26-week Follow-up Period

Participants will receive weight-based dosages as shown in Figure 1 for 26 weeks during the Treatment Period. Participants will receive loading doses of ravulizumab IV on Day 1, Day 5 and Day 10 followed by maintenance dosing of ravulizumab IV on Day 15 and q8w thereafter for participants weighing CCI kg, or q4w for participants weighing CCI kg. All participants will receive BSC for the duration of the study.

For all participants, the need for a CCI supplemental dose of ravulizumab will be assessed when the participant reaches CCI the specific study days when these assessments must be made are described in Section 8.1.7.2.1.1 (see also Table 1). For participants with body weight CCI kg, a CCI supplemental dose must be administered if the participant CCI since the last maintenance dose. For participants with body weight CCI kg or with body weight CCI kg, a clinical algorithm must be followed to assess the need for CCI supplemental dosing (see Section 8.1.7.2.1.2). In addition, for all participants, supplemental doses of ravulizumab will be allowed on an individual case basis for demonstrated clinical worsening (assessed and agreed upon by the Investigator and Alexion Medical Monitor). Details on supplemental dosing in these situations are provided in Section 8.1.7.2.

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 case of clinical need for extended treatment (for example, if a participant starts to exhibit TMA response late in the Treatment Period), the Investigator and the Alexion Medical Monitor may mutually agree on additional dosing into the Follow-up Period based on the weight-based dosing regimen.

Participants who discontinue ravulizumab 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.

For participants who discontinue study early or participants who are administered ravulizumab during the Follow-up Period, if the participant agrees, a Safety Follow-up phone call will be performed 8 weeks after the last dose of ravulizumab to collect information on concomitant medications, nonpharmacological therapies and procedures, and AEs (Section 1.3).

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

4.1.1. Dose Confirmation Analysis

Preliminary PK/PD data from the first 10 participants (including at least 3 participants CCI kg) will be analyzed to confirm that the initial weight-based ravulizumab dosing regimen and CCI supplemental dosing achieve and maintain complete terminal complement inhibition throughout the dosing interval. Once at least 10 participants have completed Visit 5 on Day 21, the enrollment into the study will be paused.

The DCA will be initiated when 10 participants complete Visit 5 on Day 21. Pharmacokinetic and free C5 data collected in all participants at this time will be analyzed and may result in a dosing regimen and/or CCI supplemental dosing change. Several analyses may be conducted prior to 10 participants completing Visit 5 at Day 21 as part of the DCA to support adjustments to the dosing regimen and/or the CCI supplemental dosing for ongoing participants. Alexion may also determine that additional participants may need to be enrolled either prior to the DCA (eg, if distribution of the initial 10 is not optimal) or after the analysis if the dosing regimen cannot be confirmed. 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.

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 are no approved therapies for pediatric patients with HSCT-TMA, and standard of care consists of treatment of any underlying conditions and supportive measures, the potential efficacy and safety of ravulizumab is being assessed in a single-arm, open-label study.

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 2 to 3 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 1 patient showing end organ recovery at 4 weeks after treatment (Jan, 2019).

4.2.2. Rationale for Primary Endpoint

Thrombotic microangiopathy response is considered a suitable primary endpoint since it 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).

It is expected that 26 weeks of treatment with ravulizumab will provide participants who will respond to complement inhibition sufficient time to achieve TMA response, defined as meeting all of the criteria in Table 4.

It is estimated that the rate of response with supportive care measurements is approximately 30%. This assumption is based on the rate of responses reported in several retrospective studies with supportive care interventions. For example, among patients with HSCT-TMA in whom immunosuppressant was withdrawn, hematologic resolution occurred in only 28% (95% CI, 19% to 37%), and for patients who were switched to a different CNI, hematologic resolution was achieved in only 29% (95% CI, 20% to 37%) (Li, 2019). Regarding the use of plasma exchange, studies in the past 15 years have reported a highly variable response rate ranging from 27% to 80% and a high mortality rate ranging from 44% to 100% (Khosla, 2018). Response rates with the use of defibrotide alone or in combination with plasma exchange are reported to be around 25%, similar to those reported with plasma exchange and rituximab (Bohl, 2017; Elemary, 2019). Neither defibrotide nor rituximab are approved therapies for HSCT-TMA.

Based on the above reported experience with supportive care measurements, the reported experience with eculizumab in HSCT-TMA, (Bohl, 2017; Jodele, 2020; Schoettler, 2019), and feedback from expert physicians, it is expected that an increase of 25% in response rates over the assumed 30% response for the supportive care measures would be a medically important benefit for patients with HSCT-TMA. The planned study sample size of approximately 40 participants yields an adequate precision level for the primary analysis that would be reflected by a half-width of 0.162 for a 95% CI of the proportion of participants with a TMA response, assuming a proportion of response of 0.55.

Complete resolution of proteinuria, although ideal, may not be possible in some patients with HSCT-TMA due to the presence of underlying factors such as: nephrotoxicity of medications used as part of treatment of the underlying disease; pretransplant conditioning and/or management of transplant-related complications such as infections or GVHD (eg, CNIs and

cyclosporine). It is considered that a reduction of at least 50% in proteinuria from baseline will provide significant benefit to patients with HSCT-TMA by minimizing the risk of progression to end stage kidney disease. This assumption is supported by published results from studies assessing factors associated with development of end stage renal disease in patients with nephropathy with or without diabetes. These studies have shown that early changes in proteinuria are predictive of long-term renal outcomes (Bakris, 2008). Notably, in patients with nephropathy without diabetes (1094 African American participants with hypertensive renal disease), change in proteinuria at 6 months predicted subsequent risk for end stage renal disease. This relationship extended to patients with baseline urinary protein excretion < 300 mg/dL. A 50% reduction in proteinuria at 6 months was associated with a 72% reduction in risk for end stage renal disease at 5 years (Lea, 2005).

4.2.3. Rationale for Secondary Endpoints

Time to achieve TMA response in participants who meet the response criteria as defined in Section 3 will provide prescribers with additional guidance to evaluate and characterize the efficacy of ravulizumab treatment. Resolution of the different TMA components may occur at different time points after treatment initiation, and some participants may experience partial response. Therefore, additional secondary endpoints including the proportion of participants that achieve the individual components of the TMA response definition, as well as the time to achieve each of them, will be evaluated to fully characterize the potential benefit of ravulizumab treatment. The proportion of participants that achieve hematological response will also be assessed.

Since HSCT-TMA is a multisystem complication, in addition to kidney involvement, participants may experience various degrees of organ involvement in different body systems (eg, renal system, cardiovascular system, pulmonary system, GI system, and CNS). Therefore, a secondary endpoint on changes from baseline in organ dysfunction at 6 months and 1 year will also be assessed (definition of organ dysfunction is provided in Section 8.2.2.4).

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 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. CCI [redacted]

CCI [redacted] revises the hemolysis criteria to CCI [redacted] from baseline and CCI [redacted]' since, in the clinical setting, LDH is often elevated for other reasons such as infections, malignancy, muscle injury, hepatic or renal disease, heart attack, etc. (Farhana and Lappin, 2024; Merck-Manual, 2024). The threshold of CCI [redacted] CCI [redacted] 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.

Prior to initiation of the ALXN1210-TMA-313 or ALXN1210-TMA-314 studies, clinical ravulizumab data were not available in patients with HSCT-TMA. Studies of eculizumab in patients with severe HSCT-TMA indicated the need for higher and more frequent doses in this population than the currently approved eculizumab dosing regimen. 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, 2014b; Jodele, 2015; Yamada, 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 aHUS and PNH patients 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 dose regimen and supplemental dosing regimen will be confirmed using PK/PD data from 10 participants 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. Alexion may determine that additional participants may need to be enrolled either prior to the DCA (eg, if distribution of the initial 10 is not optimal) or after the analysis if the dosing regimen cannot be confirmed. Additionally, several analyses may be conducted prior to 10 participants completing Visit 5 at Day 21 as part of the DCA to support adjustments to the dosing regimen and/or the CCI supplemental dosing for ongoing participants. The PK and PD of ravulizumab in patients with aHUS is currently characterized from data in 85 pediatric and adult patients with aHUS.

Literature (Jodele, 2016; Mizuno, 2022) has cautioned that pediatric patients with HSCT-TMA may have a mixed response, where, following treatment with a C5 inhibitor, some patients have a good response and others do not. The literature has suggested that individual increased drug clearance (ie, reduced exposure) may be responsible for poor response. The DCA for this study (N = [redacted]) and related dose simulations demonstrated that [redacted] out of [redacted] pediatric participants required a CCI dose of ravulizumab because they had CCI compared to the other [redacted] participants in the DCA. Therefore, a CCI dose is required to provide CCI providing the opportunity for this CCI to CCI CCI In addition, a clinical algorithm will be used to monitor the participants.

4.3.2. Supplemental Dosing

Supplemental doses of ravulizumab will be administered to participants who receive CCI CCI to address the anticipated CCI CCI CCI The need for CCI supplemental doses of ravulizumab will be determined when the participant reaches CCI. The specific study days when these assessments must be made are described in Section 8.1.7.2.1.1 (see also Table 1). Section 8.1.7.2.1.2 details the methodology for assessing whether a CCI CCI supplemental dose is required. In addition, supplemental doses will be administered to participants who receive ravulizumab and demonstrate clinical worsening as defined in Section 8.1.7.2, after discussion with the Alexion Medical Monitor.

Supplemental dosing of ravulizumab has been determined through model-assisted simulation to CCI the target threshold for complete terminal complement inhibition when patients received CCI For supplemental dosing CCI CCI, DCA results suggest that a subpopulation of HSCT-TMA pediatric patients have a CCI and thus require CCI dose of ravulizumab to CCI than expected CCI in these patients.

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 (Section 7.3) in the study globally.

5. STUDY POPULATION

- Approximately 40 treated pediatric participants with HSCT-TMA are planned to be enrolled for this study.
- Participants will be enrolled and assigned to treatment with ravulizumab at approximately 65 investigative sites globally.
- 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 to ensure consistency in ST-HUS testing globally; 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 following enrollment will not be counted towards the total sample size as described in Section 9.2.
- Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible for enrollment in the study only if they satisfy all of the following criteria:

Age

1. Participant must be ≥ 28 days of age up to < 18 years of age at the time of signing the informed consent or assent form.

Type of Participant and Disease Characteristics

2. Pediatric participants who received HSCT within the past 12 months at the time of Screening.
3. Participants must have HSCT-TMA that persists for at least 72 hours after initial management of any triggering agent/condition (including withdrawal or dose reduction of the triggering agent [eg, CNIs]; treatment of any underlying infection; or 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 or transfusion refractoriness, 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 post-transfusion
   b. Any one of the following markers of hemolysis:
      – LDH > ULN for age;
      – Presence of schistocytes ≥ 2 HPF or ≥ 1% in peripheral blood smear;
   c. Proteinuria on spot urinalysis where proteinuria is defined as protein/creatinine ratio ≥ 1 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 transfusions 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) Systolic or diastolic blood pressure that is ≥ 95th percentile for age, sex, and height on 2 consecutive measurements taken 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 ≥ 5 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 10.8.2.2) during the Treatment Period and for at least 8 months after the final dose of ravulizumab 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 10.8.1).

  OR

  – Is a WOCBP and using a highly effective or acceptable contraceptive method (except in the UK and South Korea) as described in Section 10.8.2.1 during the Treatment Period and for at least 8 months (generally 5.5 terminal half-lives) after the final dose of ravulizumab; for participants in the UK and South Korea, 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 ravulizumab. A WOCBP must have a negative serum pregnancy test at Screening and a negative urine pregnancy test before the first dose of ravulizumab. 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 ravulizumab administration are described in Section 10.2. 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 must be re-vaccinated against *Haemophilus influenzae type b (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 ravulizumab.

Informed Consent

8. Participants or their legally authorized representative must be capable of giving signed informed consent or assent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent or assent form 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 judgment of the Investigator, utilizing the ISTH scoring criteria outlined in Section 10.12.
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 10.13.
7. HIV infection evidenced by a positive HIV-1 or HIV-2 antibody titer. A documented negative HIV-1/HIV-2 test within 6 months prior to Screening is 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 1 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 Medical Monitor, 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 (eg, active hepatitis).
13. Respiratory failure from any cause requiring mechanical ventilation (including intubation, bilevel positive airway pressure [BiPAP], or continuous positive airway pressure [CPAP]) within 72 hours prior to enrollment.

Prior/Concomitant Therapy

14. Previously or currently treated with a complement inhibitor.

Prior/Concurrent Clinical Study Experience

15. 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. 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 Intervention(s) Administered

Refer to Section 1.3 SoA for ravulizumab dosing schedules and Section 8.1.7 for detailed dosing instructions. Detailed description of the study intervention is provided in the Pharmacy Manual.

Intervention Name	Ravulizumab
Type	Biologic
Dose Formulation	Vial
Unit Dose Strength(s)	300 mg (10 mg/mL concentrated solution)
Dosage Level(s)	Weight-based dosing[a]
Route of Administration	IV infusion
Use	Experimental
IMP or AxMP	IMP
Sourcing	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.

[a] Detailed information of ravulizumab dosing regimen is provided in Section 8.1.7.

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

Not applicable since the study will be conducted in an open-label manner and no randomization will be performed.

6.4. Study Intervention Compliance

During this study, participants will receive all ravulizumab dosing 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 CRFs. The dose of ravulizumab and study participant identification will be confirmed at the time of dosing 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

6.5.1.1. Best Supportive Care for HSCT-TMA

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] (Section 8.1.7.2).
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.

6.5.1.2. Other Allowed Medication and Therapies

- Supportive care for underlying conditions (eg, HSCT, GVHD) is permitted during the course of the study. For any participant who undergoes one or more additional HSCT procedures following Day 1, the Investigator should contact the Alexion Medical Monitor to discuss best care options for the individual participant and next steps.
- Use of currently approved medications being investigated alone or in combination for the treatment of the underlying disease, conditioning regimen, GVHD prevention regimen, GVHD treatment, infection prophylaxis, or infection treatment.
- Other concomitant medication may be considered on a case-by-case basis by the Investigator.

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 contact the Alexion Medical Monitor to discuss and 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 8.1.9.

- The Investigator must contact the Alexion 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 therapeutic plasma exchange 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.

6.6. Dose Modification

The adequacy of the proposed dosing regimen (including CCI dosing) will be confirmed through initial analysis of PK/PD as described in Section 4.1.1. If the proposed dose regimen does not result in the anticipated degree of free C5 inhibition, the dosing regimen will be modified 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.

Based on the final DCA, maintenance dosing (ie, dosage) and supplemental dosing (ie, dosage and clinical monitoring criteria) were revised.

6.7. Intervention After the End of the Study

Participants will not receive any additional treatment with ravulizumab as part of the protocol after completion of the study or withdrawal from the study, unless required by local regulations.

Upon completion of a participant's last study visit (ie, EoS or ED Visit), the participant 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 AE 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 Alexion Medical Monitor as soon as feasible. The Investigator should use their judgment with regard to unscheduled visits/laboratory/clinical assessments required to monitor the participant 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 Alexion Medical Monitor on a plan to resume treatment. If the Investigator or Alexion Medical Monitor decide not to resume treatment with study intervention, the participant must be permanently discontinued from treatment, complete the 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 CRF 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 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. 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 ravulizumab
6. Alexion or the Investigator deems it is necessary for the participant

If ravulizumab 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.
- At the time of discontinuing from the study, if possible, an ED Visit should be conducted. See the 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. If allowed by local regulations, information about survival status at Day 100, 6 months and 1-year post first dose of ravulizumab may be collected. If a participant's survival status is not available at the time of discontinuation, sites may attempt to collect the status (eg, via public records, or telephone call).
- 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 withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

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, 6 months, and 1 year post first dose of ravulizumab 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 to ensure consistency in ST-HUS testing globally; 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 patients 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.

8.1. General Assessments and Procedures

8.1.1. Screening Assessments and Procedures

- 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/assent form 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 (as defined in Section 10.3.1).
- Other clinical laboratory tests required for screening include HIV test, ADAMTS13 test, ST-HUS screen, and direct Coombs test (details provided in Section 10.2).

8.1.2. Informed Consent/Assent

The Investigator or qualified designee must obtain a signed and dated ICF/assent form from each participant and/or their legal guardian 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.

8.1.3. 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.

8.1.4. Demographics

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

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 the Screening Visit 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 (Section 10.14), engraftment status any other transplant complication(s), and any other 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. Study Intervention Administration

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

Dose regimen will be based on body weight obtained at the study visit. If ravulizumab needs to be prepared prior to the visit, the weight from the previous visit may be used. Refer to Section 6 for additional information on ravulizumab including preparation, handling, storage, and accountability.

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.

8.1.7.1. Ravulizumab Administration

Ravulizumab will be administered by IV infusion according to the weight-based dosing regimen in Table 6.

Table 6: Dosing Regimen

Weight[a]	Loading Phase Doses			Maintenance Doses
	Day 1	Day 5	Day 10	Starting Day 15
5 to < 10 kg	600 mg	300 mg	300 mg	400 mg q4w
10 to < 20 kg	600 mg	300 mg	300 mg	800 mg q4w
20 to < 30 kg	900 mg	300 mg	300 mg	2100 mg q8w
30 to < 40 kg	1200 mg	300 mg	300 mg	2700 mg q8w
40 to < 60 kg	2400 mg	600 mg	600 mg	3000 mg q8w
60 to < 100 kg	2700 mg	900 mg	900 mg	3300 mg q8w

Table 6: Dosing Regimen

Weight[a]	Loading Phase Doses			Maintenance Doses
	Day 1	Day 5	Day 10	Starting Day 15
≥ 100 kg	3000 mg	900 mg	900 mg	3600 mg q8w

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

CCI [redacted]

8.1.7.2. Supplemental Dosing of Ravulizumab

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

- Supplemental doses for participants following CCI [redacted] (Section 8.1.7.2.1).
- Supplemental doses for participants who demonstrate clinical worsening (as defined in Section 8.1.7.2.2).

8.1.7.2.1. Supplemental Dosing of Ravulizumab following CCI [redacted] CCI [redacted] Supplemental Dosing)

Following administration of the first Maintenance Dose on Day 15, participants CCI [redacted] CCI [redacted] within the specified timeframes (noted below) of a maintenance dose will be administered CCI [redacted] supplemental doses of ravulizumab according to body weight (ie, maintenance dose according to Table 6). CCI [redacted] supplemental doses of ravulizumab will not be administered during the loading phase or be required following CCI [redacted] CCI [redacted] The timing of CCI [redacted] supplemental dosing is described in Section 8.1.7.2.1.1 (see also SoA Section 1.3, Table 1); Section 8.1.7.2.1.2 describes the assessment to determine whether a CCI [redacted] supplemental dose is required; and Section 8.1.7.2.1.3 describes the procedures to be performed at a visit with CCI [redacted] supplemental dosing.

8.1.7.2.1.1. Timing of CCI [redacted] Supplemental Dosing

For all participants, the need for a CCI [redacted] supplement dose of ravulizumab will be assessed when the participant reaches CCI [redacted] as follows:

Weight	Timing of Assessment for CCI [redacted] Supplemental Dose
CCI [redacted] kg	CCI [redacted] weeks (± CCI [redacted] days) CCI [redacted] maintenance dose (ie, Days CCI [redacted] and CCI [redacted]).[a]
CCI [redacted] to CCI [redacted] kg	CCI [redacted] weeks (± CCI [redacted] days) CCI [redacted] maintenance dose (ie, Days CCI [redacted] and CCI [redacted]).[a]

Weight	Timing of Assessment for [redacted] Supplemental Dose
[redacted] kg	[redacted] weeks (± [redacted] days) [redacted] maintenance dose (ie, Days [redacted] and [redacted]).[a]

[a] The supplemental dose must be administered within the same window noted above for each weight categories. 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, Table 1, will remain unchanged.

8.1.7.2.1.2. Assessment of the Need for [redacted] Supplemental Dosing

For all participants, the following clinical algorithm for the assessment of [redacted] supplemental dosing must be followed at the timepoints detailed in Section 8.1.7.2.1 (see also Table 1):

Weight	Clinical Algorithm for Assessment of [redacted] Supplemental Dosing
[redacted] kg	1. Has the participant received [redacted] maintenance dose? • If yes, proceed to question #2 • If no, await [redacted] maintenance dose 2. Has the participant received [redacted] on > [redacted] days [redacted] maintenance dose? • If yes, proceed to question #3 • If no, administer supplemental dose 3. Does the participant meet criteria for clinical worsening described in Section 8.1.7.2.2? • If yes, the Investigator must contact the Alexion Medical Monitor to determine if the participant should continue study treatment and receive a supplemental dose[a] • If no, proceed to question #4 4. In the Investigator's clinical judgment, is the participant benefiting from study treatment? • If yes, administer supplemental dose • If no, Investigator must determine if study treatment discontinuation is needed
[redacted] to [redacted] kg	1. Has the participant received [redacted] maintenance dose? • If yes, proceed to question #2 • If no, await [redacted] maintenance dose 2. Has the participant received [redacted] on > [redacted] days [redacted] maintenance dose? • If yes, proceed to question #3 • If no, administer supplemental dose 3. Does the participant meet criteria for clinical worsening described in Section 8.1.7.2.2? • If yes, contact the Alexion Medical Monitor to determine if the participant should continue study treatment and receive a supplemental dose[a] • If no, proceed to question #4

Weight	Clinical Algorithm for Assessment of CCI Supplemental Dosing
	4. In the Investigator's clinical judgment is the participant benefiting from study treatment? • If yes, administer supplemental dose • If no, Investigator must determine if study treatment discontinuation is needed
CCI kg	1. Has the participant received CCI maintenance dose? • If yes, administer supplemental dose • If no, await CCI maintenance dose

For all participants, if no CCI have been administered, supplemental dosing is not required.

[a] When clinical worsening is present, the Investigator and Alexion Medical Monitor must discuss the clinical status of the participant. If the Investigator determines that the participant continues to potentially benefit from study treatment, the participant can receive a CCI supplemental dose. After administration of the CCI supplemental dose if the participant continues to meet the criteria for clinical worsening described in Section 8.1.7.2.2, an additional dose of ravulizumab can be administered for clinical worsening following a separate documented agreement between the Investigator and Alexion Medical Monitor.

Figure 2 also demonstrates the clinical algorithm for the assessment of CCI supplemental dosing.

Figure 2: Clinical Algorithm for Assessment of [redacted] Supplemental Dosing

[a] When clinical worsening is present, the Investigator and Alexion Medical Monitor must discuss the clinical status of the participant. If the Investigator determines that the participant continues to potentially benefit from study treatment, the participant can receive a [redacted] supplemental dose. After administration of the [redacted] supplemental dose if the participant continues to meet the criteria for clinical worsening described in Section 8.1.7.2.2, an additional dose of ravulizumab can be administered for clinical worsening following a separate documented agreement between the Investigator and Alexion Medical Monitor.

8.1.7.2.1.3. Procedures to be Performed at a [redacted] Supplemental Dosing Visit

Supplemental dosing may be administered at scheduled visits according to the SoA (Section 1.3, Table 1). 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

8.1.7.2.2. Supplemental Dosing of Ravulizumab for Clinical Worsening

Supplemental doses of ravulizumab will be allowed during the Treatment Period 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 6) will be determined following assessment and agreement by the Investigator and Alexion Medical Monitor.

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

8.1.8. Transfusion History and Transfusion Requirements During the Study

The number and volume of transfusions 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.

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

8.1.9. 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[1]. When clinically feasible according to national guidelines and recommendations for immune reconstitution and vaccination after HSCT[1], 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.

Once vaccination is feasible according to national guidelines for immune reconstitution and vaccination after HSCT[1], 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[1].

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 re-vaccinated. 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. Participants who cannot be vaccinated must receive antibiotic prophylaxis for the entire ravulizumab treatment period and for 8 months following the final dose of ravulizumab.

If clinically feasible, participants 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 ravulizumab treatment period 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[1], 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[1].

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

[1] 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 ravulizumab (Section 8.3.10).

8.2. Efficacy Assessments

8.2.1. Primary Efficacy Assessment

8.2.1.1. TMA Response

Laboratory assessments to determine TMA response will be performed according to the SoA (Section 1.3) and Section 10.2 and assessed against predetermined criteria for TMA response (defined in Section 3.2).

8.2.2. Secondary Efficacy Assessments

8.2.2.1. Additional Characterization of TMA Response

For time to TMA response, partial TMA response, loss of TMA response, and TMA relapse, the relevant clinical laboratory assessments will be performed according to the SoA (Section 1.3) and Section 10.2, and assessed against predetermined criteria for TMA response (defined in Section 3.2).

8.2.2.2. Hematologic Response

Clinical laboratory assessments will be performed according to the SoA (Section 1.3) and Section 10.2, and assessed against predetermined criteria for hematologic response (defined in Section 3.2).

8.2.2.3. Overall Survival and Non-Relapse Mortality

Participants' survival status will be collected continuously during 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, at 26 weeks and 52 weeks after first dose of ravulizumab 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).

8.2.2.4. 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. The following parameters to assess organ dysfunction will be assessed at the timepoints specified in the SoA (Section 1.3):

- Renal dysfunction: Kidney 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 CT-Chest, 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.
- Height and weight will also be measured and recorded.
- Additional physical examinations can be performed as medically indicated during the study at the Investigator's discretion.

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 at Screening and at each subsequent study visit.
- 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.
- 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 approximately 5 to 10 minutes before ECG collection and remain supine during 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.

8.3.4. Chest X-ray or Computed Tomography Chest

Chest X-rays (portable or posteroanterior and lateral views) or CT-Chest should be obtained while the participant is at full inspiration at the timepoints specified in the SoA. The Investigator or designee Sub-Investigator will be responsible for reviewing the X-rays or CT-Chest results 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 (Section 1.3). 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 (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 10.2 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 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 Alexion 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 10.2, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).
  - 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 sufficient. 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 10.2.

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/assent form 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 10.8.3.

- For all Alexion products, both in development or postapproval, 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 10.8.3) 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/caregivers to carry with them at all times until 8 months after the final dose of ravulizumab. 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 should check that the participant/caregiver has the Participant Safety Card. If needed, another copy of the Participant Safety Card can be provided to the participant/caregiver.

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.

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

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

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 surgery/biopsy or physical therapy) that the participant receives or undergoes within 30 days prior to first dose of ravulizumab on Day 1 will be recorded. Please refer to the inclusion/exclusion criteria for prior medication considerations for eligibility.

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 after the start of ravulizumab IV infusion on Day 1. 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.

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 in full in the participant's source document/medical chart and in the CRF.

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

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

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 10.3.

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/Assent Form until the ED/EoS Visit (Section 1.3) or 8 weeks after the final dose of ravulizumab (whichever occurs later).

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 10.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

For the participants who withdraw consent all AEs and SAEs will be collected until the time of withdrawal.

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 10.3.

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 10.3.

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 10.3.2, 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Under the EU CTR 536/2014, events other than SAEs (eg, unexpected events) that may impact the benefit-risk balance should be reported. See definitions in Section 10.3.5.
- In the European Union, Alexion will comply with safety reporting requirements and procedures as described in the EU CTR 536/2014. All SUSARs to IMP 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 10.4.

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, nontherapeutic excessive use of IMP for a perceived reward or desired nontherapeutic 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 (ravulizumab) 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 Alexion Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Alexion 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 Alexion 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 Alexion 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, are provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.

For all participants receiving ravulizumab:

  - Predose PK and PD blood samples will be collected within 90 minutes before administering ravulizumab at scheduled dosing 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 ravulizumab 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 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 ravulizumab administered.
- In the case of a participant increasing in weight from CCI kg (ravulizumab administration q4w) to CCI kg (ravulizumab administration q8w), the change in the dose interval from q4w to q8w can only happen on Days 15, 71, or 127.

Alternatively, in the case of a participant decrease in weight from to CCI kg (ravulizumab administration q8w) to CCI kg (ravulizumab administration q4w), the change in the dose interval from q8w to q4w can only happen on Days 15, 71, or 127.

8.7. Genetics

For participants 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 10.9.

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).

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

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

CCI

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

8.9. Immunogenicity Assessments

Antidrug antibodies to ravulizumab will be evaluated in serum samples collected predose (within 90 minutes prior to the start of ravulizumab 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 ravulizumab or were withdrawn from the study. 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. Quality of Life Assessment

The PedsQL 4.0 Generic Core Scales (Section 10.11) are multidimensional child self-reports and parent proxy-reports standardized instruments to measure health-related QoL in children and adolescents 2–18 years of age.

The PedsQL will be administered prior to performing other study procedures at a study visit (participants ≥ 2 years of age only).

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

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

9.2. Sample Size Determination

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

9.3. Populations for Analyses

The analysis sets are defined in Table 7.

Table 7: Analysis Sets

Analysis set	Description
Safety Set	All participants who sign the informed consent and receive at least 1 dose of ravulizumab.
Full Analysis Set	All participants who sign the informed consent and receive at least 1 dose of ravulizumab, excluding[a] participants who enroll prior to availability of ST-HUS and ADAMTS13 laboratory results and are subsequently found to be ineligible after enrollment.
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 the ALXN1210-TMA-314 study. 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 enrollment 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 enrolled subjects from the full analysis set who fail to satisfy major entry criteria (eligibility violations).

- Efficacy analyses will be performed on the FAS.
- The primary efficacy endpoint analysis, as well as selected secondary endpoint analyses, will also be performed on the Per Protocol Set.
- Safety analyses will be performed on the Safety Set.
- Pharmacokinetic and PD analyses will be performed on the PK and PD Analysis Set.

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 visit, where applicable, and by subgroups, 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.

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

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 screen and ADAMTS13 test 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.

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

9.4.1.1. Analyses of Primary Efficacy Endpoint

The primary efficacy endpoint is TMA response during the 26-week Treatment Period. The criteria for TMA response are presented in Section 3.2. Platelet and proteinuria values may be assessed based on local laboratory results in the absence of a valid central laboratory result.

The corresponding estimand will be the proportion of TMA responders among ravulizumab-treated participants during the 26-week Treatment Period for participants in the FAS. 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: meeting the criteria for clinical worsening to provide additional doses, start of disallowed therapy, treatment discontinuation, 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 Treatment Period. The proportion of participants who achieve TMA response during the 26-week Treatment Period will be summarized along with the 95% CI. The CI will be based on exact confidence limits using the Clopper-Pearson method. Non-responder imputation will be used to handle missing data.

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

9.4.1.2. Analyses of Secondary Efficacy Endpoints

9.4.1.2.1. Time to TMA Response

For time to TMA response, participants will be assigned as responders at the time of their TMA response and will be censored at the earlier of last assessment with all 3 TMA response components available (including measurements collected after treatment discontinuation), or death if they have not responded by then.

As a sensitivity analysis, CIF of TMA response will be estimated using competing risk survival analysis methods to account for death as a competing risk. Point estimates and 95% CIs will be provided.

9.4.1.2.2. TMA Response at and up to Specific Time Points

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

This analysis will be conducted using 2 different approaches. The first one will present the number and proportion of responders 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.

9.4.1.2.3. Individual Components of TMA Response

Response to each individual component of TMA response (Section 3.2) during the 26-week Treatment Period will be summarized by calculating the point estimate and a 95% CI for the proportion of responders. The CI will be based on exact confidence limits using the Clopper-Pearson method. These responses will also be summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each postbaseline time point up to Week 26.

This analysis will be conducted using 2 different approaches. The first one will present the number and proportion of responders 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.

9.4.1.2.4. Time to Response for Individual TMA Response Criteria

Time to response for each criterion of TMA response (Section 3.2) will be assessed separately. Participants will be assigned as responders for a specific criterion at the time of their response for that criterion and will be censored at the time of their discontinuation or at the end of available follow-up if they have not responded by then.

Cumulative incidence of the response criterion of interest will be estimated using competing risk survival analysis methods to account for death as a competing risk. Point estimates and 95% CIs will be provided.

9.4.1.2.5. Hematologic Response

The criteria for hematologic response are presented in Section 3.2.

Hematologic response during the 26-week Treatment Period will be summarized by calculating the point estimate and a 95% CI for the proportion of responders. The CI will be based on exact confidence limits using the Clopper-Pearson method. Response will also be summarized 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. The first one will present the number and proportion of responders 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.

9.4.1.2.6. Time to Hematologic Response

For time to hematologic response, participants will be assigned as responders at the time of their response (Section 3.2) and will be censored at their discontinuation time or at the end of available follow-up if they have not responded by then.

Cumulative incidence of hematologic response will be estimated using competing risk survival analysis methods to account for death as a competing risk. Point estimates and 95% CIs will be provided.

9.4.1.2.7. Hemoglobin Response

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

Response will also be summarized 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. The first one will present the number and proportion of responders 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.

9.4.1.2.8. Hematologic Parameters

Hematologic parameters (haptoglobin, hemoglobin, platelets, LDH, and schistocytes) 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.

9.4.1.2.9. Partial TMA Response

Partial TMA response (participant meets ≥ 1, but not all, criteria for TMA response [Section 3.2]) during the 26-week Treatment Period will be summarized by calculating the point estimate and a 95% CI for the proportion of responders. The CI will be based on exact confidence limits using the Clopper-Pearson method. This will include separate presentations for participants with the following: 1) response to only 1 component; 2) response to at least 1, but not all components; and 3) response to at least 2, but not all components.

Partial TMA response will also be summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each postbaseline time point.

9.4.1.2.10. CCI [redacted]

CCI [redacted] will be analyzed CCI [redacted]

9.4.1.2.11. Organ Dysfunction

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

Additional details on the proposed assessments are presented in the SAP.

Renal Dysfunction:

Kidney function parameters (protein/creatinine ratio, serum creatinine, and eGFR) 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.

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 and changes over time will be summarized.

Hypertension will be assessed by blood pressure measurement at every visit as part of vital signs collection, and assessment according to percentile tables for age, sex, and height as well as with assessment of the use any 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 post baseline 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 post baseline 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.

9.4.1.2.12. TMA Relapse

Among participants who will have achieved TMA response, TMA relapse will be summarized 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. A Kaplan-Meier cumulative distribution curve will be generated. 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.

9.4.1.2.13. Loss of Response/Duration of Response

Loss of response occurs when a participant achieves TMA response and fails to meet the criteria for one or more components of TMA response (Section 3.2) at a subsequent visit (must be confirmed by a second laboratory result at least 24 hours apart). Participants who experience loss of response will be summarized by calculating the point estimate and a 95% CI for the proportion of participants with a loss of TMA response. 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 will be censored at the last day with TMA response. Duration of response will be assessed by Kaplan-Meier 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. Kaplan-Meier cumulative distribution curves will be generated. A corresponding summary table will present the first quartile, median, and third quartile, along with corresponding 2-sided 95% CI, of time to loss of TMA response, and the Kaplan-Meier 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.

9.4.1.2.14. Overall Survival

Survival time will be assessed as the number of days from the start of treatment to an event of death. Participants who survive will be censored at their last known date alive. A Kaplan-Meier cumulative distribution curve will be generated. A corresponding summary table will present the first quartile, median, and third quartile, along with corresponding 2-sided 95% CI, of survival time, and Kaplan-Meier estimates with 95% CI at 100 days, 26 weeks and 52 weeks.

9.4.1.2.15. Non-relapse Mortality

Non-relapse mortality is defined as participant's death due to any cause during the study, with the exception of death due to underlying disease progression or relapse. Time to non-relapse mortality is assessed as the number of days from the start of treatment to an event of non-relapse death. Participants who die of primary disease or are alive at the EoS will be censored at their date of death or last known date alive. A Kaplan-Meier curve will be generated, and a corresponding summary table will present the first quartile, median, and third quartile of time to non-relapse mortality, along with corresponding 2-sided 95% CI.

As a sensitivity analysis, the CIF of non-relapse deaths will be estimated using competing risk survival analysis methods to account for relapse-related deaths as a competing risk. CIF estimates at fixed time points of interest and 95% CIs will be provided. Participants who do not experience a non-relapse death will be right censored at their last known date alive.

9.4.1.2.16. Platelet Response

Platelet response will be summarized by calculating the point estimate and a 95% CI for the proportion of responders. The CI will be based on exact confidence limits using the Clopper-Pearson method.

Response will also be summarized 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. The first one will present the number and proportion of responders 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 enrolled. Platelet values may be assessed based on local laboratory results in the absence of a valid central laboratory result.

9.4.1.3. Multiplicity Adjustment

This being an estimation study, no multiplicity adjustment will be implemented.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Set.

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 ravulizumab.
- TEAE: Any AE that starts between the start of the first infusion of ravulizumab and up to 8 months after the last infusion of ravulizumab, inclusive.
- TESAE: A TEAE that is serious.
- Post-treatment adverse events: Any AE that starts 8 months or later after the last dose of ravulizumab.

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. All AEs will be coded using the MedDRA Version 22 or higher and will be summarized by System Organ Class 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

Clinically significant 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. Electrocardiograms 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.

9.4.4. Analyses of Exploratory Endpoints

9.4.4.1. 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.

9.4.4.2. Quality of Life

Quality of life will be evaluated using PedsQL for participants ≥ 2 years of age (Section 10.11.1). The scales (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning), summary scores (Psychosocial Health and Physical Health) and Total Scale Score will be calculated based on the instrument instruction. Treatment of missing items will also follow the instructions: when more than half of the items from any scale are missing, the scale score will not be computed.

The scales, summary scores, and total scale score 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.

9.4.4.3. Health 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 transfusions of RBCs and/or platelets, as well as the number of transfusions.

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

9.4.4.4. Genetics

Exploratory genetics may be performed to investigate genetic variants in genes known to be associated with HSCT-TMA, as well as to identify novel genetic variants associated with HSCT-TMA, complement dysregulation, or metabolism or efficacy of ravulizumab.

9.5. Planned Analyses

9.5.1. Dose Confirmation Analysis

An early analysis of the PK/PD data will be initiated when 10 participants complete Visit 5 on Day 21. All PK and free C5 data collected in all participants by that time will be analyzed to

confirm the adequacy of the initial dosing regimen to achieve complete inhibition of C5. Several analyses may be conducted prior to 10 participants completing Visit 5 at Day 21 as part of the DCA to support adjustments to the dosing regimen and/or the CCI supplemental dosing for ongoing participants. Alexion may also determine that additional participants need to be enrolled either prior to or during the DCA (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.

Based on the final DCA, maintenance dosing (ie, dosage) and supplemental dosing (ie, dosage and clinical monitoring criteria) were revised.

9.5.2. Primary Endpoint Analysis

A primary endpoint analysis will be conducted at the time point when all participants have completed or withdrawn from the 26-week Treatment Period. The SAP will describe the planned analyses in greater detail.

9.5.3. Interim Analysis For Follow-Up Period

An interim analysis may be performed to provide interim descriptive analyses, after all participants have completed or withdrawn from the 26-week Treatment Period, prior to the final analysis, for regulatory purposes. The SAP will describe the planned analyses.

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 analyses 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.

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 (including EU CTR 536/2014)
- The protocol, protocol amendments (ie, modifications), ICF, IB, 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 and applicable regulatory authority 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 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 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.
- 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 qualified 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/EC as required, for review and approval for use.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by Alexion or designee. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, full date of birth, 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, by 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, it 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 result 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 printed or electronic CRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically 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 as per country-specific requirements 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 in 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/ED Visit, all data have been collected and entered into an 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.

The Sponsor 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 intervention to participants enrolled or continuing in the study.
- Sponsor 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. Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the study central laboratory unless otherwise noted. Please refer to the Laboratory Manual on 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 to ensure consistency in ST-HUS testing globally; however, these results are not required prior to enrollment.
  - After the Screening Period, local laboratory results are only required in the event the central laboratory results are not available in time for either study drug 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 obtained, 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.

Table 8: 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

Table 8: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
Clinical Chemistry	• 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 – Potassium – Sodium – Uric acid • Other clinical chemistry parameters: – C-reactive protein
Routine Urinalysis/Urine Chemistry	• Albumin • Bilirubin • Blood • Color • Creatinine • Glucose • Ketones • Nitrite • pH • Protein

Table 8: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
	• Specific gravity • Urobilinogen
Other Screening Tests	• 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 • Serum or urine human chorionic gonadotropin pregnancy test (as needed for WOCBP)[a]
Other Study-specific Tests	• Immunogenicity (ADA) • Serum PK • Serum PD (total and free C5) • Exploratory biomarkers • CCI • Genetic testing (whole blood and buccal swab)

[a] Serum pregnancy test at Screening and EoS Visit/ED Visit, and local urine pregnancy test at all other times as specified in SoA. 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.

The following procedures for blood collection 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. European Commission Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC

relating to the good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008.

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

10.3.1. 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 it 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 fulfill 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).

10.3.2. 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 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.

A 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 guidances 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. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs/IECs where applicable.

10.3.3. 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.
    a. 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.
    b. 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.
    c. The AE has a temporal relationship to the administration of the study intervention.
    d. The event does not have a likely alternative etiology.
    e. The event corresponds with the known pharmaceutical profile of the study intervention.
    f. 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.
- New or updated information will be recorded in the originally completed CRF.

Follow-up of AEs and SAEs
• The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.4. 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 section).

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.
• Paper source documents and/or reports should be kept in the appropriate section of the study file.

10.3.5. 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 study, 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 study, Alexion should apply for a substantial modification before restarting the clinical study.

10.4. 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.

10.5. Management of Potential Infusion-Associated Adverse Events During Ravulizumab Administration

Intravenous 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 intervention, or study procedures; or that caused the participant to discontinue ravulizumab (Section 7).

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

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

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

If anaphylaxis occurs according to the criteria listed in Table 9, 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 9: 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: ○ Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) ○ 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): ○ Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips/tongue/uvula) ○ Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) ○ Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) ○ Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
• Reduced blood pressure after exposure to known allergen for that participant (minutes to several hours): ○ Systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that participant's baseline

Source: (Sampson, 2006)

10.6. 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 10.

Table 10: 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 guidances 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.
Healthcare institution availability for non-COVID-19 related activities	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.

Table 10: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
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 is missing (eg, missed study visits or participant study discontinuations due to COVID-19).

10.7. 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 11.

Table 11: 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).

10.8. Contraceptive Guidance and Collection of Pregnancy Information

10.8.1. Definitions

WOCBP

A woman is considered fertile following menarche and until becoming postmenopausal 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.

10.8.2. Contraception Guidance

10.8.2.1. 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 childbearing potential must use a highly effective or acceptable method of contraception (for participants in the UK and South Korea, 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 ravulizumab:

Highly effective methods are:

1. Intrauterine device in place for at least 6 weeks prior to first dose of ravulizumab.
2. Progestogen-only hormonal contraception (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of ravulizumab.
3. Intrauterine progestogen-releasing system for at least 6 weeks prior to first dose of ravulizumab.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of ravulizumab.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of ravulizumab.
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 and South Korea 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 drug.

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).

10.8.2.2. 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.

10.8.2.2.1. 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.

10.8.3. 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.

10.8.3.1. 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.

10.8.3.2. 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.

10.9. 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/or 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.

10.10. 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.

10.11. Patient Reported Outcome Instruments

10.11.1. Pediatric Quality of Life Inventory 4.0 Generic Core Scale

10.11.1.1. Parent Report for Toddlers (Ages 2-4)

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month,** how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Playing with other children	0	1	2	3	4
2. Other kids not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

Please complete this section if your child attends school or daycare

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Doing the same school activities as peers	0	1	2	3	4
2. Missing school/daycare because of not feeling well	0	1	2	3	4
3. Missing school/daycare to go to the doctor or hospital	0	1	2	3	4

10.11.1.2. Young Child Report (Ages 5-7)

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

YOUNG CHILD REPORT (ages **5-7**)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

PedsQL 2

Think about how you have been doing for the last few weeks. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PHYSICAL FUNCTIONING *(problems with…)*	Not at all	Some-times	A lot
1. Is it hard for you to walk	0	2	4
2. Is it hard for you to run	0	2	4
3. Is it hard for you to play sports or exercise	0	2	4
4. Is it hard for you to pick up big things	0	2	4
5. Is it hard for you to take a bath or shower	0	2	4
6. Is it hard for you to do chores (like pick up your toys)	0	2	4
7. Do you have hurts or aches (***Where?*** _____)	0	2	4
8. Do you ever feel too tired to play	0	2	4

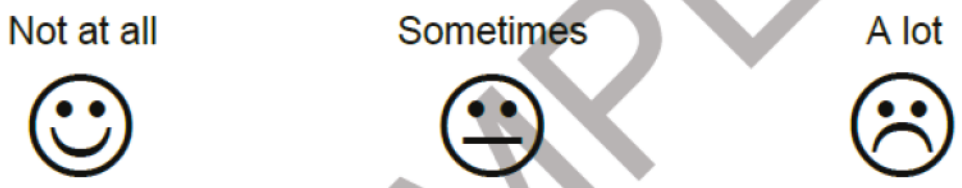
Remember, tell me how much of a problem this has been for you for the last few weeks.

EMOTIONAL FUNCTIONING *(problems with…)*	Not at all	Some-times	A lot
1. Do you feel scared	0	2	4
2. Do you feel sad	0	2	4
3. Do you feel mad	0	2	4
4. Do you have trouble sleeping	0	2	4
5. Do you worry about what will happen to you	0	2	4

SOCIAL FUNCTIONING *(problems with…)*	Not at all	Some-times	A lot
1. Is it hard for you to get along with other kids	0	2	4
2. Do other kids say they do not want to play with you	0	2	4
3. Do other kids tease you	0	2	4
4. Can other kids do things that you cannot do	0	2	4
5. Is it hard for you to keep up when you play with other kids	0	2	4

SCHOOL FUNCTIONING *(problems with…)*	Not at all	Some-times	A lot
1. Is it hard for you to pay attention in school	0	2	4
2. Do you forget things	0	2	4
3. Is it hard to keep up with schoolwork	0	2	4
4. Do you miss school because of not feeling good	0	2	4
5. Do you miss school because you have to go to the doctor's or hospital	0	2	4

How much of a problem is this for you?



10.11.1.3. Parent Report for Young Children (Ages 5-7)

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for YOUNG CHILDREN (ages 5-7)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores, like picking up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school activities	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

10.11.1.4. Child Report (Ages 8-12)

ID# _____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

10.11.1.5. Parent Report for Children (Ages 8-12)

ID# _____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

10.11.1.6. Teen Report (Ages 13-18)

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

TEEN REPORT (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT SCHOOL ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

10.11.1.7. Parent Report for Teens (Ages 13-18)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for TEENS (ages 13-18)

DIRECTIONS

On the following page is a list of things that might be a problem for **your teen**. Please tell us **how much of a problem** each one has been for **your teen** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your teen had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that other teens his or her age can do	0	1	2	3	4
5. Keeping up with other teens	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

10.12. 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

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

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, computed tomography, or MRI]) above baseline value.
  - Ascites (best if confirmed by imaging [suggested imaging: ultrasonography, computed tomography, 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. Acute 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.

Grade	Description
I	Rash on ≤ 50% of skin, no liver or gut involvement
II	Rash on > 50% of skin, bilirubin 2 to 3 mg/dL, or diarrhea 500 to 1000 mL/day, or persistent nausea
III	Bilirubin 3 to 15 mg/dL, or gut stage 2 to 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

10.15. 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 3.1	EU	27 Sep 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 3	Global	08 Feb 2023	This amendment incorporated the revised dose regimen following the pre-specified DCA.
Amendment 2.2	UK	13 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 2.1 (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 platelet transfusion, as done in Protocol Amendment 2, but remove any changes in Protocol Amendment 2 that were not related to the supplemental dosing regimen.
Amendment 2	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 1.1	UK	03 Jun 2021	To include COVID-19 risk assessment and COVID-19 vaccine risk assessment language.

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 1	UK	29 Sep 2020	To conform with The Medicines for Human Use (Clinical Trials) Regulations 2004 S.I. 2002/1031 as requested by Medicines and Healthcare products Regulatory Agency
Original protocol	Not applicable	25 Mar 2020	Not applicable

10.16. 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	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BSC	best supportive care
C5	complement component 5
CCI [redacted]	
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
CNI	calcineurin inhibitor
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Clinical Trial Facilitation Group
CTIS	Clinical Trial Information System
D	day
DCA	dose confirmation analysis

Abbreviation	Definition
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
eGFR	estimated glomerular filtration rate
EMLA	eutectic mixture of local anesthetics
EoS	End of Study
EU	European Union
EU CTR	European Union Clinical Trials Regulation
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FSH	follicle stimulating hormone
GI	gastrointestinal
GCP	Good Clinical Practice
GDS	global drug safety
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase
GVHD	graft versus host disease
Hib	*Haemophilus influenzae type b*
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPF	high power field
HRT	hormonal replacement therapy
HSCT	hematopoietic stem cell transplantation
HSCT-TMA	hematopoietic stem cell transplant-associated thrombotic microangiopathy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin

Abbreviation	Definition
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISTH	International Society on Thrombosis and Haemostasis
IV	intravenous(ly)
JAPC	Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NIH	National Institutes of Health
P	peak (ie, within 60 minutes of the end of IV infusion of dose)
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PedsQL	Pediatric Quality of Life Inventory 4.0 Generic Core Scale
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PRES	posterior reversible encephalopathy syndrome
PT	prothrombin time
q4w	every 4 weeks
q8w	every 8 weeks
QoL	quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RTSM	Randomization and Trial Supply Management
S	site visit
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
CCI	CCI
SoA	schedule of activities
SOS	sinusoidal obstruction syndrome
SP	Screening Period
ST-HUS	Shiga toxin-related hemolytic uremic syndrome
SUSAR	suspected unexpected serious adverse reaction
T	trough (ie, within 90 minutes before administering ravulizumab)
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TTP	thrombotic thrombocytopenic purpura
TMA	thrombotic microangiopathy
TMF	Trial Master File
TNF-RI	tumor necrosis factor receptor I
ULN	upper limit of normal
V	visit
VCAM-1	vascular cell adhesion molecule 1
VOD	veno-occlusive disease
WOCBP	woman of childbearing potential

11. REFERENCES

Bakris GL. Slowing nephropathy progression: focus on proteinuria reduction. Clin J Am Soc Nephrol. 2008;3 Suppl 1:S3-10.

Bohl SR, Kuchenbauer F, von Harsdorf S, et al. Thrombotic microangiopathy after allogeneic stem cell transplantation: a comparison of eculizumab therapy and conventional therapy. Biol Blood Marrow Transplant. 2017;23(12):2172-2177.

Cho BS, Min CK, Eom KS, et al. Clinical impact of thrombotic microangiopathy on the outcome of patients with acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2008;41(9):813-820.

Cho BS, Yahng SA, Lee SE, et al. Validation of recently proposed consensus criteria for thrombotic microangiopathy after allogeneic hematopoietic stem-cell transplantation. Transplantation. 2010;90(8):918-926.

Corbacioglu S, Carreras E, Ansari M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European society for blood and marrow transplantation. Bone Marrow Transplant. 2018;53(2):138-145.

Dvorak CC, Higham C, Shimano KA. Transplant-associated thrombotic microangiopathy in pediatric hematopoietic cell transplant recipients: a practical approach to diagnosis and management. Front Pediatr. 2019;7:133.

Elemary M, Sabry W, Seghatchian J, Goubran H. Transplant-associated thrombotic microangiopathy: Diagnostic challenges and management strategies. Transfus Apher Sci. 2019;58(3):347-350.

Farhana A, Lappin SL. Biochemistry, Lactate Dehydrogenase. [Updated 2023 May 1; Accessed 2024 January 05]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557536/. 2024.

Hahn T, Sucheston-Campbell LE, Preus L, et al. Establishment of definitions and review process for consistent adjudication of cause-specific mortality after allogeneic unrelated-donor hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2015;21(9):1679-1686.

Jan AS, Hosing C, Aung F, Yeh J. Approaching treatment of transplant-associated thrombotic Microangiopathy from two directions with Eculizumab and transitioning from Tacrolimus to Sirolimus. Transfusion. 2019;59(11):3519-3524.

Jodele S, Laskin BL, Dandoy CE, et al. A new paradigm: Diagnosis and management of HSCT-associated thrombotic microangiopathy as multi-system endothelial injury. Blood Rev. 2015;29(3):191-204.

Jodele S, Fukuda T, Vinks A, et al. Eculizumab therapy in children with severe hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Biol Blood Marrow Transplant. 2014a;20(4):518-525.

Jodele S, Davies SM, Lane A, et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. Blood. 2014b;124(4):645-653.

Jodele S, Fukuda T, Mizuno K, et al. Variable Eculizumab Clearance Requires Pharmacodynamic Monitoring to Optimize Therapy for Thrombotic Microangiopathy after Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2016;22(2):307-315.

Jodele S, Dandoy CE, Lane A, et al. Complement blockade for TA-TMA: lessons learned from a large pediatric cohort treated with eculizumab. Blood. 2020;135(13):1049-1057.

Khosla J, Yeh AC, Spitzer TR, Dey BR. Hematopoietic stem cell transplant-associated thrombotic microangiopathy: Current paradigm and novel therapies. Bone Marrow Transplant. 2018;53(2):129-137.

Lea J, Greene T, Hebert L, et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. Arch Intern Med. 2005;165(8):947-953.

Li A, Wu Q, Davis C, et al. Transplant-associated thrombotic microangiopathy is a multifactorial disease unresponsive to immunosuppressant withdrawal. Biol Blood Marrow Transplant. 2019;25(3):570-576.

Masias C, Vasu S, Cataland SR. None of the above: thrombotic microangiopathy beyond TTP and HUS. Blood. 2017;129(21):2857-2863.

Merck-Manual. Lactate dehydrogenase (LDH) test. [Accessed 2024 January 05]. In: Merck Manual Consumer Version [Internet]. Merck & Co., Inc. Available from: https://www.merckmanuals.com/home/multimedia/lab-tests/lactate-dehydrogenase-ldh-test. 2024.

Mizuno K, Dandoy CE, Teusink-Cross A, Davies SM, Vinks AA, Jodele S. Eculizumab precision-dosing algorithm for thrombotic microangiopathy in children and young adults undergoing HSCT. Blood Adv. 2022;6(5):1454-1463.

Oran B, Donato M, Aleman A, et al. Transplant-associated microangiopathy in patients receiving tacrolimus following allogeneic stem cell transplantation: risk factors and response to treatment. Biol Blood Marrow Transplant. 2007;13(4):469-477.

Rosenthal J. Hematopoietic cell transplantation-associated thrombotic microangiopathy: a review of pathophysiology, diagnosis, and treatment. J Blood Med. 2016;7:181-186.

Sahelijo L, Mujeebuddin A, Mitchell D, et al. First in human single-ascending dose study: safety, biomarker, pharmacokinetics and exposure-response relationships of ALXN1210, a humanized

monoclonal antibody to C5, with marked half-life extension and potential for significantly longer dosing intervals, [abstract]. Blood. 2015;126(23):4777.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397.

Schoemans HM, Lee SJ, Ferrara JL, et al. EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. Bone Marrow Transplant. 2018;53(11):1401-1415.

Schoettler ML, LE; Margossian, S; Lee, M; Kao, PC; Ma, C; Duncan, C. . Transplant Associated Thrombotic Microangiopathy (TA-TMA): Lessons Learned from a Large Pediatric Center. Biology of Blood and Marrow Transplantation. 2019;25:S18-S19.

Seaby EG, Gilbert RD. Thrombotic microangiopathy following haematopoietic stem cell transplant. Pediatr Nephrol. 2018;33(9):1489-1500.

Sheridan D, Yu ZX, Zhang Y, et al. Design and preclinical characterization of ALXN1210: a novel anti-C5 antibody with extended duration of action. PLoS One. 2018;13(4):e0195909.

Styczynski J, Tridello G, Gil L, et al. Prognostic impact of EBV serostatus in patients with lymphomas or chronic malignancies undergoing allogeneic HCT. Bone Marrow Transplant. 2019;54(12):2060-2071.

Taylor FB, Jr., Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001;86(5):1327-1330.

Wanchoo R, Bayer RL, Bassil C, Jhaveri KD. Emerging Concepts in Hematopoietic Stem Cell Transplantation-Associated Renal Thrombotic Microangiopathy and Prospects for New Treatments. Am J Kidney Dis. 2018;72(6):857-865.

Yamada R, Nemoto T, Ohashi K, et al. Distribution of Transplantation-Associated Thrombotic Microangiopathy (TA-TMA) and Comparison between Renal TA-TMA and Intestinal TA-TMA: Autopsy Study. Biol Blood Marrow Transplant. 2020;26(1):178-188.

Zini G, d'Onofrio G, Erber WN, et al. 2021 update of the 2012 ICSH Recommendations for identification, diagnostic value, and quantitation of schistocytes: Impact and revisions. Int J Lab Hematol. 2021;43(6):1264-1271.

Signature Page for VV-CLIN-015021 v1.0

eSignature Approval	PPD Clinical 04-Sep-2024 20:57:31 GMT+0000

Signature Page for VV-CLIN-015021 v1.0