TITLE PAGE

Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants Who Have Thrombotic Microangiopathy Associated With a Trigger

Protocol Number: ALXN1210-TMA-315

Amendment Number: Protocol Amendment 2 (Global)

Compound: Ravulizumab (ALXN1210)

Study Phase: 3

Short Title: Phase 3 Study of Ravulizumab in Thrombotic Microangiopathy Associated With a Trigger

Sponsor Name: Alexion Pharmaceuticals Inc.

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

Regulatory Agency Identifier Number(s)

IND: 128367

EudraCT: 2020-005328-13

Release Date: 10 Nov 2021

Sponsor Signatory:

[redacted]

11-Nov-2021 | 13:20:40 EST

Date

Alexion Pharmaceuticals Inc.

Medical Monitor Contact Information can be found in the Study 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

Amendment 2 (Global) (10 Nov 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary driver for this amendment is to allow for participants to be randomized based on local laboratory assessments (with the exception of the ST-HUS screen and ADAMTS13 activity tests which must be performed at the central laboratory) and allow for participants to be randomized prior to the availability of the ST-HUS screen and ADAMTS13 activity tests to align with current practice patterns for management of TMA patients. Additional changes update and clarify the TMA eligibility criteria, expand the window to assess eligibility for laboratory assessments to include ≤ 14 days prior to the Screening Period, define the estimands corresponding to the primary and key secondary endpoints according to ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials, add additional endpoints to assess loss of TMA response, changes in hematological and renal response parameters, and survival, elevate changes in patient-reported outcomes as measured by FACIT-Fatigue to a secondary endpoint, update the efficacy analyses to be based on the modified Intent-to-Treat analysis set, and add COVID-19 risk assessment language. Minor typographical clarifications and corrections were also made.

Section # and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis; Section 3.1, Overview of Objectives and Endpoints	Revised the primary endpoint to "Complete TMA Response during the 26-week randomized Treatment Period."	Editorial revision to align with the description of the primary efficacy endpoint in the statistical methodology section of the protocol; this endpoint was prespecified as "during the 26-week randomized Treatment Period" from study initiation but was written inconsistently throughout the original protocol.
	Added a key secondary endpoint to the table of endpoints for "on dialysis at Week 26".	To align with the efficacy endpoints described in the statistical methodology section of the protocol; endpoint was prespecified in the original protocol but omitted from the table of endpoints in error.
	Added an additional secondary endpoint to the protocol assess Loss of TMA Response	To assess the subsequent loss of TMA response in participants who achieved TMA response during the Treatment Period
	Added additional secondary endpoints to the protocol to assess changes from baseline in hematologic parameters at all scheduled assessments	To assess trends in hematologic parameters

Section # and Name	Description of Change	Brief Rationale
	Added an additional secondary endpoint to the table of endpoints to assess changes from baseline in eGFR at all scheduled assessments; Revised the endpoints for response in at least 1 TMA parameter, and renal response and hematologic response, separately, to be assessed at all scheduled assessments	To align with the efficacy endpoints described in the statistical methodology section of the protocol; endpoint was prespecified in the original protocol but omitted from the table of endpoints in error.
	Added an additional secondary endpoint to the protocol to assess increases in hemoglobin ≥ 1 gram/dL	To allow for evaluation of increases in hemoglobin at 2 separate cutoffs given that varying degrees of improvement are expected based on the heterogenicity of the population
	Elevated "change in patient-reported outcomes as measured by FACIT-Fatigue" to a secondary endpoint	To allow for patient-reported outcomes to support the value of the primary endpoint
	Added a safety endpoint to assess changes from baseline in vital signs and laboratory parameters	To further characterize participant safety
	Editorial revisions and clarifications were made to the key secondary endpoints.	Editorial revision to align with the estimands corresponding to the key secondary efficacy objectives in accordance with ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials
Section 1.1, Synopsis; Section 1.2, Schema; Section 4.1, Overall Design	Updated the description of the participant population to reflect that participants must have met protocol defined criteria during the Screening Period instead of randomization; added "and/or ≤ 14 days prior to the Screening Period" to eligibility window.	Correction; To align the window for screening labs (IC #5) with the window for clinical diagnosis of TMA (IC #4)
Section 1.2, Schema; Section 1.3, Schedule of Activities	Added language to specify local or central laboratory results may be used to determine eligibility, with the exception of the ST-HUS screen and ADAMTS13 activity tests which must be performed at the central laboratory. With the exceptions of the ST-HUS screen and ADAMTS13 activity tests, if local labs are used to establish eligibility, central laboratory tests are not required at the Screening visit.	To allow use of local labs to determine eligibility to align with current practice patterns for management of TMA patients.
Section 3.1, Overview of Objectives and Endpoints	Added an exploratory objective and endpoint to assess overall survival by Week 26 and Week 52	To assess the impact of ravulizumab on overall survival

Section # and Name	Description of Change	Brief Rationale
Section 3.2.1, Complete TMA Response	Clarified that first laboratory value for the assessment of response parameters will be based on central laboratory results; the second value will be assessed based on the earliest value obtained ≥ 24 hours after the first value and may be based on central or local laboratory results	Clarification
Section 3.2.4, Loss of TMA Response	Added section to define 'Loss of TMA Response"	Definition of new endpoint
Section 3.2.5, TMA Relapse	Revised the definition of TMA Relapse to "evidence of worsening hematologic and renal dysfunction due to TMA during the post-treatment follow-up period and requires treatment intervention, as determined by the Investigator."	The revised criterion is more clinically relevant, incorporating whether the patient requires treatment. An Investigator's decision to treat a patient for relapse depends on a number of clinical and histological factors such as renal reserve and the patient's overall functional status. The revised criterion removes thresholds for laboratory criteria and instead allows for clinical judgement, taking into account aforementioned factors to determine if a participant has experienced a relapse.
Section 4.4, Remote Visit Options in Times of Emergency	Revised language to remove home health services and specify that remote visits include virtual phone or video conference visits; Added language to specify the minimum assessments collected during remote visits which must be recorded in the source documents; Added language to specify that the Investigator should contact the Medical Monitor to determine next appropriate steps if a participant is not able to complete a visit where study drug is administered	To operationally simplify the processes associated with a remote visit when required during times of emergency
Section 5, Study Population	Updated language to specify that the eligibility window for laboratory assessments may include "≤ 14 days prior to the Screening Period"; Added language to specify local or central laboratory results may be used to determine eligibility, with the exception of the ST-HUS screen and ADAMTS13 activity tests which must be performed at the central laboratory; Added language to specify that participants may be randomized prior to availability of the central laboratory results from the ST-HUS screen and ADAMTS13.	To allow use of local labs to determine eligibility to align with current practice patterns for management of TMA patients.

Section # and Name	Description of Change	Brief Rationale
Section 5.1, Inclusion Criteria	Revised IC #4c to specify examples of solid organ transplants; Removed "Diagnosis of" from the requirement of TMA	Clarification
	Revised IC #5 to specify that the laboratory finding criteria can be confirmed during Screening or ≤ 14 days prior to the start of the Screening Period. Removed that central laboratory results were required.	To align the window for screening labs (IC #5) with the window for clinical diagnosis of TMA (IC #4) and to allow use of local labs to align with current practice patterns for management of TMA patients
	Revised IC #5c to clarify the criterion of acute kidney injury for kidney transplant recipients.	Clarification to allow for post-kidney transplant recipients to be evaluated for eligibility; the previous criterion was inadvertently worded as exclusionary towards all kidney transplant recipients
	Removed the requirement for vaccination against *Haemophilus influenzae type b (Hib)* and *Streptococcus pneumoniae* from the inclusion criteria (IC #7)	Vaccination against *Hib* and *S. pneumoniae* is only based on local requirements and is reflected in Section 8.1.5 Vaccination and Antibiotic Prophylaxis.
Section 5.2, Exclusion Criteria	Revised EC #3 to separate the requirements for participants with native kidneys and kidney transplant recipients; Added "ongoing acute kidney injury requiring dialysis treatment lasting for > 14 days prior to Screening" to the requirement for participants with native kidneys	To allow for the enrollment of kidney transplant patients; to ensure exclusion of participants with native kidneys who are on dialysis for more than 14 days
	Revised EC #7 to "Known Shiga toxin-producing Escherichia coli infections…"	To exclude patients known to have hemolytic uremic syndrome due to Shiga toxin-producing infections
	Revised EC #9 to "Positive direct Coombs test which in the judgement of the Investigator is indicative of a clinically significant immune-mediated hemolysis not due to TMA."	A positive Coombs test can result from a variety of factors and may not always be clinically significant. New criteria will allow Investigator judgment to determine the clinical significance of the Coombs test result.
	Revised EC #10 to "Clinical diagnosis of DIC in the judgement of the Investigator, utilizing the ISTH scoring criteria	Diagnosis of DIC requires clinical interpretation of lab values. This change allows the investigator to review lab values within the appropriate clinical context to confirm DIC.
	Revised EC #11 to "Presence of sepsis requiring vasopressors"	Clarification of criterion intended to exclude patients with sepsis who are on vasopressors; the previous language inadvertently excluded all patients with infection

Section # and Name	Description of Change	Brief Rationale
	Revised EC #14 to "Kidney biopsy (if available) showing the presence of any of the following in glomeruli: ≥ 50% interstitial fibrosis and tubular atrophy; ≥ 50% glomerular sclerosis; ≥ 50% active crescent formation"	Clarification of the requirement to specify that the ≥ 50% requirement applies to each condition individually
	Revised EC #18 to "Human immunodeficiency virus (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."	Clarification that patients are excluded if they are HIV positive; due to inadequate punctuation, this criterion was previously written in a way that could be perceived as contradictory
	Added EC #22: "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 randomization"	To exclude participants with a high risk of mortality from respiratory failure in order to mitigate confounding impact of respiratory failure on study endpoints
	Revised EC #24 to clarify participants will be excluded from study eligibility if they participate in an interventional treatment study for TMA or in any interventional treatment study with an unapproved therapy for any indication during the wash-out period	Clarification of the types of studies resulting in exclusion
Section 6.1, Study Drug Administered	Revised the description of dose schedule to specify that participants in the ravulizumab group will receive a blinded maintenance dose at Day 15 instead of Week 2	Clarification of the specific study time point so that the terminology is consistent throughout the protocol
Section 6.3.1, Randomization	Removed "after the Investigator has verified that they are eligible" from the timing of randomization	Allowance of randomization prior to ST-HUS or ADAMTS13 results may result in determination of ineligibility after randomization
Section 6.3.2, Blinding	Updated the description of unblinding at the time of the primary analysis to indicate that sites and participants will be unblinded at the same time as the sponsor	Clarification of the time of unblinding for all parties
Section 6.6.1, Allowed Medicine and Therapy	Added note that guidance on the use of COVID-19 vaccines is provided in Section 10.9 of protocol	To guide reader on additional information relevant to allowed medicine and therapy
Section 6.6.2, Disallowed Medicine and Therapy	Added text to specify that participants are prohibited from receiving therapeutic plasma exchange/plasma infusion following randomization during the Treatment Period	Clarification that therapeutic plasma exchange/plasma infusion is permitted during the screening period and Follow-up Period which is consistent with current practice patterns for TMA patients

Section # and Name	Description of Change	Brief Rationale
Section 6.6.2, Disallowed Medicine and Therapy; Section 7.1, Discontinuation of Study Drug	Revised text to specify that study drug may be permanently discontinued following using of disallowed medication following consultation with the Medical Monitor	To allow for Investigator's to consult with the Medical Monitor in cases of participant receipt of prohibited medications and/or therapies
Section 8.5.2, Concomitant Medications and Procedures	Clarified that concomitant dosage information including dose and frequency is not required on the CRF	Clarification
Section 8.9.3, Real Time Complement Activity; Section 10.3, Clinical Laboratory Tests; Section 1.3, Schedule of Activities	Added text to specify that RTCA plasma and urine are to be collected and frozen from all sites, and that only select sites will perform additional on-site fresh sample testing	Clarification
Section 9.3, Populations for Analyses; Section 9.4.1, Efficacy Analyses	Removed the Enrolled Set. Added the Modified Intent to Treat (mITT) Analysis Set as the primary analysis set	Patients are allowed to be randomized while results from ST-HUS and/or ADAMTS13 screen are pending. Following randomization, receipt of positive aforementioned results will exclude patients from mITT.
Section 9.4.1.1, Analyses of the Primary Efficacy Endpoint	Added descriptions on handling of missing data and intercurrent events under the estimand framework; Updated the definition of baseline value for eGFR	To align to ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials; To account for the effect of dialysis on eGFR results at baseline
Section 9.4.1.2, Analyses of Secondary Efficacy Endpoints	Revised analysis description of the key secondary endpoints	To add clarity on the planned analyses and add descriptions on handling of missing data and intercurrent events under the estimand framework
	Clarified the description of additional secondary endpoints; Added definition of baseline values for all parameters other than eGFR	Clarification
Section 9.4.1.3, Multiplicity Adjustment	Editorial revisions to the list of key secondary endpoints	To align with the revisions made within Section 1.1 and Section 3.1
Section 10.2, Mapping of Objectives to Estimands	Added a table that maps the objectives to the study estimands.	To align to ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials
Section 10.3, Clinical Laboratory Tests	Added language to specify local or central laboratory results may be used to determine eligibility, with the exceptions of the ST-HUS screen and ADAMTS13 activity tests which must be performed at the central laboratory. With the exceptions of the ST-HUS screen and ADAMTS13 activity tests, if local labs are used to establish eligibility, central laboratory tests are not required at the Screening visit.	To allow use of local labs to determine eligibility to align with current practice patterns for management of TMA patients.

Section # and Name	Description of Change	Brief Rationale
	Added language to allow for the Investigator to assess the presence of Shiga toxin-producing *E. coli* infection based on clinical judgement in participants who cannot produce a stool sample for the ST-HUS screen during the Screening Period	To allow Investigator to proceed with enrollment if stool specimen for ST-HUS is not available but collect it when stool is available.
	Revised description of the timing of serum pregnancy testing and clinical complement tests	Clarification
	Added absolute reticulocyte count and urine protein creatinine ratio to the protocol-required laboratory assessments	Correction
	Removal of RBC morphology, urea, and ST-HUS rectal swab from the list of protocol-required laboratory assessments	Assessments not needed for the assessment of safety or efficacy.
Section 10.10, COVID-19 Vaccine Risk Assessment	COVID-19 vaccine risk assessment language included.	Section newly added to provide potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic and COVID-19 vaccination rollout.
Section 10.13, International Society on Thrombosis and Haemostasis (ISTH) Criteria for Disseminated Intravascular Coagulation (DIC)	Removed 'central laboratory' from the requirement for laboratory cutoff values.	To allow the use of local labs to determine eligibility to align with current practice patterns for management of TMA patients

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants Who Have Thrombotic Microangiopathy Associated With a Trigger

Short Title: Phase 3 Study of Ravulizumab in Thrombotic Microangiopathy Associated With a Trigger

Rationale: The development of thrombotic microangiopathy (TMA) often follows activation of complement by a trigger. Such triggers include, but are not limited to, infection, drug exposure, autoimmune disease, transplant (solid organ or bone marrow), malignant hypertension, and pregnancy. The presence of one or more of these triggers is a consideration for the diagnosis of atypical hemolytic uremic syndrome (aHUS), a type of complement-mediated TMA. The first approved complement component 5 (C5) inhibitor, eculizumab, demonstrated efficacy in aHUS in clinical studies and in TMAs triggered by renal transplant in real-world data from the global aHUS registry. Multiple single-center studies have demonstrated the efficacy of eculizumab in treating a wide array of triggers. However, most studies assessing efficacy in this population are retrospective, single-arm/single-center experience, or fail to control for presentation severity or time to treatment. Thus, a randomized, controlled study is needed to assess C5 inhibition in TMA associated with a trigger.

Phase 3 studies with ravulizumab demonstrated efficacy in the treatment of TMA due to aHUS in adult and pediatric patients. In these studies, ravulizumab treatment achieved complete terminal complement inhibition resulting in Complete TMA Response, defined by normalization of hematologic parameters and improvement in renal function in the majority of patients. The study population included patients who presented with TMA after renal transplant or pregnancy, but excluded other triggers such as infection, drug exposure, and autoimmune disease.

The objective of this study is to investigate the efficacy and safety of ravulizumab administered by intravenous (IV) infusion compared to placebo in adult participants with TMA associated with a range of triggers.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of ravulizumab in the treatment of participants with TMA	Complete TMA Response during the 26-week randomized Treatment Period
Secondary	
To characterize TMA response	Time to Complete TMA Response during the 26-week randomized Treatment Period [a]
	Time to response for each TMA parameter during the 26-week Treatment Period
	Achievement of hematologic response at Week 26 [a]
	Achievement of hematologic response at all scheduled assessments
	Achievement of renal response at all scheduled assessments
	Achievement of response in at least 1 TMA parameter at all scheduled assessments
	Changes from baseline in hematologic response parameters at all scheduled assessments: • Platelets • LDH • Hemoglobin
To assess impact on hemoglobin levels	Increases in hemoglobin at Week 26 of: • ≥ 1 gram/dL • ≥ 2 grams/dL
To evaluate change in kidney function	Change from baseline in eGFR at Week 26 [a]
	On dialysis at Week 26 [a]
	Change from baseline in eGFR at all scheduled assessments
	Change from baseline in dialysis requirement at Week 26 and Week 52
	Duration of dialysis
To assess duration of Complete TMA Response and TMA Relapse	Complete TMA Response at Week 52 among participants who achieved Complete TMA Response during the 26-week Treatment Period
	Loss of TMA Response during the 26-week Treatment Period (for participants who achieved Complete TMA Response during the 26-week randomized Treatment Period)
	TMA Relapse during post treatment follow-up period (for participants who achieved Complete TMA response during the 26-week randomized Treatment Period)
To assess improvement in patient-reported QoL outcomes	Change in patient-reported outcomes as measured by FACIT-Fatigue at all scheduled assessments
PK/PD/Immunogenicity	
To assess PK/PD of ravulizumab in participants with TMA	Serum ravulizumab concentrations over time
	Absolute values, change from baseline, and percentage change from baseline in serum free C5 concentrations over time
	Absolute values, change from baseline, and percentage change from baseline in serum total C5 concentrations over time
To characterize the potential for immunogenicity of ravulizumab in participants with TMA	Incidence and titers of ADAs over time
Safety	
To characterize the safety profile of ravulizumab in participants with TMA	Incidence of AEs and SAEs by Week 26 and Week 52
	Incidence of MACEs by Week 26 and Week 52

Objectives	Endpoints
	Changes from baseline in vital signs and laboratory parameters at scheduled assessments

[a] Key secondary endpoints. The primary and key secondary efficacy analyses will use a hierarchical stepdown closed-testing procedure.

Abbreviations: ADA = antidrug antibody; AE = adverse event; C5 = complement component 5; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; MACE = major adverse cardiovascular event; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QoL = quality of life; SAE = serious adverse event; TMA = thrombotic microangiopathy.

Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled study of ravulizumab in addition to best supportive care (BSC) in adult participants (≥ 18 years of age) with TMA following a defined trigger. All participants must have severe acute kidney injury and a diagnosis of TMA based on protocol-defined criteria (ie, thrombocytopenia, microangiopathic hemolytic anemia, elevated lactate dehydrogenase [LDH]), which is associated with at least 1 trigger, such as autoimmune disease, infection, solid organ transplant, drugs, or malignant hypertension, occurring during the Screening Period and/or ≤ 14 days prior to start of the Screening Period.

The study consists of an up to 2-week Screening Period, a 26-week randomized Treatment Period, and a 26-week Post-treatment Follow-up Period. Thus, the total treatment duration is 26 weeks and the total study duration is up to 54 weeks.

Participants will be screened for eligibility for up to 2 weeks during the Screening Period (and/or ≤ 14 days prior to start of the Screening Period for laboratory parameters). Approximately 100 adult participants will be randomized in a 1:1 ratio to receive either ravulizumab or placebo. Randomization will be stratified by baseline dialysis status and by primary trigger type.

During the 26-week Treatment Period, all participants will receive a weight-based loading dose of ravulizumab or placebo on Day 1, followed by weight-based maintenance doses of ravulizumab or placebo on Day 15 and then once every 8 weeks (q8w) thereafter. All participants will receive BSC throughout the study.

During the 26-week Post-Treatment Follow-up Period, participants will continue to receive BSC, at the discretion of the Investigator and will be monitored for safety, TMA response, and clinical events of interest.

The end of the study is defined as the last participant's last visit in the Post-treatment Follow-up Period.

Disclosure Statement: This is a parallel group treatment study with 2 arms that is participant, Investigator, and outcomes assessor blinded.

Number of Participants: Approximately 100 participants will be enrolled in the study.

Intervention Groups and Duration:

Eligible participants will be enrolled into the study and will be randomized in a 1:1 ratio to receive either ravulizumab IV infusion or placebo IV infusion in combination with BSC.

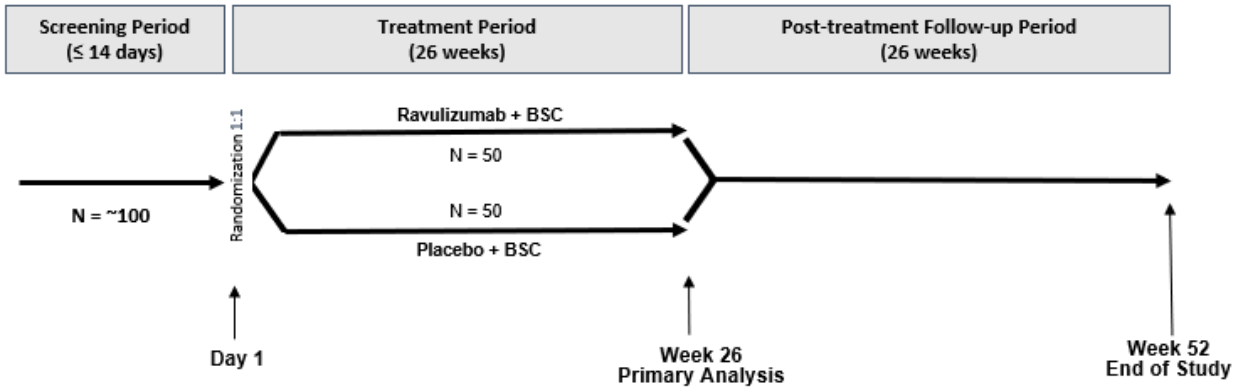
Ravulizumab will be supplied as a sterile, preservative-free 10 mg/mL solution in single-use vials, designed for administration via IV infusion by diluting into commercially available saline (0.9% sodium chloride injection). Placebo will have an identical appearance to that of ravulizumab.

Ravulizumab has been shown to achieve immediate, complete, and sustained inhibition of terminal complement in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) and in pediatric and adult patients with aHUS. It is expected that the same dosing regimen will also achieve comparable inhibition of complement-mediated damage in patients with TMA.

Data Monitoring Committee: No

1.2. Schema

Figure 1: Study Design Schematic



Note: Randomized participants will receive a weight-based loading dose on Day 1, followed by weight-based maintenance dosing on Day 15 and then q8w. Weight-based dosing regimen will be based on the last recorded study visit body weight.

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 exceptions of the ST-HUS screen and ADAMTS13 activity tests which must be performed at the central laboratory. With the exceptions of the ST-HUS screen and ADAMTS13 activity tests, if local labs are used to establish eligibility, central laboratory tests are not required at the Screening visit.

Abbreviations: ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; BSC = best supportive care; q8w = every 8 weeks; ST-HUS = Shiga toxin-related hemolytic uremic syndrome; TMA = thrombotic microangiopathy.

1.3. Schedule of Activities

Schedules of activities are provided as follows:

- Screening and 26-week Treatment Period provided in Table 1
- 26-week Post-treatment Follow-up Period provided in Table 2

Table 1: Schedule of Activities for Screening and 26-Week Treatment Period

Period	**Screen-ing**	**Treatment Period**													**Notes**
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Week	**Up to 2 W**		**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26/ ED[a]**	
Days and Window	**D -14 to -1**	**D1**	**D8 ± 2**	**D15 ± 2**	**D22 ± 2**	**D29 ± 2**	**D43 ± 2**	**D57 ±2**	**D71 ± 3**	**D85 ± 3**	**D99 ± 3**	**D127 ± 3**	**D155 ± 3**	**D183 ± 3**	
General Assessments/Procedures															
Informed consent	X														
Confirm inclusion/exclusion	X	X													Confirm eligibility prior to first dose of ravulizumab; participants may be rescreened once
Demographics	X														
Medical history	X														
TMA diagnosis/history	X														
Transfusion/dialysis history	X														Section 8.2.2 and Section 8.2.3
Prior medications and procedures	X														
Meningococcal vaccination	X	Completion of vaccination series and re-vaccination according to national and local guidelines													Section 8.1.5
Hib and *S pneumoniae* vaccination	X	Completion of vaccination series and re-vaccination according to national and local guidelines													Only required if indicated according to current national/local vaccination guidelines for participants with lupus nephritis, systemic sclerosis, or solid organ transplant (Section 8.1.5)
Full physical examination	X													X	
Abbreviated physical examination		X	X	X	X	X	X	X	X	X	X	X	X		
Weight and height[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Height only at Screening
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serology	X														Section 10.2
Specialty screening labs	X[d]														ADAMTS13, Coombs test, and ST-HUS
Pregnancy test (WOCBP only)	X	X		X	X	X			X			X		X	Serum test required at Screening, Day 183 and EOS/ED; urine test all other visits
ECG[e]	X													X	

Table 1: Schedule of Activities for Screening and 26-Week Treatment Period

Period	Screen-ing	Treatment Period													Notes
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Week	**Up to 2 W**		**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26/ ED[a]**	
Days and Window	**D -14 to -1**	**D1**	**D8 ± 2**	**D15 ± 2**	**D22 ± 2**	**D29 ± 2**	**D43 ± 2**	**D57 ±2**	**D71 ± 3**	**D85 ± 3**	**D99 ± 3**	**D127 ± 3**	**D155 ± 3**	**D183 ± 3**	
Dispense participant safety card	X														Instruct participants to carry safety card at all times and bring it to scheduled visits
Patient Reported Outcome Questionnaires		X				X					X			X	FACIT-Fatigue, EQ-5D-5L, and KDQOL-36
Blood sample and spot urine collection for clinical laboratory tests	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes hematology, coagulation (screening only), clinical chemistry panels, as well as clinical complement tests and spot urine samples (Section 10.2)
Concomitant medications, nonpharmacologic therapies, and procedures		Continuous monitoring													
Adverse events	X	Continuous monitoring													
Participant safety card review		Continuous monitoring													
Medical resource utilization	X	Continuous monitoring													
Transfusion requirements		Continuous monitoring													
Dialysis requirements		Continuous monitoring													
Survival status		Continuous monitoring													
PK/PD/Immunogenicity Assessments															
Predose blood samples for PK/PD[f]		X		X					X			X		X	Collected anytime at Week 26 and ED Visit
Postdose blood samples for PK/PD[g]		X		X					X			X			
Predose blood sample for ADA		X							X			X		X	Collected anytime at Week 26 and ED Visit
Exploratory Assessments															
Blood and urine samples for exploratory biomarkers	X[h]	X		X			X			X		X		X	Section 8.9

Table 1: Schedule of Activities for Screening and 26-Week Treatment Period

Period	Screen-ing	Treatment Period													Notes
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Week	**Up to 2 W**		**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26/ ED[a]**	
Days and Window	**D -14 to -1**	**D1**	**D8 ± 2**	**D15 ± 2**	**D22 ± 2**	**D29 ± 2**	**D43 ± 2**	**D57 ±2**	**D71 ± 3**	**D85 ± 3**	**D99 ± 3**	**D127 ± 3**	**D155 ± 3**	**D183 ± 3**	
Blood and urine samples for RTCA	X[h]	X		X			X			X		X		X	All sites are to collect and ship frozen RTCA plasma and urine samples to the central laboratory. Only selected sites will perform additional on-site testing of freshly collected blood, plasma and urine using a dedicated RTCA reader and specific instructions provided by the Sponsor and as defined in the laboratory manual. See Section 8.9.3
Blood sample for genetic testing[i]		X[i]													May be collected anytime during study
Study Intervention															
Randomization		X													
Ravulizumab or placebo		X		X					X			X			Administer after all other required tests/procedures.

Note: All assessments should be performed prior to administration of study drug on dosing days, unless otherwise specified. For participants on dialysis, study visits should be conducted on non-dialysis days, whenever possible. However, if this is not feasible, then all study-related procedures and study drug administration should be performed prior to the participant receiving dialysis.

[a] For participants who discontinue study drug prior to the end of the Treatment Period, the ED visit should be completed as soon as possible. In addition, a Follow-up Phone Call will be performed 8 weeks (56 days) ± 5 days following the participant's last dose of study drug to collect concomitant medications, nonpharmacologic therapies and procedures, and AEs.

[b] Weight should be obtained at every visit and measured predose on dosing visits. The dose regimen is based on the last recorded study visit body weight. If the study drug is prepared the day before a visit, the weight from the previous study visit may be used.

[c] Vital sign measurements include systolic and diastolic BP, pulse oximetry, heart rate, respiratory rate, and body temperature. On dosing days, vital signs will be taken predose.

[d] 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 exceptions of the ST-HUS screen and ADAMTS13 activity tests which must be performed at the central laboratory. With the exceptions of the ST-HUS screen and ADAMTS13 activity tests, if local labs are used to establish eligibility, central laboratory tests are not required at the Screening visit.

[e] Participants must be supine during ECG collection.

[f] The baseline predose sample on Day 1 will be collected within 90 minutes prior to the start of infusion. For all subsequent visits falling on dosing days, predose samples will be collected within 0.5 hours prior to the start of infusion. In order to minimize needle sticks to the participant, the predose sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose.

[g] Samples will be collected postdose at EOI (within 0.5 hours after the EOI from the participant's opposite, noninfused arm).

[h] Collect blood and urine samples for exploratory biomarker and RTCA prior to therapeutic plasma exchange/plasma infusion, if applicable. Participants are prohibited from receiving therapeutic plasma exchange / plasma infusion at any time following randomization during the Treatment Period.

[i] For participants that provide additional informed consent for genetic testing.

Abbreviations: ADA = antidrug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AE = adverse event; BP = blood pressure; D = day; ECG = electrocardiogram; ED = early discontinuation; EQ-5D-5L = EuroQoL 5 Dimension 5 Level; FACIT = Functional Assessment of Chronic Illness Therapy; KDQOL-36 = Kidney Disease Quality of Life instrument – 36 items; PD = pharmacodynamics; PK = pharmacokinetics; RTCA = Real Time Complement Activity; ST-HUS = Shiga toxin-related hemolytic uremic syndrome; TMA = thrombotic microangiopathy; W = Week; WOCBP = woman of childbearing potential.

Table 2: Schedule of Activities During the Post-treatment Follow-up Period

Period	Post-treatment Follow-up Period			Notes
Visit	**14**	**15**	**16**	
Week	**W34**	**W43**	**W52/EOS**	
Days and window	**D239 ± 7**	**D302 ± 7**	**D365 ± 7**	
General Procedures/Assessments				
Pregnancy test (WOCBP only)	X		X	Serum test required at Screening, Day 183 and EOS/ED; urine test all other visits
Abbreviated physical examination	X	X	X	
Vital signs[a]	X	X	X	
Blood samples and spot urine collection for clinical laboratory tests			X	Includes hematology, clinical chemistry panels, as well as clinical complement tests and spot urine samples (Section 10.2)
Patient Reported Outcome Questionnaires	X		X	FACIT-Fatigue, EQ-5D-5L, and KDQOL-36
Concomitant medications, nonpharmacologic therapies, and procedures	Continuous monitoring			
Adverse events	Continuous monitoring			
Participant safety card review	Continuous monitoring			Participants are to carry the card with them at all times until 8 months after the last dose of study drug
Medical resource utilization	Continuous monitoring			
Transfusion requirements	Continuous monitoring			
Dialysis requirements	Continuous monitoring			
Survival status	Continuous monitoring			
PK/PD/Immunogenicity Assessments				
Blood samples for PK/PD	X		X	Samples collected anytime
Blood sample for ADA	X		X	Samples collected anytime
Exploratory Assessments				
Blood and urine samples for exploratory biomarkers	X	X	X	Section 8.9

[a] Vital sign measurements include systolic and diastolic BP, pulse oximetry, heart rate, respiratory rate, and body temperature.

Abbreviations: ADA = antidrug antibody; D = day; EOS = end of study; EQ-5D-5L = EuroQoL 5 Dimension 5 Level; FACIT = Functional Assessment of Chronic Illness Therapy; KDQOL-36 = Kidney Disease Quality of Life instrument – 36 items; PD = pharmacodynamics; PK = pharmacokinetics; W = Week; WOCBP = woman of childbearing potential.

2. INTRODUCTION

2.1. Study Rationale

The development of TMA often follows activation of complement by a trigger. Such triggers include, but are not limited to, autoimmune disease, infection, drug exposure, transplant (solid organ or bone marrow), malignant hypertension, and pregnancy (Goodship, 2017). Ravulizumab is a humanized monoclonal antibody that binds to C5 and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin complement component 5a (C5a) and the formation of the terminal complement complex via C5b. Phase 3 studies of C5 inhibition with ravulizumab demonstrated efficacy in the treatment of TMA due to aHUS in adult and pediatric patients. In these studies, ravulizumab treatment achieved complete terminal complement inhibition resulting in Complete TMA Response, defined by normalization of hematologic parameters and improvement in renal function in the majority of patients (Rondeau, 2020). The study population included patients who presented with TMA after renal transplant or pregnancy, but excluded other triggers such as infection, drug exposure, and autoimmune disease.

The objective of this study is to evaluate the efficacy and safety of ravulizumab administered by IV infusion compared to placebo in adult participants with TMA associated with a range of triggers.

2.2. Background

Thrombotic microangiopathy is a rare, life-threatening disease often caused by complement activation that results in endothelial damage. In some patients, complement-mediated TMA may result from a trigger that injures the endothelium, such as post-partum, malignant hypertension (sometimes termed hypertensive emergency), infection, transplant (solid organ or bone marrow), autoimmune disease, and certain drugs (Aigner, 2019; Go, 2016; Goodship, 2017; Park, 2018). Many patients present in critical condition, require management in an intensive care unit, and often need dialysis. Once multiorgan dysfunction develops, patients have a poor prognosis (Le Clech, 2019).

Two complement C5 inhibitors, ravulizumab and eculizumab, are approved for the treatment of patients with aHUS, a type of complement-mediated TMA. There are currently no approved therapies for the broader complement-mediated TMA population. Treatment typically consists of corticosteroids and/or therapeutic plasma exchange (TPE) or plasma infusion. The underlying trigger may also be treated, along with other supportive measures (eg, transfusion, dialysis), as appropriate. While TPE/plasma infusion will improve hematologic parameters in complement-mediated TMA, neither corticosteroids nor TPE/plasma infusion will address the underlying complement dysregulation and the TMA process is likely to persist (Azoulay, 2017; Kavanagh, 2006; Laurence, 2013). Removal of the trigger and supportive care are sometimes sufficient to reverse TMA symptoms; however, in patients with severe renal manifestations, outcomes are not greatly improved after removing/treating the trigger and providing supportive care.

In patients with aHUS, ravulizumab achieved immediate, complete, and sustained inhibition of terminal complement and improved renal function (Rondeau, 2020). It is hypothesized that

ravulizumab will be similarly effective in the treatment of complement-mediated TMA at the approved aHUS dosing regimen.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ravulizumab is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks of ravulizumab is provided in the IB.

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 antidrug antibodies (ADAs). Monitoring of immunogenicity is planned during this study, as described in Section 8.8. Intravenous administration of any investigational product may result in infusion reactions. Management of potential infusion reactions is described in Section 10.5.

The coronavirus disease 2019 (COVID- 19) pandemic is active in many countries at the time of this protocol development. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID- 19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.9.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of ravulizumab may be found in the IB or local product labeling.

Table 3: Potential Risks and Mitigation Strategies

Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Identified risk		
Meningococcal infection	Complement C5 inhibition is known to increase the susceptibility to infections caused by *N meningitidis*.	Participants must be vaccinated against all available serotypes of *N meningitidis* (A, C, Y, W 135, and B) where available. 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 the participant is able to be vaccinated, antibiotic prophylaxis for meningococcal infections should 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 of ravulizumab, the mechanism that may lead to other serious infections in patients treated with ravulizumab remains unclear. Since the relevance of serious infection with ravulizumab therapy has not been confirmed in clinical trials, this remains a potential risk.	Increased awareness of healthcare professionals and participants about the potential risk of serious infection. Monitoring for signs and symptoms of serious infections will be conducted as part of routine safety assessments for this study.
Immunogenicity	Treatment with any therapeutic protein has the potential to induce an immune response. Potential clinical consequences may include hypersensitivity type reactions, decrease in efficacy, and induction of autoimmunity, including antibodies to the endogenous form of the protein (Casadevall, 2002; Li, 2001). Protein therapies administered intravenously have the potential risk of causing local (infusion-site) reactions and systemic reactions (infusion-associated reactions).	In Studies ALXN1210-PNH-103 and ALXN1210-PNH-201, no participant had a positive ADA sample. In Phase 3 studies in PNH (N = 261) and aHUS (N = 89) patients, there were 2 (0.57%) cases of treatment-emergent ADAs reported with ravulizumab. Presence of ADA will be assessed. 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 for a period of 8 months

Table 3: Potential Risks and Mitigation Strategies

Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		following the final dose of ravulizumab. Breastfeeding should be discontinued during treatment and for up to 8 months after treatment with ravulizumab.

Abbreviations: ADA = antidrug antibody; aHUS = atypical hemolytic uremic syndrome; C5 = complement component 5; PNH = paroxysmal nocturnal hemoglobinuria.

2.3.2. Benefit Assessment

Complement-mediated TMA is a rare and potentially fatal disease with limited treatment options, and severe renal injury is often irreversible, therefore development of new therapies is important to address unmet medical needs.

Ravulizumab represents an appropriate candidate for investigation due to demonstrated efficacy and safety in treatment of aHUS and other disorders of complement, including PNH.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the high unmet need for effective therapies for complement-mediated TMA, the outcomes of this patient population with currently available care, along with the measures taken to minimize risk to participants in this study, the potential risks of ravulizumab are justified by the anticipated benefits.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints for Study ALXN1210-TMA-315 are provided in Table 4. A mapping of objectives to estimands is provided in Section 10.2.

3.1. Overview of Objectives and Endpoints

Table 4: Mapping Objectives to Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of ravulizumab in the treatment of participants with TMA	Complete TMA Response during the 26-week randomized Treatment Period (Section 3.2.1)
Secondary	
To characterize TMA response	Time to Complete TMA Response during the 26-week randomized Treatment Period [a]
	Time to response for each TMA parameter during the 26-week Treatment Period
	Achievement of hematologic response (Section 3.2.2) at Week 26 [a]
	Achievement of hematologic response at all scheduled assessments
	Achievement of renal response (Section 3.2.3) at all scheduled assessments
	Achievement of response in at least 1 TMA parameter at all scheduled assessments
	Changes from baseline in hematologic response parameters at all scheduled assessments: • Platelets • LDH • Hemoglobin
To assess impact on hemoglobin levels	Increases in hemoglobin at Week 26 of: • ≥ 1 gram/dL • ≥ 2 grams/dL
To evaluate change in kidney function	Change from baseline in eGFR at Week 26 [a]
	On dialysis at Week 26 [a]
	Change from baseline in eGFR at all scheduled assessments
	Change from baseline in dialysis requirement at Week 26 and Week 52
	Duration of dialysis
To assess duration of Complete TMA Response and TMA Relapse	Complete TMA Response at Week 52 among participants who achieved Complete TMA Response during the 26-week Treatment Period
	Loss of TMA Response (Section 3.2.4) during the 26-week Treatment Period (for participants who achieved Complete TMA Response during the 26-week randomized Treatment Period)
	TMA Relapse (Section 3.2.4) during post treatment follow-up period (for participants who achieved Complete TMA response during the 26-week randomized Treatment Period)
To assess improvement in patient-reported QoL outcomes	Change in patient-reported outcomes as measured by FACIT-Fatigue at all scheduled assessments
PK/PD/Immunogenicity	
To assess PK/PD of ravulizumab in participants with TMA	Serum ravulizumab concentrations over time
	Absolute values, change from baseline, and percentage change from baseline in serum free C5 concentrations over time

Objectives	Endpoints
	Absolute values, change from baseline, and percentage change from baseline in serum total C5 concentrations over time
To characterize the potential for immunogenicity of ravulizumab in participants with TMA	Incidence and titers of ADAs over time
Safety	
To characterize the safety profile of ravulizumab in participants with TMA	Incidence of AEs and SAEs by Week 26 and Week 52
	Incidence of MACEs (Section 8.4.5) by Week 26 and Week 52
	Changes from baseline in vital signs and laboratory parameters at scheduled assessments
Exploratory	
To assess improvement in extrarenal manifestations	Extrarenal manifestations by Week 26 and Week 52
To assess impact of treatment on resolution of hemolysis	RBC transfusions by Week 26 and Week 52
To assess improvement in patient-reported QoL outcomes	Change in patient-reported outcomes as measured by EQ-5D-5L and KDQOL-36
To assess biomarkers and autoantibodies in participants with TMA	Exploratory biomarkers will be assessed in blood and urine for change from baseline and may include but are not limited to, markers of vascular damage, renal injury and complement dysregulation (eg, sC5b-9, factor Ba).
To assess complement pathway genetic mutations in participants with TMA associated with a trigger	Incidence of complement dysregulation-related mutations
To assess health resource utilization during the study	Number and duration of hospitalizations (including stays in intensive care unit, if applicable)
	Number of outpatient visits (including physician and emergency room visits)
To assess impact on overall survival	Overall survival by Week 26 and Week 52

[a] Key secondary endpoints. The primary and key secondary efficacy analyses will use a hierarchical stepdown closed-testing procedure as described in Section 9.4.1.3.

Abbreviations: ADA = antidrug antibody; AE = adverse event; Ba = complement factor Ba; C5 = complement component 5; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQoL 5 Dimension 5 Level; FACIT = Functional Assessment of Chronic Illness Therapy; GI = gastrointestinal; KDQOL-36 = Kidney Disease Quality of Life instrument – 36 items; LDH = lactate dehydrogenase; MACE = major adverse cardiovascular event; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PLT = platelet; QoL = quality of life; SAE = serious adverse event; sC5b-9 = soluble terminal complement complex C5b-9 (membrane attack complex); TMA = thrombotic microangiopathy.

3.2. Definitions of Endpoints

3.2.1. Complete TMA Response

Complete TMA Response is defined as the normalization of hematologic parameters (platelet count and LDH) and ≥ 30% improvement in estimated glomerular filtration rate (eGFR) from baseline (Table 5).

For Complete TMA Response, participants must have met all 3 TMA response parameters, with each parameter meeting the requirement at 2 separate assessments obtained at least 24 hours apart, and any measurement in between. The first laboratory value will be assessed based on central laboratory results; the second laboratory value will be assessed based on the earliest value obtained ≥ 24 hours after the first value and may be based on central or local laboratory results.

Table 5: Overview of Complete Thrombotic Microangiopathy Response

		TMA Response Parameter
Complete TMA Response	Hematologic Response	• Normalization of platelet count without transfusion support during the prior 7 days
		• Normalization of LDH
	Renal Response	• Improvement in eGFR of ≥ 30% compared to baseline

Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

3.2.2. Hematologic Response

Hematologic Response is defined as the normalization of platelets without transfusion support during the prior 7 days and the normalization of LDH.

3.2.3. Renal Response

Renal Response is defined as an improvement in eGFR of ≥ 30% compared to baseline.

3.2.4. Loss of TMA Response

For participants that meet the criteria for Complete 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. The first laboratory value will be assessed based on central laboratory results; the second laboratory value will be assessed based on the earliest value obtained ≥ 24 hours after the first value and may be based on central or local laboratory results.

3.2.5. TMA Relapse

For participants that meet the criteria for Complete TMA Response during the 26-week Treatment Period, TMA Relapse is defined as evidence of worsening hematologic and renal dysfunction due to TMA during the post-treatment follow-up period and requires treatment intervention, as determined by the Investigator.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled study of ravulizumab in addition to BSC in adult participants (≥ 18 years of age) with TMA following a defined trigger. All participants must have acute kidney injury and a diagnosis of TMA, based on the protocol-defined criteria (ie, thrombocytopenia, microangiopathic hemolytic anemia, elevated LDH) occurring during the Screening Period and/or ≤ 14 days prior to start of the Screening Period, and which is associated with at least 1 trigger, such as autoimmune disease, infection, solid organ transplant, drugs, or malignant hypertension.

The study consists of an up to 2-week Screening Period, a 26-week randomized Treatment Period, and a 26-week Post-treatment Follow-up Period (Figure 1). Thus, the total treatment duration is 26 weeks and the total study duration is up to 54 weeks.

Participants will be screened for eligibility for up to 2 weeks during the Screening Period (and/or ≤ 14 days prior to start of the Screening Period for laboratory parameters). Approximately 100 adult participants will be randomized in a 1:1 ratio to receive either ravulizumab or placebo. Randomization will be stratified by baseline dialysis status and by primary trigger type.

During the Treatment Period, all participants will receive a weight-based loading dose of ravulizumab or placebo on Day 1, followed by weight-based maintenance doses of ravulizumab or placebo on Day 15 and then q8w thereafter (Table 7). All participants will receive BSC throughout the study as defined in Section 6.5.

During the Post-treatment Follow-up Period, participants may continue to receive BSC, at the discretion of the Investigator, and will be monitored for safety, TMA response, and clinical events of interest. If a participant meets criteria for TMA Relapse (Section 3.2.5) during the Post-Treatment Follow-up Period, the participant may be treated with BCS at the discretion of the Investigator.

The end of the study is defined as the last participant's last visit in the Post-treatment Follow-up Period.

4.2. Scientific Rationale for Study Design

A randomized, double-blind, placebo-controlled study design is selected to provide the most robust evidence of the efficacy of ravulizumab on TMA response, disease progression, and safety. Randomization minimizes the effects of baseline differences and confounding factors on the study endpoints. The use of a placebo comparator allows for a more accurate assessment of the true effects of treatment with ravulizumab.

Randomization will be stratified by baseline dialysis status and by primary trigger type using a dynamic allocation procedure. This dynamic randomization improves treatment balance when the number of strata is large compared to the total number of participants enrolled in the study.

The 26-week treatment duration was chosen to provide adequate time to assess safety, TMA response, and other efficacy endpoints after treatment with ravulizumab.

The study will limit the time between TMA presentation and treatment initiation, as well as the duration of dialysis prior to treatment initiation, to 2 weeks to assess the benefit of early intervention with ravulizumab on recovery of renal function. Because this study aims to establish efficacy with ravulizumab as an early therapeutic option for participants with complement-mediated TMA, in combination with removal of the trigger, the targeted study population will be participants who meet TMA criteria, but have more severe renal manifestations.

4.2.1. Rationale for the Primary Endpoint

The primary endpoint is Complete TMA Response during the 26-week randomized Treatment Period.

The renal component of the primary endpoint, improvement of ≥ 30% in eGFR, closely approximate with a ≥ 25% improvement in serum creatinine, which was a component of the primary endpoint in clinical studies of ravulizumab in treating patients with aHUS (Rondeau, 2020).

Measuring GFR through renal clearance of infused exogenous agents (eg, inulin) is the gold standard technique for assessing kidney function. Serum creatinine has been the most widely used surrogate for measured GFR, however, is confounded by endogenous factors including sex, ethnicity and age and exogenous factors such as creatinine assay variability and certain classes of medications that modulate renal handling of creatinine. This makes serum creatinine a poor surrogate for kidney function. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for eGFR calculation is widely used for diagnosis and monitoring of kidney disease and was introduced because of known limitations of serum creatinine measurement (Florkowski, 2011). The CKD-EPI has been validated against measured GFR. The eGFR calculation uses sex, ethnicity, and age of the patient, some of the sources of variation when using the serum creatinine alone. However, as creatinine is effectively the only measured parameter in the eGFR equation, errors in the serum creatinine will produce errors in the eGFR. Serum creatinine has a low intra-individual coefficient of variation (CV) compared with the between individual CV. Thus, serum creatinine is not very sensitive as a marker of deteriorating renal function when an individual is compared to the population reference range. Indeed, it has been shown that the serum creatinine can remain within the population reference interval when the individual's GFR has decreased by 50% (Shemesh, 1985).

The renal component of the primary endpoint, improvement of ≥ 30% in eGFR, rather than complete recovery, is selected because renal repair after an insult is often maladaptive with inflammation, fibrosis, and vascular rarefaction leading to persistent cell and tissue malfunction and eventually chronic kidney disease (CKD). The frequency, severity, type, and duration of injury as well as the premorbid renal reserve seem to be risk factors for maladaptive repair (Venkatachalam, 2015). It is likely that maladaptive repair mechanisms will hinder complete recovery of renal function. In addition, patients with renal dysfunction are often continued on renal-protective medications, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), which are known to reduce eGFR. Moreover, post-transplant patients are maintained on calcineurin inhibitors (CNIs), which are also known to reduce eGFR.

4.2.2. Rationale for the Secondary Endpoints

Time to achieve Complete TMA Response during the 26-week Treatment Period will provide prescribers with additional guidance to evaluate and characterize efficacy of ravulizumab treatment. In addition, given the fact that the resolution of the different TMA components may occur at different time points after treatment initiation, and that some participants may experience partial response, additional key secondary endpoints including the proportion of participants that achieve the individual components of the Complete 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 an increase of $\geq$ 1 gram/dL and $\geq$ 2 grams/dL in hemoglobin will also be assessed.

Complement-mediated TMA is a multisystem complication with prominent kidney involvement. Literature shows that up to 40% or more of patients with complement-mediated TMA are on dialysis at presentation (Le Clech, 2019). Therefore, secondary endpoints to assess change in dialysis status as well as change in eGFR have been chosen.

4.3. Justification for Dose

Ravulizumab has been shown to achieve immediate, complete, and sustained inhibition of terminal complement in adult patients with PNH and in pediatric and adult patients with aHUS. It is expected that the same dosing regimen will also achieve comparable inhibition of complement-mediated damage in patients with TMA.

4.4. Remote Visit Options in Times of Emergency

To ensure participant safety and treatment continuity in times of emergency (eg, COVID-19 pandemic), the following will apply where participants are not able to reach the study sites, and until participants are able to resume study visits at the site. If a participant is not able to complete a visit where study drug is administered, the Investigator should contact the Medical Monitor to determine next appropriate steps.

Remote visit options may be at the Investigator's discretion and oversight, in accordance with the local regulations. Remote visit options include visits conducted virtually through phone or video conference. All assessments for the study visit day should be conducted according to the Schedule of Activities (Section 1.3), whenever possible. At minimum, information about AEs, concomitant medications, background therapies, and disease-related signs or symptomatology must be collected by the Investigator for evaluation on the day of the remote visit and recorded in the source documents. In case of any signs or symptoms indicating a serious adverse event (SAE), the participant will need to be evaluated at the study site.

4.5. End of Study Definition

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

The end of the study is defined as the date the last participant completes the last visit shown in the Schedule of Activities for the Post-treatment Follow-up Period.

5. STUDY POPULATION

- Eligibility evaluation may be based on laboratory results obtained during the Screening Period or ≤ 14 days prior to the start of the Screening Period.
- Local or central laboratory results may be used to determine eligibility, with the exceptions of the ST-HUS screen and ADAMTS13 activity tests which must be performed at the central laboratory. With the exceptions of the ST-HUS screen and ADAMTS13 activity tests, if local labs are used to establish eligibility, central laboratory tests are not required at the Screening visit.
- Participants may be randomized prior to availability of central laboratory results from the ST-HUS screen and ADAMTS13 test.
  - If a participant is found not to meet eligibility based on central laboratory results for the ST-HUS screen and ADAMTS13 activity tests following randomization, the participant must be discontinued and will be replaced. Participants discontinued following randomization based on ST-HUS screen and ADAMTS13 test results will not be counted towards the total sample size as described in Section 9.2. Analyses in this study are planned to be based on results from the central laboratory.
- Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

To be eligible to participate in the study, participants must meet all of the below criteria:

Age

1. Must be ≥ 18 years of age at the time of signing the informed consent

Weight

2. Body weight ≥ 30 kg at Screening

Sex

3. Male and female

   Female participants of childbearing potential and male participants must follow protocol-specified contraception guidance as described in Section 10.6.

Disease Characteristics

4. TMA within ≤ 14 days prior to Screening is associated with at least 1 of the following triggers:

   a. Autoimmune (lupus nephritis, systemic sclerosis associated TMA [SSc-TMA])
   b. Infection
   c. Solid organ transplant (eg, kidney, pancreas, liver, heart, small bowel)
   d. Drugs
   e. Malignant hypertension

5. Confirmation of all of the following laboratory findings during the Screening Period and/or ≤ 14 days prior to the start of the Screening Period:
   a. Platelet count < 150,000/μL
   b. Lactate dehydrogenase ≥ 1.5 × ULN and hemoglobin ≤ LLN (based on age and sex)
   c. Acute kidney injury as defined by meeting 1 or more of the following criteria (for kidney transplant recipients, the pre-TMA value is based on post-transplant eGFR):
      – Acute decline in eGFR ≥ 50% from pre-TMA value (pre-TMA value must be ≤ 12 months prior to Screening)
      – New acute kidney injury with an eGFR ≤ 30 mL/min/1.73 m^2
      – New initiation of dialysis due to TMA requiring > 1 session and for no more than 14 days prior to Screening

Vaccinations and Antibiotics

6. Vaccinated against meningococcal infection (*N meningitidis*), within 3 years prior to, or at the time of, randomization. Participants who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive appropriate prophylactic antibiotics for at least 2 weeks after the vaccination. If participant cannot receive the meningococcal vaccine, then participant must be willing to receive antibiotic prophylaxis coverage against *N meningitidis* during the entire Treatment Period and for 8 months following the final dose of study drug.

Informed Consent

7. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Any known gene mutation that causes aHUS (Section 10.12)
2. Post-partum aHUS
3. Known CKD:
   - In participants with native kidneys: eGFR ≤ 45 mL/min/1.73 m^2 by CKD-EPI equation (Levey, 2009) due to any cause or ongoing acute kidney injury requiring dialysis treatment lasting for > 14 days prior to Screening.
   - In kidney transplant recipients: determination of CKD threshold will be based on Investigator judgment.
4. TMA due to hematopoietic stem cell transplantation ≤ 12 months of Screening
5. Primary and secondary glomerular diseases other than lupus
6. Diagnosis of primary antiphospholipid antibody syndrome

7. Known Shiga toxin-producing *Escherichia coli* infections including but not limited to Shiga toxin-related hemolytic uremic syndrome
8. Known familial or acquired 'a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13' (ADAMTS13) deficiency (activity < 5%)
9. Positive direct Coombs test which in the judgement of the Investigator is indicative of a clinically significant immune-mediated hemolysis not due to TMA
10. Clinical diagnosis of disseminated intravascular coagulation (DIC) in the judgement of the Investigator, utilizing the International Society on Thrombosis and Haemostasis (ISTH) scoring criteria (Section 10.13)
11. Presence of sepsis requiring vasopressors within 7 days prior to or during Screening
12. Presence of monoclonal gammopathy including but not limited to multiple myeloma
13. Known bone marrow insufficiency or failure evidenced by cytopenias
14. Kidney biopsy (if available) showing any of the following in glomeruli:
    - ≥ 50% interstitial fibrosis tubular atrophy;
    - ≥ 50% glomerulosclerosis;
    - ≥ 50% crescent formation.
15. Among transplant recipients, presence of confirmed cellular or antibody-mediated graft rejection
16. Life expectancy < 6 months, hospice, or palliative care
17. Unresolved *N meningitidis* infection
18. Human immunodeficiency virus (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
19. History of malignancy within 5 years of Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence
20. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the participant's full participation in the study, pose any additional risk for the participant, or confound the assessment of the participant or outcome of the study
21. Hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins
22. 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 randomization

Prior/Concomitant Therapy

23. Use of any complement inhibitors within the past 3 years

Prior/Concurrent Clinical Study Experience

24. Participation in the following types of interventional treatment studies within 30 days before Day 1 in this study or within 5 half-lives of that interventional treatment, whichever is greater:
    - Interventional treatment study of any unapproved therapy regardless of indication
    - Interventional treatment study of any therapy (approved or unapproved) being evaluated for TMA intervention

Other Exclusions

25. Pregnant, breastfeeding, or intending to conceive during the course of the study

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 randomized to either treatment group (ravulizumab or placebo). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (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.

During the Screening Period, potential participants who fail to meet laboratory eligibility criteria (eg, LDH, platelet count, and creatinine) will be allowed to repeat the laboratory test once 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.

For this study, the study intervention will include the administration of study drug (ravulizumab or placebo) in addition to BSC.

6.1. Study Drug Administered

Ravulizumab is formulated at pH 7.0 and is supplied in 30 mL single-use vials. Each vial of ravulizumab contains 300 mg of ravulizumab (10 mg/mL) in 10 mM sodium phosphate, 150 mM sodium chloride, 0.02% polysorbate 80, and water for injection. The comparator product (placebo) is formulated as a matching sterile, clear, colorless solution with the same buffer components, but without active ingredient. Additional details are presented in Table 6.

Table 6: Study Drug

Intervention Name	**Ravulizumab**	**Placebo**
Dose Formulation	Vial	Vial
Physical description	Liquid solution practically free from particles	Liquid solution practically free from particles
Unit Dose Strength	300 mg (10 mg/mL concentrated solution)	Placebo
Route of Administration	IV infusion	IV infusion
Use	Experimental	Placebo comparator
Sourcing	Provided centrally by Alexion or contracted manufacturing organization	Provided centrally by Alexion or contracted manufacturing organization
Packaging and Labeling	Ravulizumab will be provided in glass vials and stoppered with a butyl rubber stopper with aluminum overseal and flip-off cap. Ravulizumab will be supplied in kits and labeled as required per country requirement.	Placebo will be provided in glass vials and stoppered with a butyl rubber stopper with aluminum overseal and flip-off cap. Placebo will be supplied in kits and labeled as required per country requirement.

Abbreviations: IV = intravenous.

The dosing regimen consists of a loading dose followed by maintenance dosing administered q8w. The maintenance dosing will be initiated 2 weeks after the loading dose administration.

Weight-based dosing (Table 7) will be based on the participant's body weight recorded at the day of the infusion visit. If the study intervention must be prepared the day prior to the visit, the weight from the prior visit may be used to determine the dose.

Table 7: Weight-based Doses of Ravulizumab

Body Weight Range[a]	Loading Dose (Day 1)	Maintenance Doses (Days 15, 71, and 127)
≥ 30 to < 40 kg	1200 mg	2700 mg
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

[a] Dose will be based on the last recorded study visit body weight. If the study drug is prepared the day before a visit, the weight from the most recent study visit should be used.

At the scheduled dosing visits (Section 1.3), study drug should be administered after all other tests and procedures have been completed, excluding the postdose sample collections (pharmacokinetic [PK]/pharmacodynamic [PD]/biomarkers).

During the Treatment Period, participants will be randomized 1:1 to receive blinded doses of ravulizumab or placebo:

- Participants in the ravulizumab group will receive a blinded loading dose of ravulizumab via IV infusion on Day 1, followed by a blinded maintenance dose at Day 15 then q8w thereafter through the end of the Treatment Period.
- Participants in the placebo group will receive a blinded matching placebo dose via IV infusion on Day 1, followed by a blinded matching placebo dose at Day 15, then q8w thereafter through the end of the Treatment Period.

6.2. Preparation/Handling/Storage/Accountability

- The Investigator, or designee, must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Only participants enrolled in the study may receive the study drug and only authorized site staff may supply or administer the study drug. All study drug 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.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
  - 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 study 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.
- Further guidance regarding preparation, handling, storage, accountability, and final disposition of unused study drug is provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Participants will be randomized on Day 1. Participants will be randomized 1:1 either to the ravulizumab treatment group or to the placebo treatment group. Randomization will be performed centrally using Interactive Response Technology (IRT).

To balance the effects of potential confounding factors between the ravulizumab and placebo arms, randomization will be stratified by baseline dialysis status (Yes versus No) and primary trigger type (autoimmune, infection, solid organ transplant, drugs, or malignant hypertension) using a dynamic allocation procedure (Pocock, 1975).

6.3.2. Blinding

Participants, all investigative site personnel, and any Alexion employee, or designee, directly associated with the conduct of the study will be blinded to participant treatment assignments. The blinding will be maintained by using identical study drug kits and labels for ravulizumab and placebo. The placebo will have an identical appearance to that of ravulizumab. The randomization code will be maintained by the IRT provider.

The primary analysis will occur after all participants complete the Week 26 Visit or withdraw from the study prior to Week 26. Alexion will be unblinded at the time of the primary analysis and the treatment assignment for each patient will be communicated to the investigative site personnel at that time.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable. If the Investigator decides that unblinding is warranted, the Investigator will be able to unblind the patient's treatment allocation directly using the IRT. If a patient's intervention assignment is unblinded, the Investigator should make every effort to ensure that the intervention assignment is not revealed to other individuals (eg, other clinical research site staff, study team including the Alexion Medical Monitor), unless necessary for the best clinical care of the patient.

When an AE is unexpected or related and serious, the blind will be broken for that specific participant only. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the study site, monitors, and Investigators) and those responsible for data analysis and interpretation of results, such as biometrics personnel.

Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Independent Ethics Committees (IECs), and/or Institutional Review Boards (IRBs).

6.4. Study Intervention Compliance

During this study, participants will receive dosing with study drug under the supervision of the Investigator or designee.

The date and time of each dose administered will be recorded in the source documents and in the CRF.

6.5. Best Supportive Care

In this study, participants in both treatment groups will receive BSC as background therapy, which 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, which should be provided as required per institutional guidelines and based on the participant's clinical condition
- Anti-infectives (antibiotics, antivirals, and antifungals)
- Renal replacement therapy (dialysis)
- Antihypertensive medications
- Therapy for TMA associated with lupus nephritis or SSc-TMA
- Withdrawal or dose adjustment of the suspected agent for drug-induced TMA

6.6. Concomitant Therapy

6.6.1. Allowed Medicine and Therapy

Any medication or therapy (including over-the-counter or prescription medicines, vaccines, vitamins, and/or herbal supplements) 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 6.6.2, may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the CRF. Please note that guidance on the use of COVID-19 vaccines is provided in Section 10.10. Guidance on required vaccinations and antibiotic prophylaxis is provided in Section 8.1.5.

6.6.2. Disallowed Medicine and Therapy

Participants are prohibited from receiving therapeutic plasma exchange/plasma infusion at any time following randomization during the Treatment Period. Participants are prohibited from receiving any of the following medications and therapies during the entire duration of study participation:

- Experimental interventions or therapies
- Eculizumab or other agents that act on the complement pathway

In the event that a participant receives a prohibited medication and/or therapy, the Investigator must confer with the Medical Monitor to determine if the participant should discontinue study drug (Section 7.1).

6.7. Dose Modification

Dose modification of the study drug for an individual participant is not permitted for this study.

6.8. Intervention After the End of the Study

After a participant completes the Treatment Period or withdraws from the study, study drug will not be administered.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

A participant has the right to discontinue study drug at any time.

Participants must permanently discontinue the study drug for any of the following reasons:

- Hypersensitivity reaction meeting criteria for SAE
- Severe uncontrolled infection
- Pregnancy or planned pregnancy
- Participant is unblinded during the Treatment Period

In addition, the study drug may be permanently discontinued for any of the following reasons:

- Adverse event that would, in the opinion of the Investigator, make continued participation in the study an unacceptable risk
- Use of disallowed medication (as defined in Section 6.6.2)
- Deviation(s) from the protocol
- Significant non-compliance
- Alexion or the Investigator deems it is necessary for the participant
- Termination of the study

The reason for discontinuation of study drug will be recorded in the source documents and CRF.

If the study drug is definitively discontinued, every effort should be made to have the participant continue in the study as per the Schedule of Activities (Section 1.3) through the Week 52/End of Study (EOS) Visit (for safety follow up and collection of other data). If a participant discontinues study drug due to an AE, including SAEs, the event should be followed as described in Section 10.4.3.

Participants who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per the Investigator's judgment, as applicable.

If the participant does not agree to continue with the study visits, the following activities should be completed:

- Early Discontinuation (ED) Visit should be performed as outlined in the Schedule of Activities (Section 1.3).
- A Follow-up Phone Call will be performed 8 weeks following the participant's last dose of study drug to collect information on concomitant medications, nonpharmacologic therapies and procedures, and AEs.

7.2. Participant 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.
- For participants who withdraw from the study prior to Week 26, an ED Visit should be conducted, whenever possible, per the Schedule of Activities (Section 1.3). A Safety Follow-up Phone Call should be conducted at least 8 weeks after the final dose of study drug to collect information on concomitant medications, nonpharmacologic therapies and procedures, and AEs.
- For participants who withdraw from the study during the Follow-up Period, an EOS Visit should be conducted, whenever possible, per the Schedule of Activities (Section 1.3).
- The participant will be permanently discontinued from the study drug at the time of study withdrawal.
- 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 permitted by local requirements.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator, or designee, must document this in the site study records.
- Information about survival status at time of discontinuation and at Week 52 should be collected, whenever possible. If a participant's survival status is not available at the time of discontinuation, sites should attempt to collect the status (eg, via public records or telephone call).

7.3. 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.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- If a participant is deemed lost to follow-up, information about survival status at time of discontinuation and at Week 52 should be collected, whenever possible. 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 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedules of Activities (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 Schedules of Activities (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria as described in Section 5.
- The Investigator may delegate activities as permissible and documented in site delegation log.

8.1. General Assessments and Procedures

8.1.1. Informed Consent

The Investigator or qualified designee must obtain a signed and dated ICF for each participant and/or their legally authorized representative prior to conducting any study procedures. The process for informed consent 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.

8.1.2. Inclusion/Exclusion Criteria

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

8.1.3. Demographics

Demographic parameters, including age, sex, race, and ethnicity will be documented in the CRF.

8.1.4. Medical History

The participant's relevant medical history, including prior and concomitant conditions/disorders (including TMA diagnosis), treatment history, and family history of relevant diseases will be evaluated at Screening by the Investigator, or qualified designee, and documented in the source documents and CRF. Any changes to medical history occurring during the Screening Period and prior to first dose of study drug on Day 1 will be documented prior to study drug administration.

8.1.5. Vaccination and Antibiotic Prophylaxis

Due to its mechanism of action, the use of ravulizumab increases a participant's susceptibility to meningococcal infection due to *N meningitidis*. To reduce the risk of infection, all participants must be vaccinated within 3 years prior to or at the time of the first infusion of study drug. Participants who have not been vaccinated prior to starting study drug for any reason, should receive appropriate prophylactic antibiotics prior to and for at least 2 weeks after vaccination. Vaccines against serotypes A, C, Y, W135, and B where available, are recommended in preventing the commonly pathogenic meningococcal serotypes. Participants must receive the complete primary vaccination series and be revaccinated if indicated according to current national vaccination guidelines. Vaccination may not be sufficient to prevent meningococcal infection.

Participants should be administered prophylactic antibiotics for meningococcal infection until at least 2 weeks after vaccination if randomization occurs < 2 weeks after initial vaccination. Consideration should be given per official guidance and local practice on the appropriate use of prophylactic antibacterial agents. All participants should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary. Participants who cannot receive meningococcal vaccine should receive antibiotic prophylaxis coverage against *N meningitis* during the entire Treatment Period and for 8 months following the final dose of study drug.

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the participants during the course of the study, participants will be provided a Participant Safety Card to carry with them at all times (Section 8.3.1). Additional discussion and explanation of the potential risks, signs, and symptoms will occur at specific time points as part of the review of the Participant Safety Card and throughout the study as described in the Schedule of Activities.

Meningococcal serogroups ACWY and B vaccinations are required during screening for participants who do not meet criteria for previous vaccination. The vaccination series will be completed during the study according to national and local vaccination schedule guidelines.

Participants who have TMA associated with triggers of lupus nephritis, systemic sclerosis, or solid organ transplant must also be vaccinated against *Hib* and *S pneumoniae* prior to randomization, unless previously vaccinated, if indicated according to current national/local vaccination guidelines.

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

8.2. Efficacy Assessments

8.2.1. Laboratory Assessments for Efficacy Endpoints

Laboratory assessments (platelets, LDH, and eGFR) to determine Complete TMA Response, Hematologic Response, and Renal Response will be performed according to the Schedule of Activities (Section 1.3) and will assessed based on the predetermined criteria for TMA response as defined in Section 3.2.

The eGFR calculation will be based on the CKD-EPI formula for all participants using serum creatinine collected prior to study drug administration, if applicable.

8.2.2. Dialysis Status

Participant dialysis status ≤ 14 days prior to Screening, during the Screening Period, and during the study will be documented on the CRF.

8.2.3. Transfusion History and Transfusion Requirement Status During the Study

The number and volume of transfusions ≤ 14 days prior to Screening, during the Screening Period, and during the study will be documented on the CRF. The information to be collected includes date of the transfusion, number of units, and volume of each blood component given.

8.2.4. Survival Status

Participant survival status will be assessed throughout the duration of the study.

8.3. Safety Assessments

8.3.1. Participant Safety Card

Before the first dose of the study drug, a Participant Safety Card will be provided to participants to carry with them at all times until 8 months after the final dose of study treatment. The card is provided to increase participant awareness of the risk of meningococcal infection and promote quick recognition and disclosure of any potential signs or symptoms of infection experienced during the course of the study and to inform participants on what actions must be taken if they are experiencing signs or symptoms of infection.

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

8.3.2. 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 (with emphasis on presence/degree of edema).
- An abbreviated physical examination will include, at a minimum, a body-system relevant examination based upon the Investigator's judgment and participant symptoms.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Additional physical examinations can be performed as medically indicated during the study at the Investigator's discretion.
- Weight and height (Screening only) will also be measured and recorded.

8.3.3. Vital Signs

- Body temperature (°C or °F), heart rate, respiratory rate, systolic and diastolic blood pressure (mm Hg), and pulse oximetry will be assessed.
- Blood pressure and heart rate measurements will be assessed with the participant in a seated or supine position using a completely automated device. Manual techniques will be used only if an automated device is not available.
- 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.
- Vital signs will be collected predose at ravulizumab dosing visits.

8.3.4. Electrocardiograms

- Single 12-lead electrocardiogram (ECGs) will be conducted locally to obtain heart rate, PR, QRS, interval between the start of the Q wave and the end of the T wave in an ECG (QT), and corrected QT (QTc) intervals. QT interval will be corrected for heart rate using Fridericia's formula (QTcF).
- Single 12-lead ECG will be performed at Screening and at the end of the Treatment Period (Day 183). For participants that discontinue study drug prior to Week 26, an ECG should be performed at the ED Visit.
- Participants must be supine during ECG collection.
- The 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.

8.3.5. Clinical Safety Laboratory Assessments

- All protocol-required laboratory assessments, as outlined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the Schedule of Activities (Section 1.3).
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.

  Note: For participants that withdraw from the study, all laboratory tests with values considered clinically significantly abnormal within 8 weeks after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.

8.3.5.1. Virus Serology

Human immunodeficiency virus testing for HIV-1 and HIV-2 is required for all participants prior to randomization.

8.3.6. Pregnancy

- Pregnancy testing must be performed on all women of childbearing potential (WOCBP) at protocol-specified time points in the Schedule of Activities (Section 1.3). Pregnancy tests (urine or serum) may also be performed at any time during the study at the Investigator's discretion.
- A negative pregnancy test is required for WOCBP before study drug administration.
- Pregnancy data from female participants and female spouses/partners of male participants will be collected from the first dose of study drug through the EOS Visit. Any female participant who becomes pregnant while participating in the study will be discontinued from study drug. If a pregnancy is reported, the Investigator, or designee, must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.6.3.

8.4. Adverse Events and Serious Adverse Events

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

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

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

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

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 until the EOS Visit. For participants who withdraw from the study during the Treatment Period, all AEs and SAEs should be collected through 8 weeks after last dose of study drug. For participants who discontinue study drug, but remain in the Follow-up Period, all AEs and SAEs will be collected through the EOS Visit.

All SAEs will be recorded and reported to Alexion or the designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.4. The Investigator, or designee, will submit any updated SAE data to Alexion within 24 hours of the date the study site became aware of the event.

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 concluded participation in the study, and he/she considers the event to be

reasonably related to the study drug or study participation, the Investigator must promptly notify Alexion.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.4.

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 7.3). Further information on follow-up procedures is provided in Section 10.4.

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.
- Alexion is required to submit individual suspected unexpected serious adverse reaction (SUSAR) reports (defined in Section 10.4.2) in the format of MedWatch 3500 or Council for International Organizations of Medical Sciences (CIOMS) I Form to health authorities and Investigators as required. Forms submitted to Investigators will be blinded to treatment assignment. In limited circumstances, the blind may be broken in the case of urgent safety issues that could compromise participant safety.
- An Investigator who receives an Investigator safety report describing an 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.

8.4.5. Major Adverse Cardiovascular Events

Major adverse cardiovascular events (MACEs) will be assessed as part of the planned evaluation of AEs. A MACE is defined as any of the following:

- Non-fatal myocardial infarction
- Non-fatal stroke

- Death from cardiovascular disease

The description of the MACE including the method of the diagnosis, date of diagnosis, and the date resolved (or ongoing) will be collected on the CRF as part of the participant's medical history (prior to baseline) and throughout the study.

8.4.6. Adverse Events of Special Interest

Meningococcal infections will be considered to be adverse events of special interest.

8.5. Review of Prior and Concomitant Medications and Procedures

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

8.5.1. Prior Medications and Procedures

Prior medications and/or vaccines (including vitamins, herbal preparations, and those discussed in the eligibility criteria [Section 5]) and procedures (any therapeutic drug, such as mechanical ventilation, renal replacement therapy, surgery/biopsy or physical therapy) that the participant receives or undergoes ≤ 14 days prior to Screening or during the Screening Period, as well as any meningococcal vaccine administered within the last 3 years, will be recorded in the participant's CRF.

Information regarding the BSC treatment for the participant's current complement-mediated TMA will be recorded in the participant's CRF.

8.5.2. Concomitant Medications and Procedures

Concomitant medications (including any medication, vitamin, herbal preparation or supplement) and procedures (defined in Section 6.6) are those received on or after the first study drug date (Day 1), including those started before Day 1 and continued after Day 1. At each study visit, participants should be questioned about any new medication or nonpharmacologic therapies or changes to concomitant medications and nonpharmacologic therapies since the last visit. Concomitant medications and nonpharmacologic therapies should be recorded in the source documents and the participant's CRF (unless otherwise noted) including:

- Reason for use
- 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)

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 6.6.2, may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded as described above, in the participant's source documents and CRF.

Information regarding the use of BSC (Section 6.5) and disease-specific treatment received during the course of the study will be recorded in the source documents and the participant's CRF, including treatment(s) for new thrombotic events.

Vaccination and antibiotics administered for prophylaxis of meningococcal infection (if applicable) during the study will also be recorded.

The Medical Monitor should be contacted if there are any questions regarding concomitant medications or procedures.

8.6. Treatment of Overdose

For this study, any dose of ravulizumab greater than that specified in the protocol will be considered an overdose. Any blinded dose greater than that specified in the protocol will be considered a suspected 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/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. For unblinded participants, document the quantity of the excess dose as well as the duration of the overdose in the CRF.

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

8.7. Pharmacokinetics and Pharmacodynamics

- Blood samples for determination of serum drug concentrations and PD assessments (free and total C5) will be collected before and after administration of study drug at the time points specified in the Schedule of Activities (Section 1.3).
- 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.
- The Day 1 baseline PK and PD blood samples will be collected at predose, within 90 minutes before administering study drug (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.
- All subsequent predose samples will be collected within 0.5 hours prior to the start of infusion. In order to minimize needle sticks to the participant, the predose 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 0.5 hours after completion of the study drug infusion. The postdose blood samples will be drawn from the participant's opposite, noninfused arm.
- For indicated visits not falling on dosing days, samples may be collected at any time that visit day.
- In the event of an unscheduled visit, PK and PD blood sample will be collected as soon as possible.

Study drug concentration information that may/would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.8. Immunogenicity Assessments

Antidrug antibodies to ravulizumab (ie, antidrug antibody) will be evaluated in serum samples collected from all participants according to the Schedule of Activities (Section 1.3).

The detection and characterization of antibodies to ravulizumab will be performed using a validated assay method. Confirmed antibody positive samples will be further evaluated for antibody titer and the presence of neutralizing antibodies.

8.9. Biomarkers

Please refer to the Laboratory Manual for details on sample collection, including blood volume requirements. Biomarker samples may be analyzed after study completion.

8.9.1. Blood Biomarkers

Blood (whole blood, serum, and plasma) samples for biomarker research will be collected from all participants at the time points specified in the Schedule of Activities (Section 1.3).

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

- Vascular inflammation (eg, shed tumor necrosis factor receptor I [sTNF-RI])
- Endothelial damage and/or activation (eg, thrombomodulin and shed vascular cell adhesion molecule 1 [sVCAM-1])
- Complement pathway dysregulation (eg, soluble C5b-9 [sC5b-9] and factor Ba)

8.9.2. Urine Biomarkers

Urine samples for biomarker research will be collected from all participants during Screening and at the time points specified in the Schedule of Activities (Section 1.3).

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

- Complement pathway dysregulation (eg, sC5b-9 and factor Ba)
- Renal injury biomarkers (eg, neutrophil gelatinase-associated lipocalin [NGAL])

8.9.3. Real Time Complement Activity

Blood and urine samples will be collected by all sites for exploratory Real Time Complement Activity (RTCA) during Screening and at the time points specified in the Schedule of Activities (Section 1.3) through the end of the Treatment Period (Day 183). Samples are to be collected, frozen, and shipped to the central laboratory.

Selected sites will perform additional RTCA testing using freshly collected whole blood dipotassium ethylenediaminetetraacetic acid (K2EDTA), plasma, and urine samples with same day, on-site testing using a dedicated reader and specific instructions provided by the Sponsor and as instructed in the laboratory manual; the reader output will be masked such that all site personnel will be blinded from the RTCA results.

8.9.4. Additional Biomarker Research

Residual blood and urine samples from exploratory biomarkers, PK, PD, and immunogenicity, will be stored for additional method developments of assays (eg, prognostic and/or diagnostic tests related to the study drug target, disease process, pathways associated with disease state, other TMA or complement-related diseases, and/or mechanism of action of ravulizumab).

Samples will be retained to enable further analysis on ravulizumab but for no longer than 5 years after termination of the study or other period as per local requirements.

8.10. Genetics

For participants who sign an additional optional consent, whole blood for exploratory genetics may/will be collected at the time point specified in the Schedules of Activities (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.

Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.8 for information regarding DNA sample retention and future genetics research.

8.11. Other Assessments

8.11.1. Patient-Reported Outcome Measures

Quality of life scales will be administered electronically by the Investigator or a qualified site staff member prior to other study procedures at visits specified in the Schedule of Activities (Section 1.3).

All assessments should be administered in a quiet room and should be administered electronically by the Investigator or a qualified site staff member prior to other study procedures at visits specified in the Schedules of Activities (Section 1.3). These assessments may be

recorded on paper if electronic devices are unavailable or cannot be used. If the Investigator deems that the participant is not able to self-report using any of these instruments at a particular time point, then they will not be administered to the participant.

The following quality of life scales will be administered:

- The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (Section 10.11.1), Version 4.0, is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days (Cella, 2002; Webster, 2003; Yellen SB, 1997)
- The EuroQoL 5-Dimensions 5-Level (EQ-5D-5L) (Section 10.11.2) is a self-assessed, standardized instrument to measure health-related quality of life and has been used in a wide range of health conditions. The EQ-5D-5L comprises 5 dimensions, each describing a different aspect of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- The Kidney Disease Quality of Life instrument-36 items (KDQOL-36™) (Section 10.11.3) is a 36-item kidney-specific health-related quality of life measure including Short-Form Health Survey 12 Item (SF-12) as generic core plus the burden of kidney disease, symptoms/problems of kidney disease, and effects of kidney disease scales.

8.11.2. Medical Resource Utilization

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 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 of outpatient medical encounters (including physician or emergency room visits) and the underlying reason

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary efficacy analysis will test the hypothesis that ravulizumab is superior to placebo based on the proportion of participants achieving Complete TMA Response during the 26-week Treatment Period. The estimand corresponding to the primary efficacy analysis is described in Section 10.2. Hypothesis testing will be 2-sided and performed at the 0.05 level of significance.

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

$$H_0: P_{rav} = P_{placebo} \text{ vs. } HA: P_{rav} \neq P_{placebo}$$

where P_{rav} is the proportion of participants achieving Complete TMA Response in the ravulizumab + BSC group and $P_{placebo}$ is the proportion of participants achieving Complete TMA Response in the placebo + BSC group.

9.2. Sample Size Determination

The sample size determination was based on a 2-sided Fisher's exact test performed at a 2-sided significance level of 0.05, comparing the proportion of participants achieving Complete TMA Response during the 26-week randomized Treatment Period in participants randomized to ravulizumab versus placebo. A sample size of 100 (50 participants per treatment group) has approximately 90% power to detect a statistically significant ($p \leq 0.05$) treatment difference of 35% in the proportion of responders at a 2-sided significance level of 0.05, assuming the responder rate is 35% with placebo plus BSC and 70% with ravulizumab plus BSC and an anticipated 10% drop-out rate (Caires, 2012; Humphreys, 2004; Lee, 2012; Schwarz, 2010; Song, 2013; Waters, 2007; Wu, 2013).

9.3. Populations for Analyses

The population sets used for analysis are defined in the following:

Population	Description
Intent to Treat	All randomized participants
Modified Intent to Treat (mITT)	All randomized participants, excluding participants who enroll prior to availability of ST-HUS and ADAMTS13 central laboratory results and are subsequently found to be ineligible after randomization
Safety Set	All participants who receive at least 1 dose of study drug. Participants will be analyzed according to the study drug they actually received for reporting exposure and safety data
Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis Set	All participants who receive at least 1 dose of study drug and who have evaluable PK/PD data
Per Protocol (PP) Set	To be defined in the Statistical Analysis Plan

Abbreviations: ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ST-HUS = Shiga toxin-related hemolytic uremic syndrome

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate Statistical Analysis Plan (SAP). Summary statistics will be computed and displayed by treatment group and by visit, where applicable. Descriptive statistics for continuous variables will minimally include

the number of participants, mean, standard deviation (SD), 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.

9.4.1. Efficacy Analyses

Efficacy analyses will be performed using the mITT Set, which will exclude participants who enrolled prior to availability of ST-HUS and ADAMTS13 central laboratory results and were subsequently found to be ineligible after randomization. The mITT was selected as the primary efficacy population to ensure the exclusion of participants with thrombotic thrombocytopenic purpura (TTP) or Shiga toxin *E. coli* related hemolytic uremic syndrome (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 be performed on the ITT Set and PP Set as sensitivity analyses as necessary.

9.4.1.1. Analyses of Primary Efficacy Endpoint

The estimand corresponding to the primary endpoint is defined as the difference in the proportion of participants with Complete TMA Response during the 26-week Treatment Period between treatment groups in participants in the mITT analysis set. A composite strategy will be applied where participants will be classified as nonresponders if they do not have any TMA response observed before the intercurrent events: premature discontinuation of study treatment or initiation of disallowed therapy or medicine, regardless whether the TMA response is observed after these intercurrent events (refer to Section 10.2). For other participants without the above intercurrent events, Complete TMA Response by Week 26 will be assessed using all available assessments within the 26-week randomized Treatment Period.

The primary efficacy analysis will test the hypothesis that ravulizumab is superior to placebo based on the proportion of participants achieving Complete TMA Response (Section 8.2.1) during the 26-week randomized Treatment Period. Participants must meet each TMA Response criterion at 2 separate assessments at least 24 hours apart, and any measurement in between.

The primary efficacy analysis will be performed at the end of the 26-week Treatment Period after all participants have completed 26 weeks or withdrawn early from the 26-week Treatment Period.

The primary analysis will be based on a Cochran-Mantel-Haenszel test stratified by randomization stratification factors at a 5% significance level, comparing the proportion of participants achieving Complete TMA Response during the 26-week randomized Treatment Period between the 2 treatment groups in the mITT Set. The analysis will be performed according to the randomized treatment assignment. Non-Responder Imputation (NRI) method will be used to handle missing data.

If a participant is not on dialysis at baseline, baseline eGFR will be defined as the last non-missing assessment prior to the start of study treatment. If a participant is on dialysis on Day 1, baseline eGFR will be imputed as described in the SAP. If the participant is on dialysis for the

entire 26-week Treatment Period, or through early discontinuation of study drug, then the change in eGFR will not be calculated.

As a sensitivity analysis, a 2-sided Fisher's exact test on the primary endpoint will be performed. A re-randomization test to calculate the p-value will also be explored. The p-values from sensitivity analyses for efficacy endpoints are for descriptive purpose only and not adjusted for multiplicity. Details on sensitivity analyses will be provided in the SAP.

9.4.1.2. Analyses of Secondary Efficacy Endpoints

9.4.1.2.1. Analyses of Key Secondary Endpoints

Key secondary endpoints (defined in Table 4) and corresponding estimands (defined in Section 10.2) will be analyzed as follows:

For time to Complete TMA Response (Section 3.2.1), participants will be assigned as responders at the time of their response and will be censored at the earliest of their discontinuation time or at the end of available follow-up if they have not responded by then. The corresponding estimand is the hazard ratio of time to Complete TMA Response between treatment groups in participants in the mITT. A hypothetical strategy will be applied where all data after intercurrent events of premature discontinuation of study treatment or initiation of disallowed therapy or medicine will be censored. Kaplan-Meier cumulative distribution curves will be generated for each treatment group, and a log-rank test comparing the curves will be performed. A corresponding summary table will present by treatment group the cumulative distribution function estimate, the number of participants at risk, the number of participants responding, and the number of participants censored at each post-baseline time point. The table will also present the first quartile, median, and third quartile, along with the corresponding 2-sided 95% CI, of time to response.

For hematologic response at Week 26 and on dialysis at Week 26, the corresponding estimand is the difference in the proportion of participants achieving hematologic response at Week 26 or difference in the proportion of participants on dialysis at Week 26 respectively, between treatment groups in participants in the mITT. Analyses will be based on a composite strategy where participants will be considered as nonresponders after intercurrent events of premature discontinuation of treatment or initiation of disallowed therapy or medicine. Following a similar approach as for the analyses of the primary estimand, a Cochran-Mantel-Haenszel test will be applied and NRI method will be used to handle missing data.

For change from baseline in eGFR at Week 26, the corresponding estimand is the difference in the mean of change from baseline in eGFR at Week 26 between treatment groups in participants in the mITT, if participants do not prematurely discontinue study treatment or initiate disallowed therapy or medicine. Analyses will be based on hypothetical strategy where data collected after the intercurrent events of treatment discontinuation or initiation of disallowed therapy or medicine will become irrelevant. The treatment comparison will be conducted based on a Mixed-Effect Model Repeated Measures (MMRM) method using a mixed model including observed measurement at all visits prior to treatment discontinuation or initiation of disallowed therapy or medicine. The model includes the categorical fixed effects of treatment, study visit, and study visit by treatment interaction, stratification factor, and the continuous fixed covariate of baseline measurement. An unstructured covariance matrix will be used to model the within-participant

errors. The specified MMRM analysis can produce valid statistical inference under the missing-at-random (MAR) missing data mechanism assumption.

9.4.1.2.2. Analyses of Additional Secondary Endpoints

Additional secondary endpoints defined in Table 4 will be analyzed as follows:

Time to response for each individual TMA parameter during the 26-week Treatment Period will be assessed in a similar manner as time to Complete TMA Response.

The binary additional secondary endpoints will be summarized by randomized treatment group by calculating the point estimate and 2-sided 95% CI for the response rate, based on exact confidence limits using the Clopper Pearson method. Treatment comparison of the response rate at all scheduled assessments during the 26-week randomized Treatment Period will be based on Cochran-Mantel-Haenszel test stratified by randomization stratification factors.

For continuous additional secondary endpoints, MMRM model will be used and similar statistics will be provided as described above.

For all parameters summarized during the Randomized Treatment Period other than eGFR, baseline is defined as the last non-missing assessment value prior to the start of study treatment (data from Screening or Day 1, prior to date of randomization).

For participants who require dialysis, change from baseline in dialysis requirements will be summarized.

9.4.1.3. Multiplicity Adjustment

The primary and key secondary efficacy analyses will use a hierarchical stepdown closed-testing procedure. If the null hypothesis for the primary efficacy estimand is rejected, the key secondary efficacy estimands will be tested in the following order until a non-significant test is observed, at which point no further testing of subsequent estimand will occur:

1. Time to Complete TMA Response during the 26-week randomized Treatment Period
2. Achievement of hematologic response at Week 26
3. Change from baseline in eGFR at Week 26
4. On dialysis at Week 26

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Set. Participants will be analyzed according to the study treatment they actually received.

9.4.2.1. Adverse Events

The following definitions will be used for AEs:

- Pretreatment AEs: Any AE that starts after providing informed consent, but before the first infusion of study drug
- Treatment-emergent adverse event (TEAE): Any AE that starts between the start of the first infusion of study drug and up to 8 months after the last infusion of study drug

- Treatment-emergent SAE (TESAE): A TEAE that meets the criteria for serious (Section 10.4.2)
- Post-treatment AEs: Any AE that starts 8 months or later after the last infusion of study drug

The incidence of TEAEs, TEAEs leading to withdrawal from the study, TEAEs leading to study drug discontinuation, and TESAEs will be summarized by treatment group. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 or higher, and will be summarized by System Organ Class and Preferred Term overall, by severity, and by relationship to study drug.

Detailed by-participant listings of TEAEs, TESAEs, related TEAEs, TEAEs leading to withdrawal from the study, and TEAEs leading to study drug discontinuation will be provided.

9.4.2.2. Physical Examination and Vital Signs

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

Vital signs will be summarized descriptively by treatment group at baseline and post-baseline time points and for changes from baseline.

9.4.2.3. Clinical Laboratory Tests

Observed values and changes from baseline in clinical chemistry, hematology, and spot urine collection will be summarized descriptively by treatment group at baseline and at each post-baseline time point. For laboratory results that can be classified as normal, low, or high based on normal range values, shifts from baseline in classification will be summarized for all study visits.

9.4.2.4. Electrocardiograms

By-participant data listings of ECG parameters will be provided separately for each disease cohort. Electrocardiograms will be evaluated and summarized as normal, abnormal not clinically significant, or abnormal clinically significant. A shift from baseline to worst on-study ECG table will be presented for ECG results. 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. The QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

9.4.2.5. MACE

Descriptive statistics for number and percentage of participants with MACEs will be presented by treatment group. Pre-treatment and treatment-emergent MACE rates through Day 183 (Week 26) (number per 100 participant-years) along with participant-years of follow up and total number of MACEs will be displayed by treatment group. MACE is defined in Section 8.4.5.

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. 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 concentrations over time, as appropriate. Descriptive statistics will be calculated for the PD data at each sampling time, as appropriate.

9.4.4. Immunogenicity Analyses

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

9.4.5. Exploratory Analyses

The exploratory efficacy analyses will be descriptive in nature and will be based on the mITT Set. Full details regarding the exploratory analyses will be described in the SAP.

9.4.5.1. Quality of Life

The following quality of life assessments will be summarized by treatment group at baseline and each postbaseline time point using descriptive statistics for the observed value as well as the change from baseline:

- EQ-5D-5L
- KDQOL-36

9.4.5.2. Other Exploratory Endpoints

Analyses of exploratory biomarkers and genetic testing will be described in separate SAPs and may be summarized after study completion.

9.5. Planned Analyses

9.5.1. Interim Analysis

An interim analysis to assess sample size re-estimation will be performed when 50% of the planned participants (n = 100) have been assessed for the primary estimand. This interim analysis will be performed by an unblinded independent statistical center that is not involved with study conduct or final analysis of study data. Enrollment of participants will proceed without interruption while the analysis is ongoing. There are no plans to stop the study for demonstration of efficacy or futility at the interim analysis.

The sample size re-estimation analysis will be based on the conditional power calculated using the results obtained at this interim analysis. If the conditional power falls within the promising zone based on the estimated treatment effect, the sample size will be increased up to a maximum of 150 participants. Because the total sample size could potentially be increased in a data-dependent manner following the interim analysis, the final primary analysis for the primary estimand will be tested using the Cui, Hung, Wang method for controlling the type 1 error (Cui, 1999). Full details will be provided in a separate interim SAP.

9.5.2. Primary Efficacy Analysis

The primary efficacy analysis will be performed at the end of the 26-Week Treatment Period after all participants have completed or withdrawn from the 26-Week Treatment Period. This analysis will allow for evaluation of the primary estimand.

9.5.3. Final Analysis

The final study analysis will be conducted at the end of the study (Section 4.5). The SAP will describe the planned analysis in greater detail.

9.6. Data Monitoring Committee

This study will not include a Data Monitoring Committee.

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 the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, substantial protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion and reviewed and approved by the IRB/IEC before the study is initiated.
  - If any of these documents require regulatory/health authority approval per local regulations, Alexion will also obtain such approval before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC and regulatory/health authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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, Directive 2001/20/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

The Principal Investigator and all 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 or designee to obtain signed (written or electronic signature) informed consent from all study participants, or the participant's legally authorized representative, prior to performing any study-related procedures including screening assessments.
- The Investigator or designee 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 a certified translation, if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation, ICH GCP guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must include a statement that signed (written or electronic) informed consent was obtained before any screening procedures were performed with a participant, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study, as applicable.
- A copy of the signed (written or electronic) informed consent 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. Original signed (written or electronic) consent forms must remain in each participant's study file and must be available for verification at any time.

Participants who are rescreened outside of the Screening window (Section 1.3) are required to sign a new ICF (see Section 5.4).

The ICF will contain a separate section 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 separate 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. Data Protection

- Participants will be assigned a unique identifier by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used in accordance with applicable data protection law, and participants must also be informed of any individuals rights they may have with regard to their personal data. Participants will be informed about how their personal study-related data will be disclosed, and will be required to agree to the information contained in the informed consent and provide consent to the processing of their personal data, if required by applicable data protection law.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, and inspectors from regulatory authorities.
- Alexion as a data controller has implemented privacy and security controls designed to help protect participant personal data; including information security controls, firewalls, incident detection, and secure transfer measures.
- In the event of any accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data ("breach"), the controller has implemented procedures and measures to promptly address and mitigate any risk to the data participant. In the event of a breach, the controller will notify the appropriate regulatory authorities and/or the data participant in accordance with applicable data protection law.

10.1.5. 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.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed CRF or electronic case report form (eCRF) 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.
  - Remote source data verification may be employed where permitted by local regulations.
  - The scope of the source data verification will be described in detail in the Clinical Monitoring Plan.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator after study completion per local regulations or institutional policies. No records may be destroyed without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.7. Source Documents

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

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. Case report forms must be completed by the Investigator or designee as indicated in the site delegation log. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available to Alexion, Alexion delegates, and health authorities, as requested. Source documents are filed at the study site.

Per ICH E6 (R2) guidelines and good documentation practice requirements, source documents and study records in all media (eg, paper, electronic) must be Attributable, Legible, Contemporaneous, Original, Accurate, and Complete.

10.1.8. Study and Site Start and Closure

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

Alexion reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the EOS or ED Visit, all data have been collected and entered into the electronic data capture (EDC) system, all required documents and study supplies have been collected and reconciled, 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 ICH/GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development
- Alexion or a health authority may terminate the study for reasonable cause. Conditions that may warrant termination of the study include, but are not limited to:
  - Discovery of an unexpected, serious, or unacceptable risk of the study drug to participants enrolled or continuing in the study
  - Alexion decision to suspend or discontinue testing, evaluation, or development of the study drug for the indication of TMA associated with trigger(s)

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.

10.1.9. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12 to 18 months of the primary evaluation date or end of study, 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.

- 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 as defined by the Pharmaceutical Research and Manufacturers of America and the International Committee of Medical Journal Editors and per the Alexion Publication Policy. 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.
- Alexion will Publish Patient Lay Summaries and include participants and/or caregivers as reviewers for readability and understanding of lay person language.

10.1.10. Good Clinical Practice Compliance

Alexion and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 R2, EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of Alexion and/or the company organizing/managing the research on behalf of Alexion to inspect study data, participants' medical records, and CRFs in accordance with current GCP and respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

Alexion ensures that local regulatory authority requirements are met before the start of the study. Alexion (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of study drug for shipment to the site.

10.2. Mapping Objectives to Estimands

Table 8: Mapping Objectives to Estimands

Objectives	Estimands
Primary	
To assess the efficacy of ravulizumab in the treatment of participants with TMA	• Population: Participants with TMA due to a trigger who are included in the mITT (defined in Section 9.3). • Variable: Complete TMA Response during the 26-week randomized Treatment Period (Section 3.2.1). • Treatments: Ravulizumab vs. placebo • IE: o IE1: premature discontinuation of study treatment; o IE2: initiation of disallowed therapy or medicine All participants who meet response criteria after IE1 or IE2 will be considered as nonresponders thereafter. Summary measure: Difference between treatment groups in the proportion of participants with Complete TMA response
Key Secondary	
To characterize TMA response	• Population: Participants with TMA due to a trigger who are included in the mITT. • Variable: Time to Complete TMA Response during the 26-week randomized Treatment Period. • Treatments: Ravulizumab vs. placebo • IE: o IE1: premature discontinuation of study treatment; o IE2: initiation of disallowed therapy or medicine All data after IE1 or IE2 will be censored. Summary measure: Hazard ratio between treatment groups
To characterize TMA response	• Population: Participants with TMA due to a trigger who are included in the mITT. • Variable: Achievement of hematologic response at Week 26 (Section 3.2.2). • Treatments: Ravulizumab vs. placebo • IE: o IE1: premature discontinuation of study treatment; o IE2: initiation of disallowed therapy or medicine All participants who meet response criteria after IE1 or IE2 will be considered as nonresponders thereafter. Summary measure: Difference between treatment groups in the proportion of participants with hematologic response at Week 26.
To evaluate change in kidney function	• Population: Participants with TMA due to a trigger who are included in the mITT (defined in Section 9.3). • Variable: Change from baseline in eGFR at Week 26. • Treatments: Ravulizumab vs. placebo • IE: o IE1: premature discontinuation of study treatment; o IE2: initiation of disallowed therapy or medicine All data after IE1 or IE2 will not be used. Summary measure: Difference between treatment groups in the mean of change from baseline in eGFR at Week 26.

Table 8: Mapping Objectives to Estimands

Objectives	Estimands
To evaluate change in kidney function	• Population: Participants with TMA due to a trigger who are included in the mITT (defined in Section 9.3). • Variable: On dialysis at Week 26. • Treatments: Ravulizumab vs. placebo • IE: o IE1: premature discontinuation of study treatment; o IE2: initiation of disallowed therapy or medicine All participants will be considered as nonresponders after IE1 or IE2. Summary measure: Difference between treatment groups in the proportion of participants on dialysis at Week 26.

Abbreviations: eGFR = estimated glomerular filtration rate; IE = intercurrent event; mITT = Modified Intent-to-Treat; TMA = thrombotic microangiopathy

10.3. Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the central laboratory or designated ancillary laboratories unless otherwise noted.
- As described in Section 5, local or central laboratory results may be utilized for the assessment of eligibility, with the exceptions of the ST-HUS screen and ADAMTS13 activity tests which must be performed at the central laboratory. With the exceptions of the ST-HUS screen and ADAMTS13 activity tests, if local labs are used to establish eligibility, central laboratory tests are not required at the Screening visit.
  - For participants who experience constipation and cannot produce a stool sample for the ST-HUS screen during the Screening period, an assessment of the presence of Shiga toxin-producing *E. coli* infection can be evaluated by the Investigator based on the clinical presentation of the participant. If a stool sample for the ST-HUS screen cannot be obtained during the Screening period, laboratory evaluation for the ST-HUS screen will be made from the first available stool sample, which may include samples obtained post randomization.
  - 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: WOCBP should only be enrolled after a negative serum pregnancy test result at Screening (serum pregnancy test to be collected at Screening, Day 183, and EOS/ED). Urine pregnancy testing will be performed at all other timepoints as

specified in the Schedule of Activities (Section 1.3) unless serum testing is required by site policies, local regulation, or IRB/IEC.

- Investigators must document their review of each laboratory safety report.

Table 9: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters

Hematology	• Platelet count
	• Immature platelet fraction
	• Hematocrit
	• Red blood cell count
	• RBC indices
	  ○ Mean corpuscular volume
	  ○ Mean corpuscular hemoglobin
	  ○ Absolute count and percentage of reticulocytes
	• White blood cell count with differential (including early progenitors):
	  ○ Neutrophils, segmented
	  ○ Lymphocytes
	  ○ Monocytes
	  ○ Eosinophils
	  ○ Basophils
	• Hemoglobin
	• Haptoglobin

Coagulation panel (performed at Screening only)	• INR • PT • APTT • D-dimer • Fibrinogen

Clinical chemistry	• Lactate dehydrogenase
	• Liver function tests:
	  ○ ALT
	  ○ AST
	  ○ ALP
	  ○ Albumin
	  ○ Total protein
	  ○ Total bilirubin (direct and indirect)
	  ○ GGT
	• Glucose (nonfasting)
	• C-reactive protein
	• Renal function:
	  ○ Blood urea nitrogen
	  ○ Calcium
	  ○ Chloride
	  ○ Creatinine
	  ○ Magnesium
	  ○ Phosphate
	  ○ Potassium
	  ○ Sodium
	  ○ Total carbon dioxide

Spot urine studies	• Protein • Creatinine

Table 9: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
	• Urine protein creatinine ratio
Clinical complement tests[b]	Serum samples will include, but are not limited to, assessments of the following: • C3 and C4
PK/PD	• Serum PK • Serum PD (free and total C5)
Immunogenicity	• ADA
Biomarkers	Exploratory blood samples may include, but are not limited to, assessments of the following: • Vascular inflammation (eg, sTNF-RI) • Endothelial damage and/or activation (eg, thrombomodulin and sVCAM-1) • Complement pathway dysregulation (eg, sC5b-9, C5a, and factor Ba) Exploratory urine biomarkers may include, but are not limited to, assessments of the following: • Complement pathway dysregulation (eg, sC5b-9 and factor Ba) • Renal injury biomarkers (eg, neutrophil gelatinase-associated lipocalin [NGAL]) Freshly collected whole blood K_2EDTA, plasma and urine samples, and frozen plasma and urine samples for RTCA
Other screening tests	• ADAMTS13 activity • ST-HUS screen (eg, Shiga toxin enzyme immunoassay/PCR in stool/stool culture) • Coombs test, direct • HIV-1 and HIV-2 antibody • Serum follicle-stimulating hormone and estradiol (as needed in WOCBP only) • Serum or urine human chorionic gonadotropin pregnancy test (as needed for WOCBP)[a]
Other study-specific tests	• Blood sample for genetics analysis (optional; additional consent required)

[a] Serum pregnancy test at Screening, Day 183, and EOS/ED. Urine pregnancy test at all other timepoints as specified in Schedule of Activities (Section 1.3). Additional urine pregnancy testing when deemed necessary by the Investigator.

[b] Clinical complement tests to occur together with the clinical laboratory tests as specified in Schedule of Activities (Section 1.3).

Abbreviations: ADA = antidrug antibody(ies); ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT =activated partial thromboplastin time; AST = aspartate aminotransferase; C3, C4, C5, and C5a = complement components 3, 4, 5, and 5a; ED = early discontinuation; EOS = end of study; GGT = gamma-glutamyltransferase; HIV = human immunodeficiency virus; INR = international normalized ratio; K_2EDTA = dipotassium ethylenediaminetetraacetic acid; PCR = polymerase chain reaction; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell; RTCA = Real Time Complement Activity; sC5b-9 = soluble terminal complement complex C5b-9 (membrane attack complex); ST-HUS = Shiga toxin-related hemolytic uremic syndrome; sTNF-R1 = shed tumor necrosis factor receptor 1; sVCAM-1 = shed vascular cell adhesion molecule 1; WOCBP = woman of childbearing potential.

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

10.4.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).

- **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 the study drug, whether or not considered related to the 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.

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.
- 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).

Events Not Meeting the AE Definition
• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

10.4.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent 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 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 suspected unexpected serious adverse reaction (SUSAR) is defined as:
An event that is assessed as serious by the Investigator and/or Alexion that is not listed in the appropriate Reference Safety Information (IB) and has been assessed that there is at least a reasonable possibility that the event is related to the investigational medicinal product by the Investigator and/or Alexion. Alexion has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents. Suspected unexpected serious adverse reactions will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable.

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

Recording of AE and/or SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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 Common Terminology Criteria for Adverse Events (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
- 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.

Assessment of Causality

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

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/eCRF.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.4.4. Reporting of SAEs

SAE Reporting to Alexion via an Electronic Data Collection Tool

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours of awareness.
- The primary mechanism for reporting an SAE to Alexion will be the EDC system.
- If the electronic system is unavailable or site staff are unable to process the SAE via the EDC system 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 immediately with the new information and an updated SAE report should be submitted to Alexion global drug safety (GDS) within 24 hours of Investigator/site awareness.
- After the participant has completed the study, no new data or changes to existing data are expected to be entered in the EDC system.
    - If a site receives a report of a new SAE from a study participant which the Investigator considers to be related to the study intervention, or the site receives updated data on a previously reported SAE after the EDC system has been taken offline, then the site can report this information on a paper Contingency Form for SAE Reporting via facsimile or email.

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

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

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

Participants who experience a reaction during the administration of 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 must be notified within 24 hours of any infusion-related reaction requiring interruption or discontinuation of ravulizumab. All AEs that may indicate an infusion-related response will be graded according to the Common Terminology Criteria for Adverse Events CTCAE v5.0 or higher.

If anaphylaxis occurs according to the criteria listed in Table 10 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-related reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

Table 10: Clinical Criteria for Diagnosing Anaphylaxis

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

Source: Sampson, 2006

10.6. Contraceptive Guidance and Collection of Pregnancy Information

10.6.1. Definitions

Woman of Childbearing Potential (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 drug, 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 tubal ligation or 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 prior to the Day 1 Visit.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement may be required. In the absence of 12 months of amenorrhea, the reason for not obtaining FSH levels should be documented by the Investigator at the time of Screening.
   - 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.
4. Permanent sterilization at least 6 weeks prior to the Day 1 Visit.

10.6.2. Contraception Guidance

Contraceptive use by male or female participants should be consistent with local regulations regarding the methods of contraception utilized for those participating in clinical studies. If

teratogenic effects are suspected to be transferred to a fetus/embryo from a female spouse/partner of a male participant, pregnancy follow-up information will be obtained for the partner who becomes pregnant (refer to Section 10.6.3.1). In these cases, follow-up will be conducted on the pregnant partner in the same manner as a female participant who becomes pregnant during the study.

10.6.2.1. Guidance for Female Participants

Female participants of childbearing potential must have a negative serum pregnancy test as required by local regulations within 2 weeks prior to the first dose of study drug and have a negative urine pregnancy test prior to the first dose of study drug on Day 1. Additional requirements for pregnancy testing during and after dosing with study drug are indicated in the Schedule of Activities (Section 1.3).

The Investigator is responsible for the review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

The Investigator should evaluate the potential for contraceptive method in relationship to the first dose of study drug.

Female participants of childbearing potential must use a highly effective or acceptable method of contraception, including at least 1 of the following until at least 8 months (generally 5.5 terminal half-lives) after the final dose of study drug. Highly effective methods are:

1. Intrauterine device in place for at least 6 weeks prior to first dose of study drug.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of study drug.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of study drug.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of study drug.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of study drug.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within the prior 6 months prior to the first dose of study drug). Male partner is still required to use condom during sexual intercourse.
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 must refrain from heterosexual intercourse for at least 8 months after the final dose of study drug.

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:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods)

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.

10.6.2.2. Guidance for Male Participants

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

Male participants who have had a vasectomy > 6 months prior to the dose of study drug must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to the first dose of study drug and those who have not had a vasectomy must use a condom and spermicide during heterosexual intercourse for at least 8 months after their final dose of study drug.

10.6.2.2.1. 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 participant'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 last dose of study drug.

10.6.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants from the first dose of study drug until the EOS Visit. Any female participant who becomes pregnant during the study will be discontinued from the study drug. Exposure during pregnancy (also referred to as exposure in utero) can be the result of

either maternal exposure or transmission of study drug via semen following paternal exposure. If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome 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 drug during breastfeeding must also be reported (via the "Pregnancy/Breastfeeding Reporting and Outcome Form") and any AEs experienced by the infant must be reported to Alexion GDS via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the study drug 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.

10.6.3.1. 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. After the study is unblinded, this applies only to male participants who received ravulizumab.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate "Pregnancy/Breastfeeding Reporting and Outcome 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 3 months following the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.6.3.2. 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.
- 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 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 3 months 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.

- Pregnancy is not considered as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. 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 poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion. 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 drug.

10.7. 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 complement-mediated TMA and related diseases. The samples may also be used to develop methods including prognostic and/or diagnostic tests related to the study drug target, disease process, pathways associated with complement-mediated TMA, 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 clinical study report (CSR) or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses 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 5 years after termination of the study or other period/time point per local requirements.

10.8. Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study drug, 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 samples will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to ravulizumab or complement-mediated TMA and related diseases. They may also be used to develop tests/assays including diagnostic tests related to ravulizumab and complement-mediated TMA. 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.

10.9. COVID-19 Risk Assessment

Complement-mediated TMA can cause irreversible morbidity and even mortality, if untreated. 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 complement-mediated TMA does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in participants not receiving immunosuppressants. However, there is no specific data to further inform 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 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 11.

Table 11: 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 time period, it is expected that Investigators and their staff will take all possible precautions in order to minimize a participant's potential exposure to COVID-19 infection. Depending on the site, this will consist of measures such as social distancing, temperature screening, enhanced cleaning, and use of personal protective equipment for participants, staff, and caregivers as necessary.

Table 11: Potential Risks and Mitigation Measures due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Healthcare institution availability for non-COVID-19 related activities	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 resourcing and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for 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 is also 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 eCRF that explains the reason the data is missing (eg, missed study visits or participant study discontinuations due to COVID-19).

Abbreviations: C5 = complement component 5; COVID-19 = coronavirus disease 2019; eCRF = electronic case report form.

10.10. 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, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, patients 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 12.

Table 12: 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 eCRF 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).

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form

10.11. Patient-Reported Outcome Instruments

10.11.1. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

FACIT Fatigue Scale (Version 4)

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

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

16 November 2007
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10.11.2. EuroQoL 5-Dimensions 5-Level (EQ-5D-5L)

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

Health Questionnaire

English version for the USA

EQ-5D-5L (Continued, Page 2)

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

ANXIETY / DEPRESSION

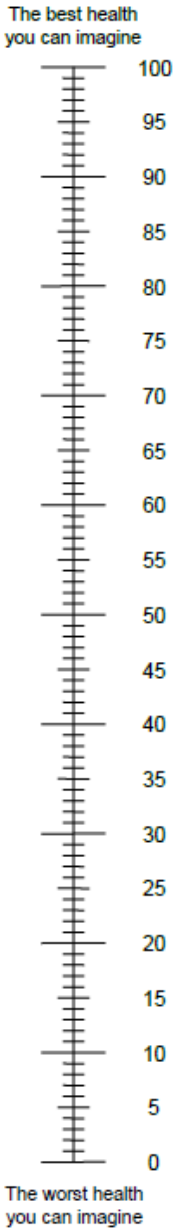
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

EQ-5D-5L (Continued, Page 3)

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

YOUR HEALTH TODAY = ☐



3

10.11.3. Kidney Disease Quality of Life instrument™–36 items (KDQOL-36)

Your Health

This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.

1. In general, would you say your health is: [Mark a ☒ in the one box that best describes your answer.]

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

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark a ☒ in a box on each line.]

	Yes, limits a lot	Yes, limits a little	No, does not limit at all
2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
3. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3

KDQOL-36 (Continued, Page 2)

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

		Yes	No
4.	Accomplished less than you would like	☐ 1	☐ 2
5.	Were limited in the kind of work or other activities	☐ 1	☐ 2

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

		Yes	No
6.	Accomplished less than you would like	☐ 1	☐ 2
7.	Didn't do work or other activities as carefully as usual	☐ 1	☐ 2

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

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

KDQOL-36 (Continued, Page 3)

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

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

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

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

KDQOL-36 (Continued, Page 4)

Your Kidney Disease

How true or false is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
13. My kidney disease interferes too much with my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Too much of my time is spent dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. I feel frustrated dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. I feel like a burden on my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

KDQOL-36 (Continued, Page 5)

During the past 4 weeks, to what extent were you bothered by each of the following?

		Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
17.	Soreness in your muscles?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18.	Chest pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19.	Cramps?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20.	Itchy skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21.	Dry skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22.	Shortness of breath?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
23.	Faintness or dizziness?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24.	Lack of appetite?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25.	Washed out or drained?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26.	Numbness in hands or feet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27.	Nausea or upset stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28[a].	(Hemodialysis patient only) Problems with your access site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28[b].	(Peritoneal dialysis patient only) Problems with your catheter site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

KDQOL-36 (Continued, Page 6)

Effects of Kidney Disease on Your Daily Life

Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease bother you in each of the following areas?

		Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
29.	Fluid restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30.	Dietary restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31.	Your ability to work around the house?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32.	Your ability to travel?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33.	Being dependent on doctors and other medical staff?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34.	Stress or worries caused by kidney disease?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35.	Your sex life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36.	Your personal appearance?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

10.12. Gene Mutations That Cause aHUS

Known gene mutations that cause aHUS may include, but are not limited to the following mutations or antibodies:

- Complement factor H (CFH)
- Complement factor I (CFI)
- Membrane cofactor protein (CD46)
- Complement component 3 (C3)
- Complement factor B (CFB)
- Thrombomodulin (THBD)
- Complement factor H-related protein 1 (CFHR1)
- Complement factor H-related protein 5 (CFHR5)
- Diacylglycerol kinase epsilon (DGKE)

10.13. The International Society on Thrombosis and Haemostasis (ISTH) Criteria for Disseminated Intravascular Coagulation (DIC)

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 prothrombin time, seconds	< 3	0
	3 to < 6	1
	≥ 6	2
Fibrinogen level, g/L	≥ 1	0
	< 1	1

[a] Use laboratory-specific cutoff values.

Interpretation

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

10.14. Abbreviations

Abbreviation	Definition
ADA	antidrug antibodies
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
BSC	best supportive care
C5	complement component 5
C5a	complement component 5a
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNI	calcineurin inhibitor
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DIC	disseminated intravascular coagulation
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FACIT	Functional Assessment of Chronic Illness Therapy
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDS	global drug safety
Hib	haemophilus influenzae type b
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISTH	International Society of Thrombosis and Haemostasis
ITT	Intent to Treat
IV	intravenous(ly)
KDQOL-36	Kidney Disease Quality of Life instrument – 36 items
LDH	lactate dehydrogenase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to treat
MMRM	Mixed-Effect Model Repeated Measures
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)

Abbreviation	Definition
PNH	paroxysmal nocturnal hemoglobinuria
q8w	every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RTCA	Real Time Complement Activity
SAE	serious adverse event
SAP	statistical analysis plan
sC5b-9	soluble terminal complement complex C5b-9 (membrane attack complex)
SSc-TMA	systemic sclerosis associated thrombotic microangiopathy
ST-HUS	Shiga toxin-related hemolytic uremic syndrome
sTNF-R1	shed tumor necrosis factor receptor 1
SUSAR	suspected unexpected serious adverse reaction
sVCAM-1	shed vascular cell adhesion molecule 1
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMA	thrombotic microangiopathy
TPE	therapeutic plasma exchange
ULN	upper limit of normal
WOCBP	woman of childbearing potential

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 1	UK	03 Jun 2021	To add COVID 19 vaccine risk assessment language
Original protocol	Not applicable	16 Dec 2020	Not applicable

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