TITLE PAGE

Protocol Title: Phase 4, Single-Arm Study of Ravulizumab in Adult Participants with Paroxysmal Nocturnal Hemoglobinuria Currently Treated with High-Dose Eculizumab

Protocol Number: ALXN1210-PNH-401

Amendment Number: 3.0

Compound: ULTOMIRIS (ravulizumab)

Study Phase: 4

Short Title:

Ravulizumab in Adult Participants with Paroxysmal Nocturnal Hemoglobinuria Currently Treated with High-Dose Eculizumab

Sponsor Name:

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Regulatory Agency Identifier Number(s)

IND: 128367

EudraCT: 2019-003440-74

Approval Date: 07 May 2021

Sponsor Signatory:

[redacted]

Date

Medical Monitor Contact Information can be found in the study contact list 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

This summary of changes document has been prepared to indicate the major changes made to Protocol ALXN1210-PNH-401, Amendment 3.0.

Amendment 3 (07 May 2021)

This amendment is considered to be non-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.

Other changes implemented through this Amendment constitute minor editorial corrections and fixing of inconsistencies.

Overall Rationale for the Amendment:

The main rationale for this Amendment is to include COVID-19 vaccine risk assessment.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Text regarding ravulizumab dosing language around home visits in Synopsis updated to match Section 4.1.	To clarify and make information consistent within the protocol.
Section 1.3 Schedule of Activities Table 1	Note added to clarify that all study assessments for a given study day are to be completed on the same day. Additionally, note added to clarify that PD sampling is measurement of serum free C5 and total C5 concentration.	Added for clarity.
Section 9.4.5 Prior and Concomitant Medication	Text updated to clarify use of medication 28 days prior to start of Screening.	To clarify and make information consistent within the protocol.
Section 10.3 Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Deleted text pertaining to reporting of serious adverse events	Safety Reporting will not be done via the RAVE Electronic Safety Gateway in this study as RAVE Classic is being used, which does not have this feature.
Section 10.7 COVID-19 Vaccine Risk Assessment	COVID-19 vaccines risk assessment language included.	Section newly added to provide potential risks identified and mitigation measures put in place in light of the COVID-19 vaccination rollout.

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

Phase 4, Single-Arm Study of Ravulizumab in Adult Participants with Paroxysmal Nocturnal Hemoglobinuria Currently Treated with High-Dose Eculizumab

Short Title:

Ravulizumab in Adult Participants with Paroxysmal Nocturnal Hemoglobinuria Currently Treated with High-Dose Eculizumab

Rationale:

To assess the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of ravulizumab in participants who are prescribed and are receiving a higher than approved dose of Soliris® (eculizumab) to treat paroxysmal nocturnal hemoglobinuria (PNH)

Objectives and Endpoints

Objectives	Endpoints
Primary • To evaluate the prevalence of free complement component 5 (C5)-associated breakthrough hemolysis (BTH) in participants on high-dose eculizumab who switch to ravulizumab (per approved dose regimen)	• Proportion of participants who experience free C5-associated BTH through Day 351. Free C5-associated BTH is defined as BTH concurrent with free C5 concentrations ≥ 0.5 μg/mL. BTH is defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], MAVE, including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN.
Secondary • To evaluate efficacy by other measures in participants on high-dose eculizumab who switch to ravulizumab	• Proportion of participants who experience BTH through Day 351 • Hemolysis as directly measured by LDH-PCHG from baseline to Day 351 • Proportion of participants who receive a transfusion, from baseline to Day 351 • Proportion of participants with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion from baseline to Day 351

Objectives	Endpoints
Exploratory To evaluate Patient-Reported Outcomes over time for those who switch to Ravulizumab from high-dose eculizumab	• Patient-reported PNH Symptoms (PRS) at baseline, Day 183 and Day 351 • Healthcare Resource Utilization (HRU) at baseline, Day 183 and Day 351
Safety • To evaluate the safety and tolerability of ravulizumab in participants on high-dose eculizumab who switch to ravulizumab	• Physical examinations, vital signs, and laboratory assessment results, and incidence of adverse events (AEs) and serious adverse events (SAEs) • Proportion of participants who develop (ravulizumab) antidrug antibodies (ADAs)
PK/PD • To characterize the PK/PD of ravulizumab in participants on high-dose eculizumab who switch to ravulizumab	• Change in serum ravulizumab concentration over time • Change in serum free and total C5 concentrations over time

Abbreviations: ADA = antidrug antibody; AE – adverse event; BTH = breakthrough hemolysis; C5 = complement component C5; LDH-PCHG = lactate dehydrogenase percent change; MAVE = major adverse vascular event; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event

Overall Design

This is a Phase 4, single-arm, open-label study to evaluate the efficacy and safety of ravulizumab in adult participants with PNH who switch from eculizumab 1200 mg every 2 weeks (q2w; ie, above the recommended dose) to ravulizumab (at the recommended dose).

The study will consist of a Screening Period of approximately 3 months and a Treatment Period of 351 days. All participants must provide informed consent prior to any procedures at the first Screening visit. All participants must have been prescribed and are receiving a stable dose of eculizumab 1200 mg q2w for at least 3 months prior to screening. During Screening, eculizumab may be administered at the participant's home at the discretion of the Investigator. During screening, participants will continue to receive eculizumab 1200 mg q2w, and blood samples will be collected for PD parameters and lactate dehydrogenase (LDH) levels.

Eligible participants will receive a loading dose of ravulizumab on Day 1, followed by maintenance doses on Day 15 and every 8 weeks (q8w), administered by intravenous (IV) infusion. Ravulizumab loading and maintenance doses will be based on participants' body weight per approved dose regimen. Ravulizumab dosing will be administered in the clinic by a trained member of the site study team; patients may have the option to receive study drug remotely at a medical facility that is located near the patient's home or at the patient's home by a qualified healthcare personnel.

The schedule of study visits and assessments is shown in Section 1.3.

An interim analysis will be performed on Day 183.

Disclosure Statement: This is a single-arm, open-label study.

Number of Participants:

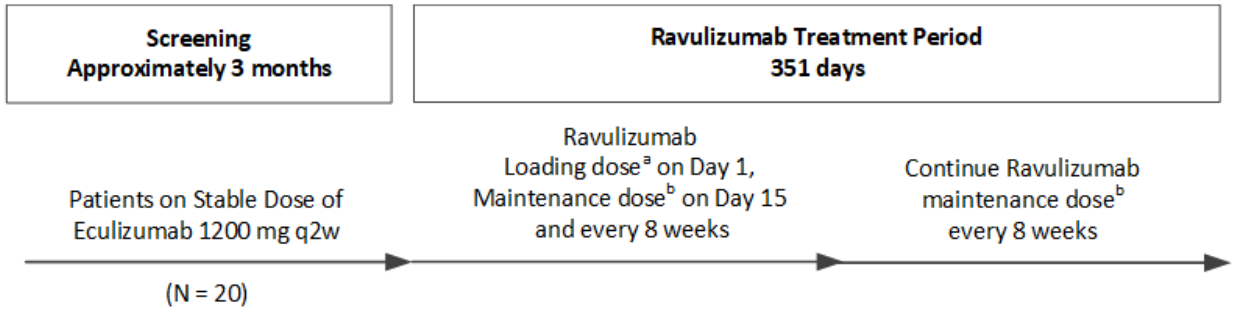
Approximately 20 participants will be enrolled.

Treatment Groups and Duration:

This single-arm study will consist of a 3-month Screening Period and a 351-day Treatment Period. All eligible participants will receive ravulizumab according to approved dose regimen during the Treatment Period.

Data Monitoring Committee: No

1.2. Schema



[a]. Ravulizumab loading dose is 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, or 3000 for participants weighing ≥ 100 kg.
[b]. Ravulizumab maintenance dose is 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, or 3600 mg for participants weighing ≥ 100 kg.

1.3. Schedules of Activities

Table 1: Schedule of Study Visits and Assessments: Screening Visit Through Confirmation Visit

Period	**Screening**						**Notes**
Study Day	**-85**	**-71**	**-57**	**-43**	**-29**	**-15**	
Window (day)	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**All study assessments for a given Study Day must be completed on the same day as the study visit. The window of ± 2 days is relative to Day 1 and allows for the Study Visit to occur ± 2 days from the indicated study day**
Informed consent	X						
Inclusion and exclusion criteria	X						
Confirmation of meningococcal vaccination	X						Refer to Section 6.5.1 for details
Abbreviated physical examination	X		X		X		Refer to Section 8.2.1 for details
Height	X						
Weight	X		X		X		
Medical history including PNH and eculizumab dosing history	X						
Serum or urine pregnancy test	X		X		X		Refer to Section 8.3.5 for details. Serum pregnancy test at Day -85, Urine pregnancy test at all other visits
HIV testing	X						
Chemistry including LDH	X		X		X		Sample to be collected within 24 hours of or immediately prior to a scheduled dose of study drug (trough) and not from a heparinized line.
Hematology including free hemoglobin and coagulation	X		X		X		Blood will be collected predose and not from a heparinized line.
Urinalysis and urine chemistry	X		X		X		Urine will be collected predose on dosing days.
Safety 12-lead ECG	X						Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Refer to Section 8.2.3 for details
Vital signs	X		X		X		Will be measured after the participant has been resting for at least 5 minutes. Refer to Section 8.2.2 for details
PNH clone size	X						WBC (granulocyte and monocyte) and RBC clone size measured by high-sensitivity flow cytometry at Screening; RBC clone size only at Screening
Record transfusions and transfusion parameters	X	X	X	X	X	X	Transfusions given during and between visits will be recorded. This can be optionally performed by a phone call on Days -71, -43, and -15

Table 1: Schedule of Study Visits and Assessments: Screening Visit Through Confirmation Visit

Period	**Screening**						**Notes**
Study Day	**-85**	**-71**	**-57**	**-43**	**-29**	**-15**	
Window (day)	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**All study assessments for a given Study Day must be completed on the same day as the study visit. The window of ± 2 days is relative to Day 1 and allows for the Study Visit to occur ± 2 days from the indicated study day**
PNH symptomatology	X	X	X	X	X	X	Investigator assessed and reported. Refer to Section 8.1.3 for details. This can be optionally performed by a phone call on Days -71, -43, and -15
PD sampling			X		X		PD sampling is measurement of serum free C5 and total C5 concentration. Refer to Sections 8.5 and 8.6 for details
Review safety card	X	X	X	X	X	X	
BTH	←Monitor continuously→						If a BTH event occurs during the Screening Period, the participant will be ineligible for the study. To confirm BTH, LDH, PK, and PD samples will be collected and analyzed. If the suspected event of BTH does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the participant and collection of the required LDH, PK, and PD samples.
Concomitant medications	←Monitor continuously→						
Adverse events	←Monitor continuously→						
Confirmation of eculizumab dose	X	X	X	X	X	X	At the Investigator's discretion and preference of the patient, eculizumab may be administered at the participant's home (except at Visits -57 and -29) by a trained qualified staff member (Section 8)

Abbreviations: ADA = antidrug antibody; AE = adverse event; BTH = breakthrough hemolysis; C5 = complement component C5; ECG = electrocardiogram; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LDH-PCHG = lactate dehydrogenase percent change; PD = pharmacodynamic; PK = pharmacokinetic; RBC = red blood cell; SAE = serious adverse event; WBC = white blood cell.

Table 2: Schedule of Study Visits and Assessments: Confirmation Visit Through Follow-up

Period	**Confirmation Visit**	**Evaluation Period**							**Unscheduled Visits**	**Follow-up call**	**Notes**
Study Day	**1**	**15**	**71**	**127**	**183**	**239**	**295**	**351/ ET**	**NA**	**407**	
Window (day)	**NA**	**± 2**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		**± 7**	
Inclusion and exclusion criteria	X										LDH and hematologic criteria assessed
Physical examination	X							X			
Abbreviated physical examination		X	X	X	X	X	X		X		Refer to Section 8.2.1 for details
Weight	X	X	X	X	X	X	X	X	X		
Serum or urine pregnancy test	X	X	X	X	X	X	X	X	X		Refer to Section 8.3.5 for details. Serum pregnancy test at Day 1, and Day 351/ET.; Urine pregnancy test at all other visits
Chemistry including LDH	X	X	X	X	X	X	X	X	X		Sample to be collected within 24 hours of or immediately prior to a scheduled dose of study drug (trough) and not from a heparinized line.
Hematology including free hemoglobin and coagulation	X	X	X	X	X	X	X	X	X		Blood will be collected predose on dosing days and not from a heparinized line.
Urinalysis and urine chemistry	X	X	X	X	X	X	X	X	X		Urine will be collected predose on dosing days.
Safety 12-lead ECG								X			Refer to Section 8.2.3 for details
Vital signs	X	X	X	X	X	X	X	X	X		Will be measured after the participant has been resting for at least 5 minutes. Refer to Section 8.2.2 for details
PNH clone size	X			X				X			WBC (granulocyte and monocyte) and RBC clone size measured by high-sensitivity flow cytometry at Day 1; RBC clone size only at Day 127 and Day 351/ET

Table 2: Schedule of Study Visits and Assessments: Confirmation Visit Through Follow-up

Period	**Confirmation Visit**	**Evaluation Period**							**Unscheduled Visits**	**Follow-up call**	**Notes**
Study Day	**1**	**15**	**71**	**127**	**183**	**239**	**295**	**351/ ET**	**NA**	**407**	
Window (day)	**NA**	**± 2**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		**± 7**	
PRS and HRU	X				X			X			Questionnaires at the confirmation visit administered prior to first dosing of Ravulizumab. PRS completed by the participant Refer to Section 8.10 for details
Record transfusions and transfusion parameters	X	X	X	X	X	X	X	X	X		Transfusions given during and between visits will be recorded
PNH symptomatology	X	X	X	X	X	X	X	X	X		Investigator assessed and reported Refer to Section 8.1.3 for details
PK/PD sampling	X	X	X	X	X			X	X		Refer to Section 8.5 and Section 8.6 for details
Immunogenicity (ADA)	X		X		X			X	X		Samples will be collected predose
Review safety card	X	X	X	X	X	X	X	X	X		
BTH	←Monitor continuously→										If a suspected event of BTH occurs, LDH, PK, and PD samples will be collected and analyzed . If the suspected event of BTH does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the participant and collection of the required LDH, PK, and PD samples.
Concomitant medications	←Monitor continuously→										
Adverse events	←Monitor continuously→										

Table 2: Schedule of Study Visits and Assessments: Confirmation Visit Through Follow-up

Period	**Confirmation Visit**	**Evaluation Period**							**Unscheduled Visits**	**Follow-up call**	**Notes**
Study Day	**1**	**15**	**71**	**127**	**183**	**239**	**295**	**351/ ET**	**NA**	**407**	
Window (day)	**NA**	**± 2**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**		**± 7**	
Ravulizumab administration	X	X	X	X	X	X	X		X		The dose of ravulizumab is based on the participant's last recorded study visit body weight as per approved dose regimen. Refer to Section 6.1.1 At the Investigator's discretion and in accordance with the local regulations, ravulizumab may be administered at the patient's home or at a medical facility close to the patient's home by a qualified healthcare personnel (see Section 8.11).

Abbreviations: ADA = antidrug antibody; AE = adverse event; BTH = breakthrough hemolysis; C5 = complement component C5; ECG = electrocardiogram; ET = early termination; LDH = lactate dehydrogenase; LDH-PCHG = lactate dehydrogenase percent change; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; RBC = red blood cell; SAE = serious adverse event; WBC = white blood cell.

Table 3: Schedule of Study Visits and Assessments: q6w Dosing

	Starting Visit	**Example Visit**	**EOS/ET**	**Unscheduled visit**	**Follow-up call**	Notes
Study Day	**q6w Day 1**	**q6w Day 43**	**Day XX**	**NA**	**EOS/ET + 56 days**	All subsequent q6w visits up to EOS/ET to follow the assessments shown in the example visit
Window (day)	**NA**	**± 7**	**± 7**		**± 7**	
Physical examination			X			
Abbreviated physical examination	X	X		X		Refer to Section 8.2.1 for details
Weight	X	X	X	X		
Serum or urine pregnancy test	X	X	X	X		Refer to Section 8.3.5 for details
Chemistry including LDH	X	X	X	X		Sample to be collected within 24 hours of or immediately prior to a scheduled dose of study drug (trough) and not from a heparinized line.
Hematology including free hemoglobin and coagulation	X	X	X	X		Blood will be collected predose on dosing days and not from a heparinized line.
Urinalysis and urine chemistry	X	X	X	X		Urine will be collected predose on dosing days.
Safety 12-lead ECG	X		X			Refer to Section 8.2.3 for details
Vital signs	X	X	X	X		Will be measured after the participant has been resting for at least 5 minutes. Refer to Section 8.2.2 for details
PNH clone size	X	X	X			WBC (granulocyte and monocyte) and RBC clone size measured by high-sensitivity flow cytometry at Day 1; RBC clone size only at Day 127 and Day 351/ET
Record transfusions and transfusion parameters	X	X	X	X		Transfusions given during and between visits will be recorded
PNH symptomatology	X	X	X	X		Investigator assessed and reported. Refer to Section 8.1.3 for details
PK/PD sampling	X	X	X	X		Refer to Section 8.5 and Section 8.6 for details

Table 3: Schedule of Study Visits and Assessments: q6w Dosing

	Starting Visit	**Example Visit**	**EOS/ET**	**Unscheduled visit**	**Follow-up call**	Notes
Study Day	**q6w Day 1**	**q6w Day 43**	**Day XX**	**NA**	**EOS/ET + 56 days**	All subsequent q6w visits up to EOS/ET to follow the assessments shown in the example visit
Window (day)	**NA**	**± 7**	**± 7**		**± 7**	
Immunogenicity (ADA)	X	X	X	X		Samples will be collected predose
Review safety card	X	X	X	X		
BTH	←Monitor continuously→					If a suspected event of BTH occurs, LDH, PK, and PD samples will be collected and analyzed. If the suspected event of BTH does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the participant and collection of the required LDH, PK, and PD samples.
Concomitant medications	←Monitor continuously→					
Adverse events	←Monitor continuously→					
Ravulizumab administration	X	X		X		The dose of ravulizumab is based on the participant's last recorded study visit body weight as per approved dose regimen. Refer to Section 6.1.1 At the Investigator's discretion and in accordance with the local regulations, ravulizumab may be administered at the patient's home or at a medical facility close to the patient's home by a qualified healthcare personnel (see Section 8.11)

Abbreviations: ADA = antidrug antibody; AE = adverse event; BTH = breakthrough hemolysis; C5 = complement component C5; ECG = electrocardiogram; ET = early termination; LDH = lactate dehydrogenase; LDH-PCHG = lactate dehydrogenase percent change; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; RBC = red blood cell; SAE = serious adverse event; WBC = white blood cell.

2. INTRODUCTION

2.1. Study Rationale

Some patients are prescribed a higher dose of eculizumab than the approved dose in order to achieve complete blockade of complement component 5 (C5) (Kelly, 2008). The main purpose of this study is to provide clinical evidence that participants on high dose eculizumab can be switched to ravulizumab without a change in the benefit/risk profile.

2.2. Background

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare and life-threatening acquired hemolytic disorder caused by uncontrolled activation of the terminal complement pathway (Brodsky, 2014; Brodsky, 2015). The disease begins with the clonal expansion of a hematopoietic stem cell that has acquired a somatic mutation in the PIGA gene (Brodsky, 2014). Consequently, PNH blood cells lack the glycophosphatidylinositol anchor protein and are deficient in the membrane-bound complement inhibitory proteins CD55 and CD59. In the absence of CD55, there is increased deposition of complement protein C3 cleavage products on blood cell membrane surfaces, in turn leading to cleavage of C5 into C5a and C5b. The pathology and clinical presentations in patients with PNH are driven by uncontrolled terminal complement activation on red blood cells (RBCs).

C5a is a potent anaphylatoxin, chemotactic factor, and cell-activating molecule that mediates multiple pro-inflammatory and pro-thrombotic activities (Matis, 1995; Prodinger, 1999). C5b recruits the terminal complement components C6, C7, C8, and C9 to form the pro-inflammatory, pro-thrombotic cytolytic pore molecule C5b-9, a process that under normal circumstances would be blocked on the RBC membrane by CD59. In patients with PNH, however, these final steps proceed unchecked, culminating in hemolysis and the release of free hemoglobin, as well as platelet activation (Hill, 2013).

The signs and symptoms of PNH can be attributed to chronic, uncontrolled complement C5 cleavage and release of C5a and C5b-9 leading to RBC hemolysis, which together result in the release of intracellular free hemoglobin and lactate dehydrogenase (LDH) into circulation; irreversible binding to and inactivation of nitric oxide (NO) by hemoglobin, and inhibition of NO synthesis; vasoconstriction and tissue-bed ischemia due to absence of vasodilatory NO as well as possible microthrombi manifesting as abdominal pain, dysphagia, and erectile dysfunction; platelet activation; and a pro-inflammatory and prothrombotic state (Brodsky, 2014; Hill, 2013). A substantial proportion of patients with PNH experience renal dysfunction and pulmonary hypertension (Hill, 2013; Hill, 2012; Hillmen, 2010). Patients also experience venous or arterial thrombosis in diverse sites, including the abdomen or central nervous system (Brodsky, 2014).

Approved treatments for PNH include eculizumab and ravulizumab. Eculizumab and ravulizumab are humanized monoclonal antibodies (mAb) that specifically bind to the complement protein C5 with high affinity. They have no known off-target interactions with other proteins in vitro or in vivo. In addition, eculizumab and ravulizumab are predicted to be effectorless, having no detectable binding to complement C1q or most Fcγ receptors (FcγR I, IIb/c IIIa, IIIb) and more than 10-fold weaker binding than an IgG1 isotype to FcγR IIa. These

attributes underlie the established safety and therapeutic efficacy profile of eculizumab and ravulizumab in the treatment of PNH, demonstrated in clinical studies and supported by subsequent postmarketing experience.

Patients treated with eculizumab are required to receive maintenance infusions q2w. Ravulizumab was engineered from eculizumab to preserve immediate and complete C5 inhibition while providing sustained complement inhibition throughout a prolonged dosing interval (1 month or longer), allowing for maintenance infusions every 8 weeks (q8w). Ravulizumab and eculizumab share > 99% sequence homology, as ravulizumab was derived through minimal targeted engineering to substitute 4 amino acids in the eculizumab heavy chain. Two of these substitutions are in the complementarity determining regions, lowering the affinity of ravulizumab for C5; the other two are in the Fc binding region which improves recycling of ravulizumab into the vascular space instead of degrading. These changes were specifically designed (and have subsequently been proven) to increase the half-life of ravulizumab relative to eculizumab, increasing the duration of terminal complement inhibition, while preserving both the high degree of specificity for binding to C5 and the effectorless nature of the antibody.

The recommended eculizumab maintenance dose of 900 mg every 14 days is sufficient to maintain inhibition of hemolysis in most patients with PNH. However, approximately 11% to 27% of patients experience BTH during treatment with the approved dose of eculizumab and require the dosing interval to be shortened to < 14 days or the dosage to be increased (Hill, 2005; Peffault de Latour, 2015).

In this Phase 4 open-label study, the efficacy and safety of ravulizumab will be assessed in participants with PNH who are clinically stable, having been treated with eculizumab 1200 mg q2w for at least the past 3 months prior to study entry. The choice of study design is further discussed in Section 4.2.

More information about the PK, mechanism of action, known and expected benefits, risks, and reasonably anticipated safety profile of ravulizumab may be found in the current edition of the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

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 *Neisseria meningitidis*.	Participants must be vaccinated or revaccinated according to current national vaccination guidelines for vaccination use prior to or at the time of initiating dosing with complement inhibitors (eg, eculizumab or ravulizumab).

Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential Risks		
Serious hemolysis after drug discontinuation	This potential disease-associated risk is based on a theoretical possibility, associated with abrupt ravulizumab discontinuation, resulting in a so-called rebound effect. Rebound effect is described for many biologicals but has not been observed in ravulizumab clinical trials.	The effects are most likely not completely preventable, but their severity can be minimized by avoiding abrupt drug discontinuation. Participants who discontinue the drug will be followed up for 16 weeks if participants remain in the study.
Serious infection	This potential risk is a based on the mode of action of ravulizumab and experience with the use of eculizumab. 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 participant 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.
Malignancies and hematologic abnormalities	The natural evolution of PNH disease makes PNH patients more prone to development of hematologic abnormalities or malignancies as approximately 30-70% of PNH patients eventually develop aplastic anemia or myelodysplastic syndrome. The potential role of ravulizumab in the risk of such abnormalities or malignancies (if any) is unknown	Monitoring 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 severe 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 IV have the potential risk of causing local (infusion-site reactions) and systemic reactions (infusion-associated reactions).	In the ALXN1210-PNH-103 and ALXN1210-PNH-201 studies, no participants have returned a positive ADA sample. 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 trial. 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 following the last dose of ravulizumab. Breastfeeding should be discontinued during treatment and up to 8 months after treatment with ravulizumab.

2.3.2. Benefit Assessment

PNH is an ultra-rare, progressive, debilitating, and life-threatening disease, driven by chronic uncontrolled complement activation. The resulting inflammation and cellular damage lead to systemic complications, principally through intravascular hemolysis and thrombophilia (Brodsky, 2014; Socié, 1996). Chronic intravascular hemolysis due to continuous activation of the complement pathway leads to the release of free hemoglobin, NO consumption and persistent smooth muscle cell contraction, chronic anemia, and an increased risk of severe thromboembolism. Patients with PNH are at risk of substantial morbidity and mortality and altered quality of life. The current standard of care for the treatment of PNH is eculizumab, a recombinant humanized mAb that binds to the human C5 complement protein and inhibits the activation of terminal complement. The efficacy and safety of eculizumab for the treatment of PNH are well established. The approved dosing regimen for eculizumab for PNH involves 4 weekly induction doses, followed by maintenance doses administered q2w starting at Week 5.

Given that PNH is a chronic disease, the current eculizumab regimen may significantly affect patients, many of whom have to miss days of work or school to accommodate treatment. In some cases, patients may refuse treatment or may be unable to comply with the treatment frequency of eculizumab. Practice survey research supports the assumption that less frequent infusions associated with ravulizumab will have a positive impact on daily life for patients and their caregivers.

Ravulizumab (ALXN1210) is a recombinant, humanized mAb derived through minimal targeted engineering of eculizumab by introducing 4 unique amino acid substitutions. Ravulizumab has been designed to have the same rapid onset of action and effective blockade of complement, with an increased serum half-life to yield an increased duration of pharmacologic activity relative to eculizumab. In PNH, this may reduce the potential risk of breakthrough, complement-mediated hemolysis, as suggested by preliminary clinical data from the ongoing PNH studies, which demonstrate rapid and sustained reduction in LDH levels, a direct measure of hemolytic activity that is of comparable magnitude to that seen in studies of eculizumab.

The benefit to this population includes less-frequent dosing which creates less burden on the patient and will allow greater access to care for those patients who may not initiate treatment or may discontinue eculizumab due to the frequency of dosing. Additionally, the substantially longer half-life of ravulizumab is expected to produce sustained terminal complement inhibition during a longer dosing interval.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with ravulizumab are justified by the anticipated benefits that may be afforded to patients with PNH.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • To evaluate the prevalence of free C5-associated BTH in participants on high-dose eculizumab who switch to ravulizumab (per approved dose regimen)	• Proportion of participants who experience free C5-associated BTH through Day 351. Free C5-associated BTH is defined as BTH concurrent with free C5 concentrations ≥ 0.5 µg/mL. BTH is defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], MAVE, including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN.
Secondary • To evaluate efficacy by other measures in participants on high-dose eculizumab who switch to ravulizumab	• Proportion of participants who experience BTH through Day 351 • Hemolysis as directly measured by LDH-PCHG from baseline to Day 351 • Proportion of participants who receive a transfusion, from baseline to Day 351 • Proportion of participants with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion from baseline to Day 351
Exploratory To evaluate patient-reported outcomes over time for those who switch to Ravulizumab from high-dose eculizumab	• Patient-reported PNH Symptoms (PRS) at baseline, Day 183 and Day 351 • Healthcare Resource Utilization (HRU) at baseline, Day 183 and Day 351
Safety • To evaluate the safety and tolerability of ravulizumab in participants on high-dose eculizumab who switch to ravulizumab	• Physical examinations, vital signs, and laboratory assessment results, and incidence of adverse events (AEs) and serious adverse events (SAEs) • Proportion of participants who develop antidrug antibodies (ADAs) to ravulizumab
PK/PD • To characterize the PK/PD of ravulizumab in participants on high-dose eculizumab who switch to ravulizumab	• Change in serum ravulizumab concentration over time • Change in serum free and total C5 concentrations over time

Abbreviations: ADA = antidrug antibody; AE = adverse event; BTH = breakthrough hemolysis; C5 = complement component C5; LDH-PCHG = lactate dehydrogenase percent change; MAVE = major adverse vascular event; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 4, multicenter, single-arm, open-label study to evaluate safety and efficacy of ravulizumab in adult participants with PNH who switch from eculizumab 1200 mg q2w to ravulizumab.

The study will consist of a Screening Period of approximately 3 months and a Treatment Period of 351 days.

Approximately 20 participants will be enrolled. Eligible participants will be administered eculizumab 1200 mg q2w optionally at home at the discretion of the Investigator, and preference of the patient (see Section 8) during the Screening Period followed by a loading dose of ravulizumab on Day 1, and maintenance treatment with ravulizumab on Day 15 and q8w thereafter until Day 351. Ravulizumab loading and maintenance doses will be based on the participant's body weight measured at the prior visit, per approved dosing regimen. Ravulizumab dosing will be administered in the clinic by a trained member of the site study team; patients may have the option to receive study drug remotely at a medical facility that is located near the patient's home or at the patient's home through a qualified healthcare personnel (see Section 8.11). The schedule of study visits and assessments is shown in Section 1.3.

An interim analysis will be performed on Day 183.

4.2. Scientific Rationale for Study Design

The purpose of this study is to evaluate the safety and efficacy of ravulizumab q8w in adult participants with PNH who are currently receiving maintenance treatment with eculizumab 1200 mg q2w, a dosage that is higher than the approved maintenance dose of eculizumab (900 mg q2w). Use of this higher dose has been reported in the literature to prevent the occurrence of BTH in some patients (Peffault de Latour, 2015). Some patients require a shortened dosing interval to completely block serum hemolytic activity despite sufficient levels of eculizumab (Hill, 2005). They may benefit from the longer half-life and less frequent dosing interval with ravulizumab.

A Phase 3 study demonstrated the safety and efficacy of ravulizumab in eculizumab-experienced participants (Kulasekararaj, 2019). However, this study excluded participants on eculizumab 1200 mg q2w therefore, the current study is designed to demonstrate the safety and efficacy in these participants.

The safety parameters being evaluated are commonly used in clinical studies per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) guidances.

4.3. Justification for Dose

The ravulizumab dose regimen in this study is the approved dose for the treatment of PNH in adult participants.

4.4. End of Study Definition

The end of the study is defined as the date of the last participant's last visit.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 years of age or older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry evaluation of RBCs and WBCs, with granulocyte or monocyte clone size of ≥ 5%.
3. Received 1200 mg eculizumab every 12 to 16 days (q2w) for at least 3 months prior to Screening.
4. Lactate dehydrogenase (LDH) ≤ 2 x upper limit of normal (ULN) according to central laboratory, at screening. Sample must be obtained within 24 hours of or immediately prior to a schedule eculizumab dose administration (ie, at trough eculizumab level).
5. To reduce the risk of meningococcal infection (*N. meningitidis*), all participants must be vaccinated against meningococcal infections within 3 years prior to initiating study drug.

Weight

6. Body weight ≥ 40 kg.

Sex

7. Male or female

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

   a. Male participants:

   - Male participants must agree to use contraception as detailed in the protocol during the treatment period and for at least 8 months after last dose of study drug and refrain from donating sperm during this period.

   b. Female participants:

   A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

   - Not a woman of childbearing potential (WOCBP)

   OR

   - Is a WOCBP and using a highly effective or acceptable contraceptive method as described in Appendix 4 during the treatment period and for at a minimum of 8 months after the last dose of study drug.

- The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study drug. A WOCBP must have a negative highly sensitive pregnancy test (serum pregnancy test) within 24 hours before the first dose of study drug. Additional requirements for pregnancy testing during and after study drug are described in Section 10.4. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. 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. History of major adverse vascular events (MAVEs) within 6 months of Day 1.
2. History of bone marrow transplantation.
3. History of *N. meningitidis* infection
4. History of unexplained, recurrent infection.
5. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
6. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study drug administration on Day 1.
7. History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease (eg, active hepatitis) that, in the opinion of the Investigator or Alexion, precludes the participant's participation in an investigational clinical trial.
8. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of Day 1, coexisting chronic anemia unrelated to PNH) that would make them unlikely to tolerate the requirements of the protocol.
9. Hypersensitivity to the active substance or to any of the excipients.
10. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
11. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator or Alexion, 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.
12. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not

limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).

13. Lymphoma, leukemia, myelodysplastic syndrome, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
14. Major surgery within 90 days prior to dosing on Day 1.

Prior/Concomitant Therapy

15. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.
16. Concomitant use of any of the following medications and not on a stable regimen (as judged by the investigator) for the time period indicated prior to Screening:
    - Erythropoietin or immunosuppressants for at least 8 weeks
    - Systemic corticosteroids for at least 4 weeks
    - Vitamin K antagonists (eg, warfarin) with a stable international normalized ratio (INR) level for at least 4 weeks
    - Iron supplements or folic acid for 4 weeks
17. Live vaccine(s) within 1 month prior to Screening or plans to receive such vaccines during the study.

Prior/Concurrent Clinical Study Experience

18. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater.

Diagnostic Assessments

19. More than one LDH value > 2 × ULN within the 6 months prior to Day 1.
20. Platelet count < 30,000/mm^3 (30 × 10^9/L) at Screening.
21. Absolute neutrophil count < 500/μL (0.5 × 10^9/L) at Screening.
22. Positive human immunodeficiency virus (HIV) antibody test.

Other Exclusions

23. Females who plan to become pregnant, are currently pregnant or breastfeeding, or are sexually active and unwilling to use effective birth control for the duration of the study.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 (Schulz, 2010) and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any AEs or SAEs occurring during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved may be rescreened based on discussion and agreement between the Investigator and Medical Monitor.

6. STUDY TREATMENTS

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

6.1. Study Drug(s) Administered

Ravulizumab is a humanized, anti-C5a mAb. Ravulizumab was derived through minimal targeted engineering of eculizumab by introducing 4 unique amino acid substitutions to its heavy chain. Ravulizumab and eculizumab share over 99% primary sequence identity and have very similar pharmacology.

Ravulizumab drug product is supplied for clinical studies as a 10-mg/mL solution in a 30-mL single-use vial and is designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via IV infusion.

Each vial of ravulizumab drug product includes a nominal overfill to ensure that 30 mL (300 mg of the ravulizumab antibody) of solution can be withdrawn for IV administration.

ARM Name	**Ravulizumab**
Drug Name	Ravulizumab
Type	Biologic
Dose Formulation	Concentrated sterile, preservative-free aqueous solution
Unit Dose Strength(s)	300 mg (10 mg/mL concentrated solution)
Dosage Level(s)	Doses based on participant weight
Route of Administration	IV infusion
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by Alexion or contracted manufacturing organization.
Packaging and Labeling	Study drug will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits and labeled as required per country requirement.

Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product

6.1.1. Ravulizumab Dosing

The approved body weight-based ravulizumab dosing is shown in Table 4.

Table 4: Dosing Reference Chart for Ravulizumab Dose Preparation

Dose Type	Body Weight (kg)[a]	Dose (mg)	Ravulizumab Volume (mL)	Saline Volume (mL)	Total Volume (mL)	Minimum Infusion Duration minutes (hours)	Maximum Infusion Rate (mL/hour)
Loading	≥ 40 to < 60	2400	240	240	480	114 (1.9)	253
	≥ 60 to < 100	2700	270	270	540	102 (1.7)	318
	≥ 100	3000	300	300	600	108 (1.8)	333
Maintenance	≥ 40 to < 60	3000	300	300	600	140 (2.4)	250
	≥ 60 to < 100	3300	330	330	660	120 (2.0)	330
	≥ 100	3600	360	360	720	132 (2.2)	328

Note: Please refer to the Pharmacy Manual for additional dose preparation instructions.
[a] Dose regimen will be based on the last recorded study visit body weight.

6.2. Preparation/Handling/Storage/Accountability

Upon arrival of the study drug at the study site, study drug kits should be removed from the shipping container and stored in their original cartons under refrigerated conditions at 2°C to 8°C (35°F to 47°F) and protected from light. Ravulizumab should not be frozen.

Study drug must be stored in a secure, limited-access storage area with temperature monitored daily.

Infusions of study drug should be prepared using aseptic technique. Ravulizumab will be further diluted in a 1:1 ratio with compatible diluent. Ravulizumab will be filtered with a 0.2 micron filter during infusion. Study drug will be prepared and administered by a trained member of the site study team.

1. 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.
2. Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer 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.
3. 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).
4. For detailed instruction on study drug preparation, handling, storage, and accountability, refer to the Pharmacy Manual. Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. All study participants, site personnel, Alexion staff, designees, and all staff directly associated with the conduct of the trial will be unblinded to participant treatment.

6.4. Study Drug Compliance

Study drug will be administered in a controlled setting under the supervision of the Investigator or designee, thereby ensuring compliance with study drug administration.

The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

6.5. Concomitant Therapy

Any medication including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prior medications (including vitamins and herbal preparations), including those discussed in the exclusion criteria (Section 5.2) and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the participant takes or undergoes within 28 days prior to the start of Screening until the first dose of study drug, will be recorded in the participant's case report forms. In addition, history of meningococcal vaccination must be collected for the 3 years prior to first dose of study drug.

Transfusions of packed red blood cells received within 1 year prior to first study drug administration will be recorded in the participant's eCRF.

All medications or therapies and procedures undertaken during the study will be recorded in the participant's source document/medical chart and eCRF. This record will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and current medications for PNH. Concomitant medications will be recorded from the first infusion of study drug through 30 days after the participant's last dose of study drug. Any changes in concomitant medications also will be recorded in the participant's source document/medical chart and eCRF. Any concomitant medication deemed necessary for the participant's standard of care during the study, or for the treatment of any AE, along with the allowed medications described below may be given at the discretion of the investigator.

The following concomitant medications are allowed if the following conditions apply, and dose adjustments are not expected during the treatment period:

- Erythropoietin, if the participant has been receiving a stable dose for at least 8 weeks before Screening.
- Immunosuppressants, if the participant has been receiving a stable dose for at least 8 weeks before Screening.
- Corticosteroids, if the participant has been receiving a stable dose for at least 4 weeks before Screening.
- Vitamin K antagonists (eg, warfarin), if the participant has had a stable INR level (per investigator's discretion) for at least 4 weeks before Screening.
- Iron supplements or folic acid, if the participant has been receiving a stable dose for at least 4 weeks before Screening.

Adjustments in the frequency or dose level in any of the above medications can be made if the Alexion Medical Monitor or the Investigator deems it is in the best interest of the participant.

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study drug until completion of the follow-up visit, unless, in the opinion of the Investigator and Alexion, the medication will not interfere with the study.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor, if required.

6.5.1. Meningococcal Vaccination

As with any terminal complement antagonist, the use of ravulizumab increases the participant's susceptibility to meningococcal infection (*N. meningitidis*). To reduce the risk of meningococcal infection, all participants must have been vaccinated against meningococcal infections within 3 years prior to initiating study drug.

Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes. Participants must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, eculizumab). Participant's vaccination status will be confirmed.

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given per official guidance and local practice on the appropriate use of 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.

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 safety card to carry with them at all times. 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 (SoA [Section 1.3]).

6.5.2. Rescue Medicine

Not applicable.

6.6. Dose Modification

6.6.1. Supplemental Dosing

If a BTH event occurs during the Screening Period, the participant will be ineligible for the study. If a participant experiences BTH during maintenance treatment with ravulizumab, an additional weight-based maintenance dose of ravulizumab may be administered or the next scheduled maintenance dose may be accelerated as per Table 5 at the Investigator's discretion after discussion with the Medical Monitor.

Table 5: Dosing Guidance for Patients with Breakthrough Hemolysis

			Timing of Subsequent Dose after Next Maintenance Dose	
Time of BTH	**Supplemental Dosing**	**Next Maintenance Dose**	**if free C5 is < 0.5µg/mL**	**if free C5 is ≥ 0.5 µg/mL**
≤ 2 weeks after previous dose	Decision to be made based on results of Free C5 at Investigator's discretion	As per SoA[a]	As per SoA[a]	6 weeks after the last maintenance dose[b]
>2 to < 6 weeks after previous dose	Supplemental dose	As per SoA[a]	As per SoA[a]	6 weeks after the last maintenance dose[b]
≥ 6 weeks after previous dose	Not applicable	Accelerate next dose at Investigator's discretion	As per SoA[a]	6 weeks after the last maintenance dose[b]

[a]Timing of next dose will be per SoA (Section 1.3)
[b] See Section 6.6.2
Abbreviations: BTH = breakthrough hemolysis; C5 = complement component 5; SoA = Schedule of Activities

6.6.2. Permitted Change in Dosing Interval

If a participant experiences a free C5-related BTH during maintenance treatment with ravulizumab, shortening the dosing interval to every 6 weeks (q6w) is permitted at the discretion of the Investigator after discussion with Alexion's Medical Monitor. For these participants, the assessments performed at the first q6w visit would be those indicated in the SoA (Section 1.3). Subsequent q6w visit assessments would continue to be aligned to the example visit illustrated in Table 3, with the EOS/ET visit being on/after Day 351. Between the SoA-specified visits occurring at 6-week dosing frequency and the EOS/ET visit, any additional visits are to be classified as unscheduled visits and would follow the study procedures for unscheduled visits (Table 3).

6.7. Intervention after the End of the Study

At the end of the study, participants will be transitioned to standard of care.

All participants will be followed for safety for an additional 16 weeks after the last dose of study drug if they discontinue from the study early.

7. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study drug. If the study drug is definitively discontinued, the participant should remain in the study to be evaluated for safety follow up. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of the study drug and follow-up and for any further evaluations that need to be completed.

Participants should be considered for discontinuation from study drug if any of the following occur during the study:

1. Serious hypersensitivity reaction
2. Use of disallowed medication as defined in Section 6.5
3. Alexion or the Investigator deems it is necessary for the participant
4. Withdrawal of consent.

Participants who become pregnant must have study drug discontinued.

7.2. Participant Discontinuation/Withdrawal from the Study

All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify their site monitor and Alexion of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and eCRF.

If a participant withdraws consent, the assessments specified for the Early Termination (ET) visit (as shown in the SoA, Section 1.3) will be performed and Alexion and site monitor notified as soon as possible. Participants who withdraw from the study will not be replaced.

Participants should be permanently discontinued from ravulizumab treatment if any of the following occur during the study:

- Serious infusion reaction (such as bronchospasm with wheezing or requiring ventilator support or symptomatic hypotension) or serum sickness-like reactions manifesting 1 to 14 days after drug administration;
- Severe uncontrolled infection;
- Pregnancy or planned pregnancy; or
- If the Alexion Medical Monitor or the Investigator deems it is in the best interest of the participant.

The Investigator should speak with the Medical Monitor prior to discontinuing a participant's study treatment. If a participant is discontinued from study drug, the participant should be encouraged to return for the remainder of his or her scheduled protocol visits until starting a different complement-targeted therapy.

If a participant is discontinued from the study with an ongoing AE or an unresolved laboratory result that, in the opinion of the Investigator, is significantly outside of the reference range and

clinically significant (Section 10.3), the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

If a female participant is permanently discontinued from ravulizumab treatment due to pregnancy, the Investigator will attempt to follow-up until the outcome of the pregnancy (Section 10.4).

- 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. This is expected to be uncommon.
- If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow up

If a participant fails to return, or is otherwise unavailable, for a scheduled visit within the acceptable visit window (Section 1.3), the site study staff must make a reasonable attempt to contact the participant to determine the reason for missing the appointment.

Participants who fail to return for a scheduled visit must be contacted by the site's study staff to determine the reason for missing the appointment. As it is vital to obtain any participant's missing visit information to ensure the missed appointment was not due to an AE or potential relapse, every effort must be made to undertake protocol-specified safety follow-up procedures.

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.

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 SoA (Section 1.3).
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should receive the study drug.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- During Screening, eculizumab may be administered at the participant's home at the discretion of the Investigator and preference of the patient, in accordance with the local procedures and Standard Operating Procedures at the site. These visits will be conducted by a trained qualified staff member. During a home administration visit, all assessments will be performed according to the SoA (Table 1). Patients must return to the study site for any visit at which PD sampling (Day –57 and Day –29) is scheduled, as specified in the SoA (Table 1). In countries where local legislation does not allow infusions outside authorized study sites, the Investigators will be notified in writing that this provision is prohibited
- 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 and were performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

8.1.1. Transfusions

Administration of a pRBC transfusion, including the hemoglobin result and symptoms that triggered the transfusion and the number of units transfused, will be documented in the eCRF.

8.1.2. Lactate Dehydrogenase and Other Disease-Related Laboratory Parameters

Blood and urine samples will be collected at the times indicated in the SoA (Section 1.3) and as indicated in Section 10.2.

The following disease-related laboratory parameters will be measured during the study (refer to Section 8.5 and Section 8.6 for PK/PD assessments):

- LDH
- free hemoglobin
- occult blood, urine
- haptoglobin

- reticulocyte count
- PNH RBC clone size evaluated by high-sensitivity flow cytometry (Borowitz, 2010)
- estimated glomerular filtration rate (calculated using the Schwartz formula)

8.1.3. Paroxysmal Nocturnal Hemoglobinuria Symptomatology

The Investigator or designee will record for each participant the presence or absence of the following signs and symptoms of PNH: fatigue, chest pain, hemoglobinuria, abdominal pain, dyspnea, dysphagia, erectile dysfunction, and red/dark urine or hemoglobinuria.

8.1.4. Major Adverse Vascular Events

Major adverse vascular events will be assessed as part of the planned evaluation for AEs as described in Section 8.3.

The description of the MAVE including the method of diagnosis (eg, magnetic resonance imaging, ultrasound, angiogram), date of diagnosis, and date resolved (or ongoing) will be collected on the eCRF as part of the participant's medical history (prior to baseline).

A MAVE is defined as follows:

- Thrombophlebitis/deep vein thrombosis
- Pulmonary embolus
- Myocardial infarction
- Transient ischemic attack
- Unstable angina
- Renal vein thrombosis
- Acute peripheral vascular occlusion
- Mesenteric/visceral vein thrombosis or infarction
- Mesenteric/visceral arterial thrombosis or infarction
- Hepatic/portal vein thrombosis (Budd-Chiari syndrome)
- Cerebral arterial occlusion/cerebrovascular accident
- Cerebral venous occlusion
- Renal arterial thrombosis
- Gangrene (nontraumatic; nondiabetic)
- Amputation (nontraumatic; nondiabetic)
- Dermal thrombosis
- Other, specify

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
- An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- 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.

8.2.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with an automated device. Manual techniques will be used only if an automated device is not available.
- Vital sign measurements will be taken after the participant has been resting for at least 5 minutes and will include systolic and diastolic blood pressure (millimeters of mercury [mmHg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). On dosing days, vital signs will be taken before study drug administration.

8.2.3. Electrocardiograms

- A single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- The Investigator or qualified designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and to determine the clinical significance of the results. These assessments will be recorded in the source documents and the eCRF.

8.2.4. Clinical Safety Laboratory Assessments

- Detailed instructions on the procedure for collection, processing, storage, and shipment of the samples for laboratory analyses will be provided in the Laboratory Study Manual. All sample analyses will be performed by Alexion or its designee.

- See Section 10.2 for the clinical laboratory tests to be performed and the SoA (Section 1.3) for their timing and frequency.
- If a suspected event of BTH occurs, LDH, PK, and PD samples will be collected and analyzed. If the suspected event of BTH does not occur at a scheduled visit, an unscheduled visit should be conducted for evaluation of the participant and collection of the required LDH, PK, and PD samples.
- 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 eCRF. 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 discussed by the Investigator and Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs are specified in Section 10.3.

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 of 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).

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3 (Appendix 3).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs will be collected from the signing of the Informed Consent Form until the follow-up call.

All SAEs will be recorded and reported to Alexion or designee within 24 hours of awareness, as indicated in Section 10.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (AESI) (as defined in Section 8.3.6), will be followed 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 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to Alexion of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug 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 drug under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review, sign a document stating they have reviewed it, and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Pregnancy testing must be performed on all WOCBP at protocol-specified timepoints in the SoA (Section 1.3). Serum samples will be collected at Day 85, Day 1, and Day 351/ET. At all other

time points urine samples will be collected for pregnancy test. 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.

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study drug and until the termination of the pregnancy.
- If a pregnancy is reported, the Investigator should inform Alexion within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Pregnancy alone is not considered an AE.

If a participant becomes pregnant, the study drug must be immediately discontinued, and Alexion must be notified as per Section 10.4. Each pregnancy will be followed to term and Alexion notified regarding the outcome.

8.3.6. Adverse Events of Special Interest

Meningococcal infections will be collected as AESI.

8.4. Treatment of Overdose

For this study, any dose of study drug greater than that specified in the label will be considered an overdose.

Accidental overdose without any association with laboratory abnormalities or clinical symptoms should not be considered as an AE. Overdose must be reported by the Investigator within 24 hours to Alexion regardless of its association with or without an AE.

Alexion does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE.
3. Obtain a serum sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the timing of the overdose in the eCRF.

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

8.5. Pharmacokinetics/Pharmacodynamics Sampling

8.5.1. Sample Collection During the Screening Period

Serum samples will be collected for free and total C5 analyses (before eculizumab dosing) during Screening on Day -57 and Day -29. The predose (within 0.5 hours prior to the start of infusion) free C5 sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. All collection times will be recorded in the eCRF. In the event of BTH, a serum sample for PK/PD analysis will be collected.

In the event of an unscheduled visit, PK and PD blood sample will be collected as soon as possible.

8.5.2. Sample Collection during Confirmation Visit Through Follow-up

Blood samples for determination of serum drug concentrations and PD assessments will be collected before and after administration of study drug at the time points as specified in the SoA (Section 1.3). The predose (within 0.5 hours prior to the start of infusion) PK/PD sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion (within 0.5 hours after the end of infusion) PK/PD samples will be drawn from the participant's opposite, non-infused arm. All collection times will be recorded in the eCRF. In the event of BTH, a serum PK/PD sample will be collected.

8.6. Pharmacodynamics

Changes in serum free C5 and total C5 concentrations over time will be assessed.

8.7. Genetics

No samples will be collected for genetic analyses.

8.8. Biomarkers

Biomarkers will not be evaluated in this study.

8.9. Immunogenicity Assessments

Antibodies to ravulizumab will be evaluated in serum samples collected predose (within 5 to 90 minutes prior to the start of infusion of study drug) from all participants according to the SoA (Section 1.3).

Additionally, serum samples will be collected at the final visit from participants who discontinue study drug or are withdrawn from the study.

In the event of a BTH, serum samples for ADA analysis will be collected per SoA (Table 1).

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

The detection and characterization of antibodies to ravulizumab will be performed using a validated assay method by or under the supervision of Alexion. Samples may be further

characterized to determine the titer and the presence of neutralizing antibodies if deemed necessary. Samples may be stored for a maximum duration according to local regulations following the last participant's last study visit at a facility selected by Alexion.

8.10. Patient-Reported Symptoms and Health Resource Utilization questionnaires

Patient-reported PNH symptoms (PRS) and Health Resource Utilization (HRU) data, will be collected at Day 1 (baseline), Day 183 and Day 351/ET in the eCRF by the Investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

For PRS, each participant will record the presence or absence of the signs and symptoms of PNH: fatigue, chest pain, abdominal pain, dyspnea, dysphagia, headache, confusion, erectile dysfunction (if applicable), discoloration of urine, discoloration of eyes (see Appendix 10.5.1).

For HRU, the Investigator or designee will record for each participant the number of clinic visits, emergency services utilized, hospitalization, missed work and also record the number of times the participant had darkened urine (see Appendix 10.5.2).

8.11. Visits during COVID-19 Pandemic

To ensure patient safety and treatment continuity during the COVID-19 pandemic, the following will apply until patients are able to resume study visits at the site.

Patients may have an opportunity to receive ravulizumab administration (see Section 1.3 for SoA) remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

Remote visit options may be at the Investigator's discretion and oversight, in accordance with the local regulations, and conducted by a qualified healthcare personnel. Information about AEs concomitant medications, samples for protocol-defined laboratory parameters must be sent to the Investigator's site for evaluation on the day of the remote visit.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This is an estimation study; no formal statistical hypotheses will be tested.

9.2. Sample Size Determination

The proposed sample size for this estimation study is approximately 20 participants. The range of possible proportions of participants experiencing free C5-associated BTH during the Treatment Period (with 95% exact confidence intervals) is as follows:

Proportion of BTH (participants with BTH/total population)	**95% CI**
95% (19/20)	75%, 100%
75% (15/20)	51%, 91%
50% (10/20)	27%, 73%
25% (5/20)	9%, 49%
10% (2/20)	1%, 32%
5% (1/20)	0%, 25%
0% (0/20)	0%, 17%

9.3. Populations for Analyses

Efficacy analyses will be performed on the Full Analysis Set (FAS). The FAS is the primary population for all efficacy analyses. The FAS will include all participants who receive at least 1 dose of ravulizumab.

Safety analyses will be performed on the Safety Set, defined as all participants who receive at least 1 dose of ravulizumab.

Pharmacokinetic analyses will be performed on the PK analysis set, defined as all participants who receive at least 1 dose of study drug and who have evaluable PK data.

9.4. Statistical Analyses

Details of the statistical analyses described below will be specified in a separate Statistical Analysis Plan (SAP) before first database lock and analysis, including procedures for accounting for missing data. Any change to the data analysis methods described in the protocol will require an amendment only if it changes the primary or secondary objectives or the study conduct. Any other change to the data analysis methods described in the protocol or SAP, and the justification for making the change, will be described in the clinical study report (CSR). Additional analyses of the data to address the impact of COVID-19 may be conducted as deemed appropriate.

All data collected will be presented using summary tables, figures, and data listings. All data, as well as any outcomes derived from the data, will be presented in detailed data listings. Graphical displays may also be provided, when appropriate. All analyses will be performed using SAS® release, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software. Continuous variables will be summarized using descriptive statistics, including the number of observations, and mean, standard deviation, median, minimum, and maximum values.

Categorical variables will be summarized by frequency counts and the percentage of participants. All statistical tests performed will be based on a 2-sided 5% level of significance unless otherwise specified.

A CSR to summarize efficacy, safety, PK, PD, and immunogenicity data will be produced at study completion.

9.4.1. Efficacy Analyses

The primary efficacy endpoint is proportion of participants who experience free C5-associated BTH. The proportion along with a two-sided 95% exact CI will be calculated. The same approach will be employed for proportion of participants who experience BTH and stabilized hemoglobin.

The percentage change in LDH will be analyzed using a mixed model for repeated measures (MMRM) (Mallinckrodt, 2001; Mallinckrodt, 2004) with the fixed categorical effects of study visit, and the continuous fixed covariate of baseline LDH. Baseline is defined as the average of all assessments analyzed by the central laboratory prior to first study drug administration. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. A p-value testing whether percent changes differ from zero at each visit will be calculated.

Transfusion rates will be summarized.

Exploratory data of PRS and HRU will be summarized descriptively.

9.4.2. Safety Analyses

All safety data will be summarized using the Safety Set.

9.4.2.1. Analysis of Adverse Events

The analysis and reporting of AEs will be based on treatment-emergent adverse events (TEAEs), defined as AEs with onset on or after the first dose of ravulizumab. The incidence of TEAEs will be summarized by system organ class (SOC) and preferred term (PT), with additional summaries showing severity, relationship to study drug, TEAEs leading to study drug discontinuation, and TEAEs resulting in death. Summaries of treatment-emergent serious adverse events (TESAEs) will also be summarized by SOC and PT, with an additional summary showing relationship to study drug. All AEs will be coded using the latest MedDRA version.

9.4.2.2. Analysis of Clinical Laboratory Parameters, Vital Sign Measurements and Electrocardiogram Parameters

Laboratory measurements as well as their changes from baseline at each visit and shift from baseline, if applicable, will be summarized. Data on ECGs, including ECG interpretation heart rate, PR, QRS, QT, and QTc intervals, and vital signs will also be summarized.

9.4.3. Demographics and Baseline Characteristics

Participant demographic and baseline characteristics will be summarized by treatment group, using the Safety Set. Summary statistics will be presented. No formal hypothesis testing will be performed.

9.4.4. Participant Disposition

The number of participants screened, treated, completing the study, discontinued from the study, reasons for discontinuation, and those included in each analysis set will be summarized.

Important protocol deviations will be summarized by prespecified deviation categories.

9.4.5. Prior and Concomitant Medications

Any medication taken up to 28 days prior to the start of Screening or are ongoing at the first dose of study drug will be considered prior medications or concomitant medications. Prior and concomitant medications will be summarized for all participants in the Safety Analysis Set, including immunosuppressant therapies for relapse prevention and acute relapse treatment. Medications will be coded using the World Health Organization Drug Dictionary based on the most current version available at the time of the analyses.

9.4.6. Pharmacokinetics and Pharmacodynamics Analyses

Individual serum concentration data for all participants who receive at least 1 dose of ravulizumab and who have evaluable PK data will be used to derive PK parameters for ravulizumab.

Graphs of mean serum concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual participants may also be provided. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate. Assessment of population-PK may be considered using data from this study or in combination with data from other studies.

Pharmacodynamic analyses will be performed for all participants who receive at least 1 dose of ravulizumab and who have evaluable PD data.

Descriptive statistics will be presented for all ravulizumab PD endpoints at each sampling time (Section 1.3). The PD effects of ravulizumab administered IV will be evaluated by assessing the absolute values and changes and percentage changes from baseline in total and free C5 serum concentrations over time, as appropriate.

Immunogenicity analyses and subgroup and sensitivity analyses will be described in the SAP and finalized before database lock.

9.5. Interim Analyses

An interim analysis will be conducted on accrued data through Day 183 for publication purposes.

The SAP will describe the planned interim analyses in greater detail.

9.6. Data Monitoring Committee

This study will not include a Data Monitoring Committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative, defined according to local and country regulations where the study is taking place, will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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 or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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 a printed or 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 eCRF.
- 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 eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

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

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Alexion or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion-s procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study drug development

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 therapy and/or follow-up.

10.1.9. Publication Policy

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Study Agreement.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by both the central laboratory and the local laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study drug administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study drug decision or response evaluation, the results must be entered into the eCRF.
- 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 (see Section 10.4.3)

Table 6: Protocol-Required Safety Laboratory Assessments

Hematology Free hemoglobin Haptoglobin Hematocrit Hemoglobin Mean corpuscular hemoglobin Platelet count RBC count RBC distribution width RBC mean corpuscular volume Reticulocyte count WBC count WBC differential **Coagulation Panel** D-dimer International normalized ratio Partial thromboplastin time Prothrombin time **Urinalysis** Albumin Appearance Bilirubin Blood Color Creatinine Glucose Ketone Nitrite pH Protein Specific gravity Urobilinogen	**Clinical Chemistry** Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride C-reactive protein Creatinine Gamma-glutamyltransferase Glucose Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Total bilirubin (direct and indirect) Total protein Uric acid **Virus Serology** HIV-1 HIV-2 **Other** Antidrug antibody Beta human chorionic gonadotropin (women of childbearing potential only) Free and total C5 Pharmacokinetic assay PNH clone size Serum follicle-stimulating hormone (postmenopausal females only)

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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

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 drug administration even though it may have been present before the start of the study. • Signs, symptoms, or clinical sequelae whether or not related to a suspected drug-drug interaction. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• 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. • 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 (social and/or convenience admission to a hospital). • 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.

Serious Adverse Event Definition

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 an AE 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 were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization

An SAE is defined as an AE that, at any dose:
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 drug 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.

Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording
• 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 or SAE information in the eCRF. • 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 eCRF 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 1 of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017: • Grade 1: Mild (awareness of sign or symptom, but easily tolerated) • Grade 2: Moderate (discomfort sufficient to cause interference with normal activities) • Grade 3: Severe (incapacitating, with inability to perform normal activities) • Grade 4: Life-threatening • Grade 5: Fatal

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study drug 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 eCRF 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 adverse event.**
    - **The adverse event 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 adverse event.**
    - **The adverse event 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 drug administration will be considered and investigated.
- This protocol will use the current Investigator's Brochure as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by Alexion, based on the Reference Safety Document. The Investigator will also consult the Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
  - There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, **it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Alexion or designee.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a 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 Adverse Events and Serious Adverse Events

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

10.4. Appendix 4: Pregnancy Information

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential

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

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

10.4.1.2. Women in the following categories are not considered WOCBP

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

- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
- Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        – A high 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 one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Before receiving study drug, female participants who consider themselves to be postmenopausal must provide evidence of menopause based on a combination of amenorrhea for at least 1 year and increased serum FSH level (> 30 IU/L).

Women of childbearing potential must use a highly effective or acceptable method of contraception (as defined below) starting at Screening and continuing for at least 8 months after the last dose of study drug.

Highly effective contraceptive 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

10.4.3. Pregnancy Testing

Participants of childbearing potential should only be included after a menstrual period and a negative highly sensitive serum pregnancy test.

Additional pregnancy testing should be performed per the time points specified in the SoA (Section 1.3).

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

10.4.4. Collection of Pregnancy Information

10.4.4.1. Male Participants with Partners who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate 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 of the baby will be no longer than 3 months after the birth of the baby. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.4.2. Female Participants who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial Information will be recorded on the appropriate form and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to Alexion. Generally, follow-up of the baby will occur at 3 months after birth. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study drug by the Investigator will be reported to Alexion as described in Section 8.3.5. 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, and each pregnancy will be followed to term and Alexion notified regarding the outcome.

10.5. Appendix 5: Questionnaires PNH Symptoms and Health Resource Utilization

10.5.1. PNH Patient-Reported Symptoms questionnaire

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Form: PNH Symptoms Patient Questionnaire
Generated On: 11 Jun 2018 17:23:55

PNH Symptoms Patient Questionnaire completed? ☐ Yes ☐ No

Date Completed (dd/mon/yyyy) _____

Below are listed symptoms that are sometimes associated with PNH. Read each carefully.

If you have had the symptom in the past week, please indicate how OFTEN you have had it, how SEVERE it was, and how much it DISTRESSED or BOTHERED you.

If you DID NOT HAVE the symptom, Select DID NOT HAVE.

During the past week did you have any of the following symptoms?

- ☐ 1. Yellow discoloration of eyes
- ☐ 2. Discoloration of urine (in the morning)
- ☐ 3. Chest Pain
- ☐ 4. Shortness of breath
- ☐ 5. Headache
- ☐ 6. Fatigue
- ☐ 7. Abdominal pain
- ☐ 8. Confusion
- ☐ 9. Erectile Dysfunction (if applicable)
- ☐ 10. Trouble swallowing
- ☐ 11. Other
- ☐ 12. Other

If other, specify _____

DID NOT HAVE _____

If YES, how often did you have it?

- ☐ Rarely
- ☐ Occasionally
- ☐ Frequently
- ☐ Almost Constantly

If YES, how severe was it usually?

- ☐ Slight
- ☐ Moderate
- ☐ Severe

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Form: PNH Symptoms Patient Questionnaire
Generated On: 11 Jun 2018 17:23:55

PNH Symptoms Patient Questionnaire completed?	Yes ☐ No ☐
Date Completed (dd/mon/yyyy)	

Below are listed symptoms that are sometimes associated with PNH. Read each carefully.

If you have had the symptom in the past week, please indicate how OFTEN you have had it, how SEVERE it was, and how much it DISTRESSED or BOTHERED you.

If you DID NOT HAVE the symptom, Select DID NOT HAVE.

During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐ 2. Discoloration of urine (in the morning) ☐ 3. Chest Pain ☐ 4. Shortness of breath ☐ 5. Headache ☐ 6. Fatigue ☐ 7. Abdominal pain ☐ 8. Confusion ☐ 9. Erectile Dysfunction (if applicable) ☐ 10. Trouble swallowing ☐ 11. Other ☐ 12. Other ☐
If other, specify	
DID NOT HAVE	
If YES, how often did you have it?	Rarely ☐ Occasionally ☐ Frequently ☐ Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐ Moderate ☐ Severe ☐

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Form: PNH Symptoms Patient Questionnaire
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	Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much ☐
During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐ 2. Discoloration of urine (in the morning) ■ 3. Chest Pain ☐ 4. Shortness of breath ☐ 5. Headache ☐ 6. Fatigue ☐ 7. Abdominal pain ☐ 8. Confusion ☐ 9. Erectile Dysfunction (if applicable) ☐ 10. Trouble swallowing ☐ 11. Other ☐ 12. Other ☐
If other, specify	_____
DID NOT HAVE	_____
If YES, how often did you have it?	Rarely ☐ Occasionally ☐ Frequently ☐ Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐ Moderate ☐ Severe ☐ Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐

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Form: PNH Symptoms Patient Questionnaire
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	A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much ☐
During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐ 2. Discoloration of urine (in the morning) ☐ 3. Chest Pain ■ 4. Shortness of breath ☐ 5. Headache ☐ 6. Fatigue ☐ 7. Abdominal pain ☐ 8. Confusion ☐ 9. Erectile Dysfunction (if applicable) ☐ 10. Trouble swallowing ☐ 11. Other ☐ 12. Other ☐
If other, specify	
DID NOT HAVE	
If YES, how often did you have it?	Rarely ☐ Occasionally ☐ Frequently ☐ Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐ Moderate ☐ Severe ☐ Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐ A little bit ☐ Somewhat ☐

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	Quite a bit ☐
	Very much ☐
During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐
	2. Discoloration of urine (in the morning) ☐
	3. Chest Pain ☐
	4. Shortness of breath ■
	5. Headache ☐
	6. Fatigue ☐
	7. Abdominal pain ☐
	8. Confusion ☐
	9. Erectile Dysfunction (if applicable) ☐
	10. Trouble swallowing ☐
	11. Other ☐
	12. Other ☐
If other, specify	
DID NOT HAVE	
If YES, how often did you have it?	Rarely ☐
	Occasionally ☐
	Frequently ☐
	Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐
	Moderate ☐
	Severe ☐
	Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐
	A little bit ☐
	Somewhat ☐
	Quite a bit ☐
	Very much ☐

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Form: PNH Symptom: Patient Questionnaire
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During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐ 2. Discoloration of urine (in the morning) ☐ 3. Chest Pain ☐ 4. Shortness of breath ☐ 5. Headache ■ 6. Fatigue ☐ 7. Abdominal pain ☐ 8. Confusion ☐ 9. Erectile Dysfunction (if applicable) ☐ 10. Trouble swallowing ☐ 11. Other ☐ 12. Other ☐
If other, specify	
DID NOT HAVE	
If YES, how often did you have it?	Rarely ☐ Occasionally ☐ Frequently ☐ Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐ Moderate ☐ Severe ☐ Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much ☐
During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐

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Form: PNH Symptoms Patient Questionnaire
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	3. Chest Pain ☐ 4. Shortness of breath ☐ 5. Headache ☐ 6. Fatigue ☐ 7. Abdominal pain ■ 8. Confusion ☐ 9. Erectile Dysfunction (if applicable) ☐ 10. Trouble swallowing ☐ 11. Other ☐ 12. Other ☐
If other, specify	
DID NOT HAVE	
If YES, how often did you have it?	Rarely ☐ Occasionally ☐ Frequently ☐ Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐ Moderate ☐ Severe ☐ Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much ☐
During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐ 2. Discoloration of urine (in the morning) ☐ 3. Chest Pain ☐ 4. Shortness of breath ☐

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Form: PNH Symptoms Patient Questionnaire
Generated On: 11 Jun 2018 17:23:55

	5. Headache ☐
	6. Fatigue ☐
	7. Abdominal pain ☐
	8. Confusion ■
	9. Erectile Dysfunction (if applicable) ☐
	10. Trouble swallowing ☐
	11. Other ☐
	12. Other ☐
If other, specify	
DID NOT HAVE	
If YES, how often did you have it?	Rarely ☐
	Occasionally ☐
	Frequently ☐
	Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐
	Moderate ☐
	Severe ☐
	Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐
	A little bit ☐
	Somewhat ☐
	Quite a bit ☐
	Very much ☐
During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐
	2. Discoloration of urine (in the morning) ☐
	3. Chest Pain ☐
	4. Shortness of breath ☐
	5. Headache ☐
	6. Fatigue ☐

V10.000 PROD 24MAY2018: Review

Form: PNH Symptoms Patient Questionnaire
Generated On: 11 Jun 2018 17:23:55

	7. Abdominal pain ☐
	8. Confusion ☐
	9. Erectile Dysfunction (if applicable) ☐
	10. Trouble swallowing ☐
	11. Other ☐
	12. Other ☐
If other, specify	
DID NOT HAVE	
If YES, how often did you have it?	Rarely ☐
	Occasionally ☐
	Frequently ☐
	Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐
	Moderate ☐
	Severe ☐
	Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐
	A little bit ☐
	Somewhat ☐
	Quite a bit ☐
	Very much ☐
During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐
	2. Discoloration of urine (in the morning) ☐
	3. Chest Pain ☐
	4. Shortness of breath ☐
	5. Headache ☐
	6. Fatigue ☐
	7. Abdominal pain ☐
	8. Confusion ☐

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Form: PNH Symptoms Patient Questionnaire
Generated On: 11 Jun 2018 17:23:55

	9. Erectile Dysfunction (if applicable) ☐
	10. Trouble swallowing ■
	11. Other ☐
	12. Other ☐
If other, specify	
DID NOT HAVE	
If YES, how often did you have it?	Rarely ☐
	Occasionally ☐
	Frequently ☐
	Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐
	Moderate ☐
	Severe ☐
	Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐
	A little bit ☐
	Somewhat ☐
	Quite a bit ☐
	Very much ☐
During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐
	2. Discoloration of urine (in the morning) ☐
	3. Chest Pain ☐
	4. Shortness of breath ☐
	5. Headache ☐
	6. Fatigue ☐
	7. Abdominal pain ☐
	8. Confusion ☐
	9. Erectile Dysfunction (if applicable) ☐

V10.000 PROD 24MAY2018: Review

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Generated On: 11 Jun 2018 17:23:55

	10. Trouble swallowing ☐ 11. Other ■ 12. Other ☐
If other, specify	
DID NOT HAVE	
If YES, how often did you have it?	Rarely ☐ Occasionally ☐ Frequently ☐ Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐ Moderate ☐ Severe ☐ Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much ☐
During the past week did you have any of the following symptoms?	1. Yellow discoloration of eyes ☐ 2. Discoloration of urine (in the morning) ☐ 3. Chest Pain ☐ 4. Shortness of breath ☐ 5. Headache ☐ 6. Fatigue ☐ 7. Abdominal pain ☐ 8. Confusion ☐ 9. Erectile Dysfunction (if applicable) ☐ 10. Trouble swallowing ☐ 11. Other ☐

V10.000 PROD 24MAY2018: Review

Form: PNH Symptoms Patient Questionnaire
Generated On: 11 Jun 2018 17:23:55

	12. Other ☐
If other, specify	
DID NOT HAVE	
If YES, how often did you have it?	Rarely ☐ Occasionally ☐ Frequently ☐ Almost Constantly ☐
If YES, how severe was it usually?	Slight ☐ Moderate ☐ Severe ☐ Very Severe ☐
If YES, how much did it distress or bother you?	Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much ☐

10.5.2. Health Resource Utilization questionnaire

Resource utilization patient questionnaire completed?	Yes ☐ No ☐
Date Completed (dd/mon/yyyy)	
This questionnaire asks about health care services you may have received during the past **month**.	
1. **How many times within the past month** have you visited your **health care provider primarily for treatment of your PNH**? Enter "0" if you have not seen a physician for PNH within the past month.	
2. **How many times within the past month** have you gone to an **Emergency Room primarily for treatment of your PNH**? Enter "0" if you have not seen visited an Emergency Room for PNH within the past month.	
3. **How many times within the past month** have you been **admitted to a Hospital primarily for treatment of your PNH**? Enter "0" if you have not been admitted to a hospital for PNH within the past month.	
4. **How many times within the past month** have you **had darkened urine**? Enter "0" if you have not experienced darkened urine within the past month.	
5. **How many times within the past month** did you **miss work as a result of symptoms of PNH**? Enter "0" if you have not missed work as a result of PNH symptoms within the past month.	

4. In general would you say your health is:	o Excellent o Very Good o Good o Fair o Poor

10.6. Appendix 6: COVID-19 Risk Assessment

Paroxysmal nocturnal hemoglobinuria 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. The fact that Study ALXN1210-PNH-401 is open-label and every participant is treated with the study intervention also contributes to the potential benefit a participant may derive from partaking in the study. Given that treatment for PNH 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. The Investigator will therefore balance the risk/benefit considerations for 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 7. Depending on the availability of approved COVID-19 vaccines and country-specific and/or local recommendations, a participant may have been vaccinated against COVID-19.

Table 7: 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.

Table 7: Potential Risks and Mitigation Measures due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		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).

Abbreviation: COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

10.7. Appendix 7: COVID-19 Vaccine Risk Assessment

Following a review of the available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore, the efficacy of the vaccination) would be diminished with concomitant ALXN1210 administration, based on ALXN1210's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ALXN1210. The same precautions should be taken as described in Section 6.5.1. 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 8.

Table 8: 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 the data is missing (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

10.8. Appendix 8: Abbreviations

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
BTH	breakthrough hemolysis
C5	component C5
CDR	complementarity determining region
CFTG	Clinical Trials Facilitation and Coordination Group
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CSR	clinical study report
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GPI	glycophosphatidylinositol
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
HRU	Health Resource Utilization
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgA	immunoglobulin A
INR	international normalized ratio
IRB	Institutional Review Board
IST	immunosuppressant therapy
IV	Intravenous
LDH	lactate dehydrogenase
LDH-PCHG	lactate dehydrogenase percent change
mAb	monoclonal antibody
MAVE	major adverse vascular events
MMRM	mixed model for repeated measures
N. meningitidis	*Neisseria meningitidis*
NO	nitric oxide
PD	Pharmacodynamics
PK	Pharmacokinetics
PNH	Paroxysmal Nocturnal Hemoglobinuria
PRS	PNH Patient-Reported Symptoms
PT	Preferred Term

Abbreviation	Definition
q2w	every 2 weeks
q8w	every 8 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary
WOCBP	woman of childbearing potential

10.9. Appendix 9: Protocol Amendment History

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

Amendment 1 (29 Jan 2020)

Overall Rationale for the Amendment:

The main rationale for this Amendment was to allow administration of eculizumab at the participant's home at the discretion of the Investigator during Screening to reduce the burden of clinical visits. In addition, 2 specific patient-reported outcomes (Patient-Reported Symptoms [PRS] and Healthcare Resource Utilization [HRU]) are being included for exploratory data analysis.

Other changes implemented through this Amendment constitute minor editorial corrections and fixing inconsistencies.

Amendment 2 (15 Feb 2021)

Overall Rationale for the Amendment:

The main rationale for this Amendment was to allow treatment continuity and ensure patient safety during the Coronavirus Disease 2019 (COVID-19) pandemic by introducing the option for patients to receive ravulizumab administration from a qualified healthcare personnel at the patient's home or at a medical facility that is located near the patient's home.

Other changes implemented through the Protocol Amendment constituted updating the contraception guidance based on the most recent Clinical Trials Facilitation and Coordination Group (CFTG) requirements.

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