TITLE PAGE

Protocol Title:

A Phase 3, Single-arm, Open-label, Multicenter Study to Assess the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Ravulizumab in Complement Inhibitor Treatment Naïve Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH) in China

Alexion Protocol Number: ALXN1210-PNH-323

AstraZeneca D Code: D9289C00008

Compound: Ravulizumab (ALXN1210)

Brief Title:

Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Ravulizumab in Chinese Adults Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Study Phase: 3

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address:

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Regulatory Agency Identifier Number(s): Not applicable

Approval Date: 12 Mar 2024

Sponsor Signatory:

PPD

12-Mar-2024

Date

Alexion Pharmaceuticals, Inc.

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

INVESTIGATOR'S AGREEMENT

I have read the study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline 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

_____

Primary Site Address of Investigator

_____

Date

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LIST OF ABBREVIATIONS

Table 1: Abbreviations and Terms

Abbreviation or Term	Explanation
ADA	antidrug antibody
AE	adverse event
AESI	adverse events of special interest
AxMP	auxiliary medicinal product
BP	blood pressure
BTH	breakthrough hemolysis
C5	complement component 5
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	data cutoff
DPS	data point set
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EOS	end of study
EU CTR	European Union Clinical Trials Register
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPS	Global Patient Safety
Hgb	hemoglobin
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IAS	Immunogenicity Analysis Set
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IE	intercurrent event
IEC	Independent Ethics Committee

Table 1: Abbreviations and Terms

Abbreviation or Term	Explanation
IMP	investigational medicinal product
INR	international normalized ratio
IP	intellectual property
IQRMP	Integrated Quality Risk Management Plan
IRB	Institutional Review Board
IV	intravenous
LAR	legally authorized representative
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAC	membrane attack complex
MAR	missing at random
MAVE	major adverse vascular event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
NA	not applicable
NAb	neutralizing antibody
NDA	new drug application
PD	pharmacodynamic(s)
PDAS	Pharmacodynamic Analysis Set
PK	pharmacokinetic(s)
PKAS	Pharmacokinetic Analysis Set
PNH	paroxysmal nocturnal hemoglobinuria
pRBC	packed red blood cells
PT	preferred term
Q4w	once every 4 weeks
q8w	once every 8 weeks
QoL	quality of life
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTc	corrected QT interval
QTcF	corrected QT interval by Fredericia formula
QTL	quality tolerance limit
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQ	Standardised MedDRA (Medical Dictionary for Regulatory Activities) Query
SoA	schedule of activities

Table 1: Abbreviations and Terms

Abbreviation or Term	Explanation
SOC	System Organ Class
SS	Safety Set
SUSAR	suspected unexpected serious adverse reactions
TA	transfusion avoidance
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMF	Trial Master File
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 3, Single-arm, Open-label, Multicenter Study to Assess the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Ravulizumab in Complement Inhibitor Treatment Naïve Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH) in China

Brief Title:

Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Ravulizumab in Chinese Adults Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Regulatory Agency Identifier Number(s):

Not Applicable

Rationale:

PNH is a chronic disease of uncontrolled terminal complement activation leading to intravascular hemolysis, thrombosis, organ damage and premature mortality if not treated. PNH is one of the rare diseases listed in the first catalogue of 121 rare diseases in 2018 in China.

The main objective of effective treatment is to provide immediate, complete, and sustained inhibition of terminal complement activity to block intravascular hemolysis and prevent thrombosis. Although eculizumab (SOLIRIS®; a recombinant humanized monoclonal antibody), which is the first-generation terminal complement inhibitor, can provide strong inhibition of terminal complement activation, it requires frequent biweekly infusions. Given that PNH is a chronic disease, this dosing regimen may have a significant impact on patients' professional (missed days at work) and private lives. It also may negatively impact treatment adherence which will lead to incomplete C5 blockade, and consequently increase the risk of potentially life-threatening breakthrough hemolysis.

Ravulizumab (ULTOMIRIS®) was engineered from eculizumab to provide immediate, complete and sustained C5 inhibition throughout a prolonged dosing interval, which requires less frequent (q8w) infusions. Thus, treatment with ravulizumab leads more effective control of intravascular hemolysis with greater patient satisfaction and treatment adherence.

Ravulizumab was first approved for marketing in the US for the treatment of PNH under priority review procedure on 21 Dec 2018. To date, ravulizumab has been approved in 60 countries/regions for the treatment of PNH. The therapeutic efficacy and safety, as well as clinical pharmacological characteristics of ravulizumab have been demonstrated in multiple clinical studies for registration and supported by subsequent postmarketing real-world evidence (Usuki, 2023, Kulasekararaj, 2019, Lee, 2019). This study aims to provide efficacy, safety, PK, PD and immunogenicity data for ravulizumab in Chinese adults with PNH to be used for

registration in China.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints/Estimands
Primary	
To evaluate the efficacy of ravulizumab in adult participants with PNH	**Primary estimand:** • Population: Adult participants with PNH in China who are naïve to complement inhibitor treatment and meet all of the inclusion criteria and none of the exclusion criteria • Endpoint: Percentage change in LDH from baseline to Day 183 (Week 26) • Treatment condition: Ravulizumab • Handling of IEs: Discontinuation of study intervention and initiation of disallowed medication will be addressed by hypothetical strategy. • Population-level summary: Mean percentage change in LDH from baseline to Day 183 (Week 26)
Secondary	
To evaluate the effect of ravulizumab on the following: - LDH - TA - FACIT-Fatigue - Breakthrough hemolysis - Hgb	• Participants achieving LDH < 1.5 × ULN at Day 183 (Week 26) • Participants achieving transfusion avoidance (TA) through Week 26 • Participants experiencing breakthrough hemolysis through Day 183 (Week 26) • Change in FACIT-Fatigue score from baseline to Day 183 (Week 26) • Change in Hgb from baseline to Day 183 (Week 26)
Safety	
To evaluate the safety and tolerability of ravulizumab	• Safety and tolerability will be evaluated in terms of TEAEs/SAEs, vital signs and clinical laboratory variables.
Pharmacokinetics/Pharmacodynamics	
To evaluate the PK and PD of ravulizumab in adult participants with PNH throughout the study.	• Serum ravulizumab concentration over time. • Change in serum free C5 concentration over time.
Immunogenicity	

Objectives	Endpoints/Estimands
To assess immunogenicity to ravulizumab in adult participants with PNH for the duration of the study.	• ADA incidence, response categories, and titer, as well as NAb incidence for the duration of the study
Exploratory	
To evaluate the efficacy of ravulizumab on other variables	• Percentage change in LDH from baseline through end of study • Participants achieving LDH < 1.5 × ULN through end of study • Participants achieving TA through end of study • Participants experiencing breakthrough hemolysis through end of study • Change in FACIT-Fatigue score from baseline through end of study • Change in Hgb from baseline through end of study • Participants achieving LDH normalization through end of study • Time to first occurrence of LDH normalization through end of study • Participants achieving stabilized hemoglobin through end of study • Participants achieving hemoglobin normalization through end of study • Total number of units of pRBC transfused through end of study • Participants experiencing MAVEs through end of study

Abbreviation(s): ADA = antidrug antibody; AE = adverse event; C5 = complement component 5; FACIT = Functional Assessment of Chronic Illness Therapy; FAS = Full Analysis Set; Hgb = hemoglobin; IE = intercurrent event; LDH = lactate dehydrogenase; MAVE = major adverse vascular event; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; pRBCs = packed red blood cells; SAE = serious adverse event; TA = transfusion avoidance; TEAE = treatment-emergent adverse event; ULN = upper limit of normal

Overall Design Synopsis:

This is a Phase 3, single-arm, open-label, multicenter study to assess the efficacy, safety, PK, PD and immunogenicity of ravulizumab in complement inhibitor treatment-naïve adult participants with PNH in China. The study will enroll approximately 18 participants.

The study consists of an up to 4-week Screening Period, a 26-week Primary Treatment Period, and a 32-week Extension Treatment Period. During the Primary Treatment Period, all eligible participants will receive a loading dose of ravulizumab (body weight dependent) on Day 1, followed by maintenance doses of ravulizumab (body weight dependent [Table 2]) on Day 15 and q8w thereafter for a total of 26 weeks (Day 183) of treatment. After completion of all

assessments on Day 183, all participants will enter a 32-week Extension Treatment Period and receive ravulizumab q8w.

Table 2: Weight-Based Dosages

Body Weight[a]	Loading Dose (Day 1)	Maintenance Dose (From Day 15, q8w)
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

[a] Dosage regimen will be based on the last recorded study visit body weight. If the study intervention is prepared the night before a visit, the body weight from the most recent study visit should be used.

Study Population: Chinese complement inhibitor treatment naïve adult participants with PNH

Study Intervention and Intervention Form: Participants will receive ravulizumab as concentrated solution for infusion, every 8 weeks (q8w)

Treatment Groups and Duration:

The study consists of an up to 4-week Screening Period, a 26-week Primary Treatment Period, and a 32-week Extension Treatment Period.

The purpose of this study is to measure efficacy, safety, PK, PD and immunogenicity with ravulizumab IV infusion in participants with PNH.

Study details include:

- The study duration will be up to 62 weeks.
- The treatment duration will be up to 58 weeks.
- The visit frequency in the Primary Treatment Period will be on Days 1, 8, 15, 29 and 43 and q4w thereafter; and once q8w in the Extension Treatment Period.
- The dose frequency will be once q8w from Day 15.

Number of Participants:

Approximately 18 participants will be assigned to investigational intervention.

Data Monitoring Committee: No

Ethical Considerations and Benefit-Risk Assessment

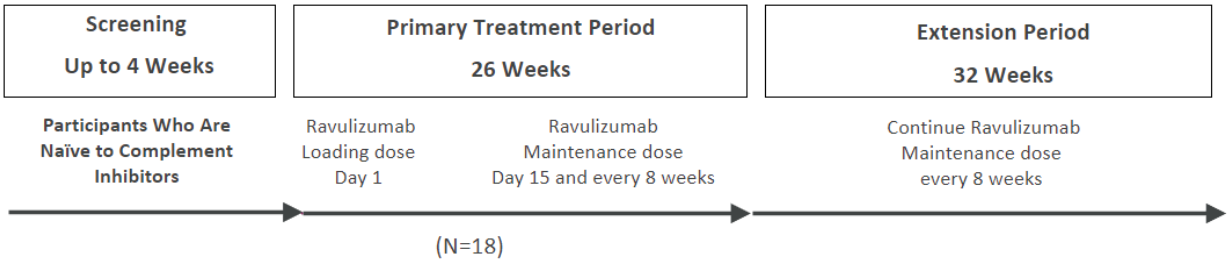
This study will be conducted as specified in this protocol and in accordance with the following:

- 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 Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

A thorough benefit-risk assessment has been performed for the ravulizumab. Measures will be taken to minimize risk to study participants. The potential risks identified in association with ravulizumab are justified by the anticipated benefits that may be afforded to participants with PNH.

1.2. Schema

Figure 1: Study Schematic



1.3. Schedule of Activities (SoA)

Table 3: Schedule of Activities for Screening through End of Primary Treatment Period

Period	**Screening**	**Primary Treatment Period**										**Notes**
Study Day	**–28 to –1**	**1**	**8**	**15**	**29**	**43**	**71**	**99**	**127**	**155**	**183[a]/ ED[b]**	
Window (day)	**NA**		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
End of Week			**1**	**2**	**4**	**6**	**10**	**14**	**18**	**22**	**26**	
Informed consent	X											Section 8.1.1
Confirmation or administration of meningococcal vaccination[c]	X	X										Section 6.9.3
Medical history and demographics	X											Section 8.1.3 and Section 8.1.4
HIV testing	X											Section 10.2
PNH clone size[d]	X	X					X				X	Section 8.2.4
Height	X											Section 8.3.1
Weight	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.1
Pregnancy test[e] (WOCBP only)	X	X		X			X		X		X	Section 8.3.6
Record transfusions and transfusion parameters[f]	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.2
PNH symptomatology[g]	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.3
FACIT-Fatigue[h]	X	X	X		X		X		X		X	Section 8.2.6
Physical examination	X											Section 8.3.1
Abbreviated physical examination[i]		X					X				X	Section 8.3.1
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.2
12-lead ECG[k]	X						X				X	Section 8.3.3
Chemistry including LDH[l]	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.4
Hematology including free hemoglobin and coagulation[l]	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.4

Table 3: Schedule of Activities for Screening through End of Primary Treatment Period

Period	**Screening**	**Primary Treatment Period**										**Notes**
Study Day	**–28 to –1**	**1**	**8**	**15**	**29**	**43**	**71**	**99**	**127**	**155**	**183[a]/ ED[b]**	
Window (day)	**NA**		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
End of Week			**1**	**2**	**4**	**6**	**10**	**14**	**18**	**22**	**26**	
Urinalysis and urine chemistry	X	X		X	X		X		X		X	Section 8.3.4
Review participant safety card		X	X	X	X	X	X	X	X	X	X	Section 8.3.7
Breakthrough hemolysis[m]		←Monitor continuously→										Section 8.2.7
Concomitant medications	X	←Monitor continuously→										Section 6.9
Adverse events	X	←Monitor continuously→										Section 8.4
Ravulizumab administration[n]		X		X			X		X		--[o]	Section 6.1
PK/PD[p]		B/P		T/P			T/P		T/P		T	Section 8.5, Section 8.6
Immunogenicity[q]		B					T				T	Section 8.9

[a] For participants who complete the Primary Treatment Period and will not continue to the Extension Treatment Period, Day 183 Visit will be the EOS Visit.

[b] An ED Visit is required for any participant who early discontinues ravulizumab treatment at any time during the study. A Safety Follow-up phone call should be performed 8 weeks after the last dose of ravulizumab.

[c] All participants must be vaccinated against meningococcal infections at least 2 weeks prior to but no more than 3 years prior to initiating study intervention administration on Day 1. If meningococcal vaccination occurs < 2 weeks from Day 1, participants must receive treatment with appropriate prophylactic antibiotics for at least 2 weeks after the vaccination.

[d] WBC (granulocyte and monocyte) and RBC clone size measured by high-sensitivity flow cytometry at Screening, Day 1 and Day 183; RBC clone size only on Day 71.

[e] Follicle-stimulating hormone levels will be measured during screening only to confirm postmenopausal status. Serum pregnancy tests at Screening. For participants who complete the Primary Treatment Period and will not continue to the Extension Treatment Period or early discontinues from the study, a serum pregnancy test is required at Day 183 (EOS) or ED Visit. Urine pregnancy tests at all other required timepoints. A negative urine pregnancy test result is required prior to administering ravulizumab to WOCBP at the indicated visits. A serum pregnancy test is required as a confirmatory test if the urine pregnancy test is positive.

Table 3: Schedule of Activities for Screening through End of Primary Treatment Period

[f] The number and units of transfusions prior to screening, during the Screening Period, and during the study will be documented for each participant at the timepoints specified in the SoA. The information to be collected includes the hemoglobin result and symptoms that triggered the transfusion, the date of transfusion and number of units of each blood component given.

[g] Investigator or designee assessment of the following events: Fatigue, red/dark urine, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.

[h] Physician- and participant-reported assessments will be performed prior to study intervention administration.

[i] Abbreviated physical examination consists of a body system relevant examination based on Investigator (or designee) judgment and participant symptoms. At least 1 body system must be checked for an abbreviated physical examination.

[j] Vital sign measurements will be taken after the participant has been resting for at least 5 minutes and before blood collection for laboratory tests, including systolic and diastolic BP (mm Hg), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (°C or °F). On dosing days, vital signs measurement will be taken before study intervention administration.

[k] Single 12-lead ECG will be collected at Screening and predose on Day 71 and Day 183. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[l] Clinical laboratory tests will be performed predose on dosing days from a non-heparinized line.

[m] If a suspected event of breakthrough hemolysis occurs, LDH, PK, PD and other safety parameters (as determined by the Investigator) will be analyzed at the central laboratory. If the suspected event of breakthrough hemolysis does not occur at a scheduled visit, an unscheduled visit should occur.

[n] The dose of ravulizumab is based on the participant's last recorded study visit body weight.

[o] The primary efficacy endpoint assessment is before dosing on Day 183. Dosing on Day 183 is the start of the Extension Treatment Period (Table 3).

[p] Baseline (B) and trough (T) blood samples for serum PK, free C5 (PD), will be collected pre-dose (within 30 minutes prior to the start of infusion of study intervention). Peak (P) blood samples for serum PK, free C5 (PD) are to be taken within the 30 minutes following completion of study intervention infusion. The B/T samples may be drawn through the venous access created for the dose infusion, prior to administration of the dose. The P samples will be drawn from the patient's opposite, noninfused arm. On Day 183 (Week 26), the T sample is considered a Primary Treatment Period assessment and the P sample is considered an Extension Treatment Period assessment. All collection times will be recorded in an eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.

[q] Baseline (B) and trough (T) blood samples for ADA will be collected pre-dose (within 30 minutes prior to the start of infusion of study intervention) on Day 1, Day 71 and Day 183; or any time on ED Visit. Additional ADA samples may be collected at or near the event, in case of suspected SAEs such as hypersensitivity or anaphylaxis. ADA samples should be time matched with PK/PD samples.

Abbreviations: ADA = antidrug antibody; B = baseline; C5 = complement component 5; ECG = electrocardiogram; ED=early discontinuation; EOS = end of study; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; LDH = lactate dehydrogenase; N/A = not applicable; P= peak; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; T = trough; WBC = white blood cell; WOCBP = women of childbearing potential.

Table 4: Schedule of Activities: Extension Treatment Period

Period	**Extension Treatment Period**					**Notes**
Study Day	**183**[a]	**239**	**295**	**351**	**407 (EOS)/ED**[b]	
Window (day)	**± 2**	**± 7**	**± 7**	**± 7**	**± 7**	
End of Week	**26**	**34**	**42**	**50**	**58**	
PNH clone size[c]		X	X	X	X	Section 8.2.4
Weight		X	X	X	X	Section 8.3.1
Pregnancy test[d] (WOCBP only)	X	X	X	X	X	Section 8.3.6
Record transfusions and transfusion parameters[e]		X	X	X	X	Section 8.2.2
PNH symptomatology[f]		X	X	X	X	Section 8.2.3
FACIT-Fatigue[g]				X		Section 8.2.6
Abbreviated physical examination[h]		X		X		Section 8.3.1
Vital signs[i]		X	X	X	X	Section 8.3.2
Chemistry including LDH[j]		X	X	X	X	Section 8.3.4
Hematology including free hemoglobin and coagulation[j]		X	X	X	X	Section 8.3.4
Urinalysis and urine chemistry		X	X	X	X	Section 8.3.4
Review participant safety card		X	X	X	X	Section 8.3.7
Breakthrough hemolysis[k]	←Monitor continuously→					Section 8.2.7
Concomitant medications	←Monitor continuously→					Section 6.9
Adverse events	←Monitor continuously→					Section 8.4
Ravulizumab administration[l]	X	X	X	X		Section 6.1
PK/PD[m]	P		T/P		X	Section 8.5, Section 8.6
Immunogenicity[n]					X	Section 8.9

[a] All participants who enter the Extension Treatment Period will receive ravulizumab on Day 183 after all assessments have been performed.
[b] An ED Visit is required for any participant who early discontinues ravulizumab treatment at any time during the study. A safety follow-up phone call should be performed 8 weeks after the last dose of ravulizumab as needed.
[c] WBC (granulocyte and monocyte) and RBC clone size measured by high-sensitivity flow cytometry on Day 407; RBC clone size only at other visits.
[d] Serum pregnancy tests at EOS or ED only; urine pregnancy tests at all other timepoints. A negative urine pregnancy test result is required prior to administering ravulizumab to female participants of childbearing potential on dosing days. A serum pregnancy test is required as a confirmatory test if the urine pregnancy test is positive.
[e] The number and units of transfusions prior to screening, during the Screening Period, and during the study will be documented for each participant at the timepoints specified in the SoA. The information to be collected includes the hemoglobin result and symptoms that triggered the transfusion, the date of transfusion and number of units of each blood component given.
[f] Investigator or designee assessment of the following events: Fatigue, red/dark urine, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.
[g] Physician- and participant-reported assessments will be performed prior to study intervention administration.
[h] Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or qualified designee) judgment and participant symptoms. At least 1 body system must be checked for an abbreviated physical examination.
[i] Vital sign measurements will be taken after the participant has been resting for at least 5 minutes and before blood collection for laboratory tests, including systolic and diastolic BP (mm Hg), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (°C or °F). Vital signs measurement will be taken before each study intervention administration.
[j] Clinical laboratory tests will be performed predose on dosing days from a non-heparinized line.
[k] If a suspected event of breakthrough hemolysis occurs, LDH, PK, PD and other safety parameters (as determined by the Investigator) will be analyzed at the central laboratory. If the suspected event of breakthrough hemolysis does not occur at a scheduled visit, an unscheduled visit should occur.
[l] The dose of ravulizumab is based on the participant's last recorded study visit body weight.
[m] Blood samples for serum PK, free C5 (PD), will be collected pre-dose (within 30 minutes prior to the start of infusion of study intervention) on Day 295; post-dose (within the 30 minutes following completion of study intervention infusion) on Day 183, Day 295; and any time for Day 407 or ED. The pre-dose (T) samples may be drawn through the venous access created for the dose infusion, prior to administration of the dose. The post-dose (P) samples will be drawn from the patient's opposite, noninfused arm. All collection times will be recorded in an eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.
[n] Blood sample for ADA will be collected at any time on Day 407 or ED Visit. Additional ADA samples may be collected at or near the event, in case of suspected SAEs such as hypersensitivity or anaphylaxis. ADA samples should be time matched with PK/PD samples.

Abbreviations: ADA = antidrug antibody; C5 = complement component 5; ECG = electrocardiogram; EOS = end of study; ED = early discontinuation; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; LDH = lactate dehydrogenase; P = peak; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; T = trough. WOCBP = women of childbearing potential.

2. INTRODUCTION

2.1. Study Rationale

The purpose of this study is to assess efficacy, safety, PK, PD and immunogenicity of ravulizumab in complement inhibitor treatment-naïve Chinese adult participants with PNH for China registration use.

PNH is a chronic disease of uncontrolled terminal complement activation leading to intravascular hemolysis, thrombosis, organ damage and premature mortality if not treated. The main objective of effective treatment with targeted therapy is to provide immediate, complete, and sustained inhibition of terminal complement activity to block intravascular hemolysis and prevent thrombosis. What is important is that the blockade of complement activation should be complete and sustained, as incomplete inhibition of terminal complement may increase risk of potentially life-threatening breakthrough hemolysis (Hill, 2012; Lee, 2013).

Prior to the development of ravulizumab, the first approved product targeting the pathogenesis of PNH is eculizumab (Soliris®), which is the first generation of terminal complement inhibitor. However, eculizumab treatment requires frequent biweekly infusions at a hospital or care center. Given that PNH is a chronic disease, this dosing regimen may have a significant impact on patients' professional (missed days at work) and private lives. It also may negatively impact treatment adherence. As mentioned, complete and sustained inhibition of the terminal complement system is crucial for PNH treatment. Any missed doses due to inconvenience of frequent dosing intervals may lead to incomplete blockade of the complement system and put patients at substantial risk of serious complications.

Ravulizumab is a long-acting mAb with high affinity for C5 that can reduce the risk of breakthrough hemolysis and other medical complications resulting from insufficient adherence to the biweekly dosing regimen required by eculizumab. It was engineered from eculizumab to preserve immediate and complete C5 inhibition while providing sustained complement inhibition throughout a prolonged dosing interval (up to 8 weeks). Ravulizumab was first approved for marketing in the US for the treatment of PNH under priority review procedure on 21 Dec 2018. To date, ravulizumab has been approved in 60 countries/regions for the treatment of PNH. The therapeutic efficacy and safety, as well as clinical pharmacological characteristics of ravulizumab have been demonstrated in multiple clinical studies for registration and supported by subsequent postmarketing real-world evidence (Usuki, 2023; Kulasekararaj, 2019; Lee, 2019). In addition, in 2020 a consensus statement for diagnosis and treatment of PNH, it is highly recommended to use ravulizumab as a new generation of C5 inhibitor in terms of reliable efficacy and safety by presenting a longer half-life to meet the demand for a therapy that completely suppresses intravascular hemolysis during the entire dosing interval (Cançado, 2021).

In conclusion, ravulizumab has been designed to have the rapid onset of action and effective complete and sustained blockade of complement, with an increased serum half-life to yield an increased duration of pharmacologic activity relative to eculizumab. The substantially longer half-life of ravulizumab is expected to produce sustained terminal complement inhibition during a longer dosing interval and thus reduce the potential risk of breakthrough complement-mediated hemolysis during the treatment period, thus improving the overall health of patients.

2.2. Background

2.2.1. Overview of PNH

PNH is a chronic disease of uncontrolled terminal complement activation leading to hemolysis, thrombosis, organ damage and premature mortality if not treated. It may occur at any age across gender and race, but is more prevalent among young adults. The median age at diagnosis is the early 30s, and the median survival changed from a previous 10 to 15 years in adults prior to the introduction of complement-inhibiting agents such as eculizumab (Hillmen, 1995; Brodsky, 2014), to a current normal life span when compared to data reported in the general population (Sørensen, 2023). The prevalence is 15.9 cases per million individuals worldwide. In China, the prevalence of PNH is estimated to be 22.9 patients per million inhabitants (Richards, 2021). The incidence rate in Western countries is only 1 to 2 per million per year, while it occurs more frequently in Asia than in Western countries with approximately 10 per million per year in China (China Rare Diseases Diagnosis and Treatment Guide, 2019).

In adults, the clinical manifestations of PNH include hemoglobinuria, chronic renal insufficiency, fatigue, erectile dysfunction, thrombosis, abdominal pain, dyspnea, and dysphagia. However, children with PNH usually present with nonspecific symptoms related to the underlying bone marrow disorder. The disease eventually evolves into one of the symptoms more typically seen in adults. Thus, pediatric patients can be expected to suffer substantial morbidity related to hemolysis, as seen in adult PNH patients (Parker, 2005). Moreover, pediatric PNH patients demonstrate similarities with adults from major clinical parameters, medical history, and clinical practice in treatment and diagnosis after bone marrow symptoms resolved (Urbano-Ispizua, 2017). The median survival for pediatric PNH patients is also similar to that of adults (Ware, 1991). Compared to adults, the pediatric patients are sparse, and the prevalence is low, accounting for 5% to 10% of reported PNH cases (Urbano-Ispizua, 2015; van den Heuvel-Eibrink, 2007; Ware, 1991).

It is worth mentioning that there is similar trend of disease characteristics between Chinese and overseas PNH patients from the perspective of mechanism of disease, clinical manifestation, main cause morbidity, median survival year, and the process of diagnosis and treatment (Urbano-Ispizua, 2017). These elements provide the foundation for extrapolation between the overall patient population and Chinese patients with PNH.

2.2.2. Terminal Complement System and PNH

The complement system includes more than 30 components. The intrinsic components of complement exist in the blood in an inactive form and are activated through a cascade reaction to produce biologically active products. The 3 pathways that have been discovered have a common terminal pathway, that is, the terminal complement C3 is cleaved to form C5 convertase, activates downstream C5 and cleavages C5 into C5a and C5b. C5a is a potent anaphylatoxin, chemotactic factor, and cell-activating molecule that mediates multiple proinflammatory and prothrombotic activities (Matis, 1995; Nicholson-Weller, 1993; Prodinger, 1999); while C5b recruits the terminal complement components C6, C7, C8, and C9 to form the proinflammatory, prothrombotic cytolytic pore molecule C5b-9, also called membrane attack complex (MAC) causing cell lysis and destruction, a process that under normal circumstances would be blocked on the blood cell membrane by CD55/CD59.

In PNH, due to the *PIG-A* gene mutation and the consequent lack of GPI-linked complement regulatory protein CD55 and CD59 on the blood cell membrane, the PNH red blood cells lack the shield of proteins that protect normal red blood cells from the complement system, leaving them open to attack and destruction by the complement system proteins, resulting in clinical consequences, such as hemolysis, hemoglobinuria, and thrombosis.

Therefore, providing immediate, complete, and sustained inhibition of complement activity is essential for control of intravascular hemolysis and reduction in symptoms and complications in PNH.

2.2.3. Ravulizumab Mechanism of Action and its Development in PNH

As mentioned, C5 plays an essential role in the complement system, its cleavage to C5a and C5b leads to the core mechanism and related clinical manifestations of PNH, which is considered a key target for drug development. Ravulizumab, engineered from eculizumab, specifically binds to human complement protein C5, inhibiting its cleavage to C5a and C5b during complement activation. This inhibition prevents the release of the proinflammatory mediator C5a and the formation of the cytolytic pore-forming MAC while preserving the proximal or early components of complement activation (eg, C3 and C3b) which is essential for the opsonization of microorganisms and clearance of immune complexes.

To date, multiple clinical studies have been conducted in healthy volunteers and PNH patients, including 3 safety, tolerability, PK, and PD clinical studies in healthy adult participants (Studies ALXN1210-HV-101, ALXN1210-HV-102, and ALXN1210-HV-104), 2 dose and regimen ranging safety and efficacy studies in patients with PNH (Studies ALXN1210-PNH-103 and ALXN1210-PNH-201), and 3 confirmatory safety and efficacy studies in adult and pediatric patients with PNH (Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 in adults, Study ALXN1210-PNH-304 in pediatric patients). The therapeutic efficacy and safety profile, as well as the pharmacological characteristics of ravulizumab have been demonstrated very well.

More information about the PK, mechanism of action, known and expected benefits, risks, and reasonably anticipated AEs of ravulizumab is provided in the current edition of the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Table 5: Study Intervention Risk Assessment

Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Identified risk		
Meningococcal infection	C5 inhibition is known to increase the susceptibility to infections caused by *Neisseria meningitidis*.	Participants must be vaccinated against serotypes of *N meningitidis* A, C, Y, W 135 (and serotype B where available) per the Schedule of Activities (Section 1.3) and inclusion criteria (Section 5.1). If vaccination occurs < 2 weeks from Day 1, the participant will receive prophylactic antibiotics for at least 2 weeks after initial meningococcal vaccination. Each participant will be provided with a Participant Safety Card with signs and symptoms of meningococcal infection, instructions on when to contact a healthcare provider, and relevant contact information. The Participant Safety Card will be reviewed at each visit (Section 1.3).
Potential Risks		
Serious infection	Apart from the identified risk of infection with *Neisseria* species, which is well known and directly related to the mechanism of action of ravulizumab, the mechanism that may lead to other serious infections in participants treated with ravulizumab remains unclear.	Healthcare professionals and participants should have increased awareness about the potential risk of serious infection. Monitoring for signs and symptoms of serious infections will be conducted as part of the safety assessments for this study. In addition, all participants are required to be up to date on all vaccinations according to local and national guidelines.

Table 5: Study Intervention Risk Assessment

Immunogenicity	Treatment with any therapeutic protein has the potential to induce an immune response. Potential clinical consequences may include hypersensitivity, anaphylaxis or related type of reactions, or loss of efficacy.	Monitoring for hypersensitivity and infusion-related reactions will be conducted as part of routine safety assessments for this study. Infusion should be stopped in the event of any intervention-related severe adverse events like systemic hypersensitivity or anaphylaxis.
Serious hemolysis after study intervention discontinuation in PNH patients	This potential 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 studies.	The effects are most likely not completely preventable, but their severity can be minimized by avoiding abrupt drug discontinuation. Close monitoring of participants who discontinue the study intervention is recommended.
Malignancies and haematologic abnormalities in PNH patients	The natural evolution of the underlying bone marrow failure associated with PNH makes patients more prone to development of hematologic abnormalities or malignancies. Approximately 30%-70% of patients with PNH may have or develop aplastic anemia or myelodysplastic syndrome. The potential role of ravulizumab in such abnormalities or malignancies (if any) is unknown.	Close monitoring of patients who reported malignancies and haematologic abnormalities, and take appropriate action.
Pregnancy exposure/lactation	No studies of ravulizumab have been conducted in pregnant or breastfeeding women. There are no data available on excretion of ravulizumab in breast milk.	Pregnant or nursing female participants will be excluded from the clinical study. Female and male 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 final dose of study intervention (Section 10.5). Breastfeeding should be discontinued during treatment and up to 8 months after the last dose of ravulizumab.

2.3.2. Benefit Assessment

Ravulizumab has a more convenient treatment schedule than eculizumab, which is expected to yield a positive impact on daily life for Chinese PNH patients. By providing patients and physicians with an option for less frequent dosing in the treatment of patients with PNH, ravulizumab is expected to improve the quality of life (QoL) of Chinese patients who are

currently on therapy receiving eculizumab biweekly. Less frequent IV infusions may reduce the risk of missed dose and reduce the risk of breakthrough hemolysis due to dosing incompliance.

Additionally, the substantially longer half-life of ravulizumab was demonstrated to produce sustained terminal complement inhibition during a longer dosing interval. In PNH, this will reduce the potential risk of breakthrough, complement-mediated hemolysis, which demonstrate rapid and sustained reduction in LDH levels.

2.3.3. Overall Benefit-Risk Conclusion

Considering the severity of PNH, the established safety profile of ravulizumab, and the measures taken to minimize risk to participants in this study, the identified and potential risks in association with ravulizumab are justified by the anticipated benefits that may be afforded to Chinese participants with PNH.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The primary clinical question of interest is:

What is the mean percentage change in LDH from baseline to Day 183 (Week 26) in participants with PNH treated with intervention if participants would not have discontinuation of study intervention and initiation of disallowed medication during the Primary Treatment Period (Table 6).

Table 6: Objectives and Endpoints/Estimands

Objectives	Endpoints/Estimands
Primary	
To evaluate the efficacy of ravulizumab in adult participants with PNH	**Primary estimand:** • Population: Adult participants with PNH in China who are naïve to complement inhibitor treatment and meet all of the inclusion criteria and none of the exclusion criteria • Endpoint: Percentage change in LDH from baseline to Day 183 (Week 26) • Treatment condition: Ravulizumab • Handling of IEs: Discontinuation of study intervention and initiation of disallowed medication will be addressed by hypothetical strategy. Details of data handling is in Section 9.3.2.2. • Population-level summary: Mean percentage change in LDH from baseline to Day 183 (Week 26)
Secondary	
To evaluate the effect of ravulizumab on the following: - LDH - TA - FACIT-Fatigue - Breakthrough hemolysis - Hgb	• Participants achieving LDH < 1.5 × ULN at Day 183 (Week 26) • Participants achieving transfusion avoidance (TA) through Week 26 • Participants experiencing breakthrough hemolysis through Day 183 (Week 26) • Change in FACIT-Fatigue score from baseline to Day 183 (Week 26) • Change in Hgb from baseline to Day 183 (Week 26)
Safety	
To evaluate the safety and tolerability of ravulizumab	• Safety and tolerability will be evaluated in terms of TEAEs/SAEs, vital signs and clinical laboratory variables
PK/PD	
To evaluate the PK and PD of ravulizumab in adult	• Serum ravulizumab concentration over time

Table 6: Objectives and Endpoints/Estimands

Objectives	Endpoints/Estimands
participants with PNH throughout the study.	• Change in serum free C5 concentration over time.
Immunogenicity	
To assess immunogenicity to ravulizumab in adult participants with PNH for the duration of the study.	• ADA incidence, category of immune response, and titer, as well as NAb incidence for the duration of the study
Exploratory	
To evaluate the efficacy of ravulizumab on other variables	• Percentage change in LDH from baseline through end of study • Participants achieving LDH < 1.5 × ULN through end of study • Participants achieving TA through end of study • Participants experiencing breakthrough hemolysis through end of study • Change in FACIT-Fatigue score from baseline through end of study • Change in Hgb from baseline through end of study • Participants achieving LDH normalization through end of study • Time to first occurrence of LDH normalization through end of study • Participants achieving stabilized hemoglobin through end of study • Participants achieving hemoglobin normalization through end of study • Total number of units of pRBC transfused through end of study • Participants experiencing MAVEs through end of study

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, single-arm, open-label, multicenter study to evaluate the safety, efficacy, PK/PD, and immunogenicity of ravulizumab administered by intravenous (IV) infusion in complement inhibitor treatment naïve adult participants with PNH in China. The study will enroll approximately 18 participants.

The study consists of an up to 4-week Screening Period, a 26-week Primary Treatment Period, and a 32-week Extension Treatment Period.

After providing informed consent, participants will be screened for eligibility for the study during an up to 4-week Screening Period. If all inclusion criteria and none of the exclusion criteria are met, participants will be enrolled and vaccinated against *N meningitidis* if not already vaccinated within the period of active coverage specified by the vaccine manufacturer. Participants who are vaccinated less than 2 weeks prior to receiving the first dose of ravulizumab will receive treatment with appropriate prophylactic antibiotics at least 2 weeks after the vaccination.

During the Primary Treatment Period, all eligible participants will receive a loading dose of ravulizumab (body weight dependent) on Day 1 followed by maintenance doses of ravulizumab (body weight dependent [Table 7]) on Day 15 and q8w thereafter for a total of 26 weeks of treatment. After completion of all assessments on Day 183, all participants will enter a 32-week Extension Treatment Period and receive ravulizumab. Beginning on Day 183, participants will receive a maintenance dose (as described in Table 7) of ravulizumab q8w for an additional 32 weeks.

Table 7: Weight-Based Dosages

Body Weight[a]	Loading Dose (Day 1)	Maintenance Dose (From Day 15, q8w)
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

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

Participants who early discontinue ravulizumab treatment at any time during the study will have an ED Visit at the time of discontinuation from the study, and a Safety Follow-up Phone Call should be performed 8 weeks after the last dose of ravulizumab to collect information on concomitant medications and AEs (see SoA, Section 1.3).

- A safety follow-up phone call will be performed 8 weeks after the last dose of ravulizumab, unless the participant has an ED Visit within that time period.

Clinical measures and laboratory tests will be performed to assess safety, clinical and biochemical parameters associated with hemolysis, anemia, thrombosis, and renal function.

4.2. Scientific Rationale for Study Design

As mentioned in Section 2.2.3, multiple clinical studies (ALXN1210-PNH-301 and ALXN1210-PNH-302, etc.) conducted in PNH patients have provided sufficient data to demonstrate the efficacy and safety of ravulizumab and supported its approval globally. The aim of this study is to provide additional efficacy, PK/PD, immunogenicity and safety data with ravulizumab specifically in a Chinese PNH population. Therefore, the study design, including treatment duration, endpoints selection, and other related parameters, is based on previous studies.

4.2.1. Single Arm, Open-label Design

This study is designed to assess the efficacy, safety, PK, PD and immunogenicity of ravulizumab in adult participants with PNH in China.

The safety and efficacy of ravulizumab to reduce hemolysis in participants with PNH has been previously demonstrated in clinical studies. Considering the low risk of ethnical sensitivity in efficacy, safety, PK, PD, and immunogenicity in Asian versus non-Asian PNH population, it is expected ravulizumab will provide similar benefits to Chinese PNH patients as observed in global studies. This single-arm study will provide efficacy, safety, PK/PD, and immunogenicity data in Chinese patients to support ravulizumab registration for the treatment of the Chinese patients with PNH. The primary endpoint of percentage change in LDH from baseline to Day 183 (Week 26) is an objective measure that will be analyzed by a central laboratory. Such an endpoint could minimize bias in this open-label study.

4.2.2. Rationale for Selected Endpoints

Data support LDH as a reliable, objective, and direct measure of intravascular hemolysis in patients with PNH; therefore, LDH is considered by experts as the best measure of complement-mediated hemolysis, the hallmark of PNH disease activity (Canalejo, 2014; Dale, 1972). Results from ravulizumab clinical studies showed that ravulizumab-treated patients had immediate reductions in LDH level. This reduction was correlated with a rapid reduction in symptoms and long-term effective measure for risk reduction of thrombosis (Lee, 2013).

The safety parameters being evaluated are commonly used in clinical studies per ICH and GCP guidelines.

The PK, PD (free C5), and immunogenicity assessment will help to further confirm the clinical pharmacology characteristics, as well as dose of ravulizumab in Chinese patients with PNH.

4.2.3. Rationale for Treatment Duration

The primary endpoint of the study is reduction in hemolysis as evaluated by percentage change from baseline in LDH at Week 26. In previous studies, the reduction of intravascular hemolysis as measured by LDH occurred as soon as 1 week after the first ravulizumab dose, and the

reduction was sustained during the treatment period. A Primary Treatment Period of 26 weeks is sufficient to reach the nadir of LDH reduction (Lee, 2013). A 32-week Extension Treatment Period will allow to evaluate ravulizumab longer-term treatment, similarly to what was done in the global Study ALXN1210-PNH-301.

4.3. Justification for Dose

The body weight-based dosages of ravulizumab in this study are the globally approved dosages in PNH treatment and have been well-established to provide immediate, complete, and sustained terminal complement inhibition in global pivotal PNH Phase 3 studies. Based on the ethnic sensitivity analyses of Asian population versus non-Asian/overall population, ethnic factors are unlikely to impact the efficacy, safety, PK, PD, exposure-response (both PD effect and safety) relationship, and immunogenicity of ravulizumab. Thus, in this study, the same dosage regimen is chosen. Full details of dose selection are available in the ravulizumab Package Insert.

4.4. End-of-Study Definition

The end of the study is defined as the date the last participant completes the last visit as shown in the SoA (Section 1.3).

A participant is considered to have completed the Primary Treatment Period if the participant completes the Day 183 (Week 26) Visit shown in the SoA (Table 3). A participant is considered to have completed the Extension Treatment Period if the participant completes the Day 407 (Week 58) Visit shown in the SoA (Table 4).

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 inclusive, 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 (Borowitz, 2010) of RBCs and white blood cells (WBCs), with granulocyte or monocyte clone size of ≥5%.
3. Presence of 1 or more of the following PNH-related signs or symptoms within 3 months of Screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin < 10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion due to PNH.
4. LDH level ≥ 1.5 × ULN at Screening (evaluated through central laboratory).

Weight

5. Body weight ≥ 40 kg at Screening.

Sex and Contraceptive/Barrier Requirements

6. Male and/or female.
7. Female participants of childbearing potential and male participants with female partners of childbearing potential must follow protocol-specified guidance as described in Section 10.5 for avoiding pregnancy while on treatment and for 8 months after last dose of study intervention.

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

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 ICF and in this protocol.

Other Inclusion Criteria

9. To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all participants must be vaccinated against meningococcal infections from serogroups A, C, W, Y (and B where available) at least 2 weeks but no more than 3 years prior to initiating study intervention on Day 1. If Day 1 occurs < 2 weeks after the vaccination, participants will receive prophylactic antibiotics for at least 2 weeks after the meningococcal vaccination.

5.2. Exclusion Criteria

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

Medical Conditions

1. History of malignancy within 5 years of Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
2. History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease (eg, active hepatitis) that, in the opinion of the Investigator or Sponsor, precludes the participant's participation in an investigational clinical study.
3. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of the first dose, coexisting chronic anemia unrelated to PNH) that would make them unlikely to tolerate the requirements of the protocol (eg, transfusion guidelines).
4. History of *N meningitidis* infection or unresolved meningococcal disease.
5. History of unexplained, recurrent infection.
6. Active systemic bacterial, viral, or fungal infection within 14 days prior to study intervention administration on Day 1.
7. Presence of fever, temperature ≥ 38°C (100.4°F) within 7 days prior to study intervention administration on Day 1.
8. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer).

Prior/Concomitant Therapy

9. Current or previous treatment with a complement inhibitor.
10. History of bone marrow transplantation.
11. Immunized with a live-attenuated vaccine 1 month prior to study intervention administration on Day 1.
12. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

14. Participants who have a positive pregnancy test at Screening or Day 1.
15. Platelet count < 30000/mm^3 (30×10^9/L) at Screening.
16. Absolute neutrophil count < 500/μL (0.5×10^9/L) at Screening.

17. Female participants who have a positive pregnancy test result at Screening or on Day 1.

Other Exclusions

18. History of hypersensitivity to any ingredient contained in the study intervention, including hypersensitivity to murine proteins.
19. Female participants who plan to become pregnant or are currently pregnant or breastfeeding.
20. Known or suspected history of intervention or alcohol abuse or dependence within 1 year prior to the start of Screening.
21. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the participant's full participation in the study, pose any additional risk for the participant, or confound the assessment of the patient or outcome of the study.

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg. failed eligibility criteria), and any AEs, including any SAEs, and any related concomitant medication, occurring during the Screening Period.

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 a single time based on discussion and agreement between the Investigator and the Medical Monitor. Rescreened participants should be assigned the same participant number as for the initial screening.

Generally, all assessment should be repeated for screening unless they are within 28 days of enrollment.

Participants who are rescreened outside of the original screening window (SoA Table 3) are required to sign a new ICF.

These participants should have the reason for study withdrawal recorded in eCRF as "eligibility criteria not fulfilled". This reason for study withdrawal is only valid for screen failure.

5.5. Criteria for Temporarily Delaying Enrollment/Administration of Study Intervention

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified, investigational and non-investigational medicinal products, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1. Study Intervention(s) Administered

In this study, participants will receive open-label ravulizumab during the Primary Treatment Period and Extension Treatment Period. Specific details of the study intervention are provided in Table 8.

Table 8: Study Intervention(s) Administered

IMP or AxMP	IMP
Intervention name	Ravulizumab
Intervention description	Concentrated solution for infusion, q8w
Type	Monoclonal antibody
Dose formulation	Sterile liquid
Unit dose strength(s)	100 mg/mL (1100 mg/11 mL) as a yellow-tinted solution in a single-dose vial
Dosage level(s)	Dosage will based on body weight (Table 7); Loading dose on Day 1; maintenance dose on Days 15, 71, 127, 183, 239, 295, and 351.
Route of administration	IV infusion
Use	Experimental
Sourcing	Provided centrally by Alexion or contracted manufacturing organization
Packaging and labeling	Ravulizumab will be provided in glass vials and stoppered with a butyl rubber. Each container will be labeled as required per country/regional requirements.

6.2. Preparation, Handling, Storage, and Accountability

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

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

6.3. Assignment to Study Intervention

This study is an open-label single-arm study; therefore, all participants who satisfy all of the inclusion and none of the exclusion criteria will receive ravulizumab.

6.4. Blinding

This is an open-label study. Methods to ensure blinding are not applicable.

6.5. Study Intervention Compliance

When participants are dosed at the investigational site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each

dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

For additional information on study intervention compliance and management, refer to the Pharmacy Manual. Confirm with Clinical Supply Team that this manual is planned.

6.6. Dose Modification

Individual dose modification is not allowed.

6.7. Continued Access to Study Intervention after the End of the Study

Upon completion of the last study visit, participants will return to the care of their Treating Physician. The study intervention will not be provided to the participants after the last scheduled dosing.

6.8. Treatment of Overdose

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

Alexion does not recommend specific treatment for an overdose.

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

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

6.9. Prior and Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine 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

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

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 intervention, will be recorded in the participant's eCRF. In addition, history of meningococcal vaccination must be collected.

Transfusions of pRBC received within 1 year prior to first study intervention administration will be recorded in the participant's eCRF.

All medications and therapies or 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 per the SoA (Section 1.3). 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. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full in the participant's source document/medical chart and eCRF.

6.9.1. Allowed Medicine and Therapy

The following are some general guidelines for concomitant medication use based on currently available data:

- Concomitant erythropoiesis-stimulating agents, if on stable doses for at least 4 weeks prior to screening.
- Concomitant iron supplements or folic acid, if the participant has been receiving a stable dose for at least 4 weeks before screening.
- Concomitant immunosuppressants, if the participant has been receiving a stable dose for at least 8 weeks before screening.
- Concomitant 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 international normalized ratio (INR) level (per Investigator's discretion) 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 Medical Monitor or Investigator deems it is in the best interest of the participant. The Medical Monitor should be contacted with any questions regarding concomitant or prior therapy.

The Medical Monitor should be contacted with any questions regarding concomitant or prior therapy.

6.9.2. Disallowed Medicine and Therapy

- Whole blood transfusion
- Traditional Chinese herbal preparations that in the opinion of the Investigator or Alexion might confound the assessment of the participant
- Chemotherapy
- Use of other complement inhibitors

6.9.3. Vaccination and Antibiotic Prophylaxis

Due to its mechanism of action, the use of ravulizumab increases a participant's susceptibility to meningococcal infection (*N meningitidis*). To reduce the risk of meningococcal infection, all participants must be vaccinated against *N meningitidis* serogroups A, C, W135, Y (and serogroup B where available) at least 2 weeks prior to but no more than 3 years prior to Day 1.

- Participants who initiate study intervention less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics at least 2 weeks after the meningococcal vaccination.
- Participants must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, ravulizumab).
- 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 timepoints as part of the review of the safety card and throughout the study as described in the SoA (Section 1.3).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Closure of specific sites or termination of the study are detailed in Section 10.1.8.

7.1. Discontinuation of Study Intervention

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

A participant/LAR has the right to discontinue study intervention at any time.

Participants must be permanently discontinued from study intervention treatment if any of the following occur during the study:

- Serious infusion-related reaction;
- Serious hypersensitivity reaction to the study intervention;
- Pregnancy or planned pregnancy;
- Severe uncontrolled infection;
- Sponsor or the Investigator deems it necessary for the participant.

Participants may be permanently discontinued from study intervention if any of the following occur during the study:

- Begin treatment with another complement inhibitor;
- AE that would, in the opinion of the Investigator, make continued participation in the study an unacceptable risk;
- Use of disallowed medication as determined on a case-by-case basis (defined in Section 6.9.2);
- Significant non-compliance;
- Termination of the study.

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 Sponsor and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and eCRF.
- A participant may withdraw from the study at any time at the participant's own request/LAR or may be withdrawn at any time at the discretion of the Investigator.

- If the decision to withdraw from the study is made, the participant will be permanently discontinued both from the study intervention and the study at that time.
- At the time of discontinuing from the study, if possible, an ED Visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation, and follow-up and for any further evaluations that need to be completed.
- A safety follow-up phone call will be performed 8 weeks after the last dose of study intervention as needed to collect information on concomitant medications and AEs.
- If the participant/LAR 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, the participant/LAR 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

A participant will be considered lost to follow-up if the participant 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/LAR and reschedule the missed visit as soon as possible, counsel the participant/LAR on the importance of maintaining the assigned visit schedule, and ascertain whether 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/LAR (where possible, 3 telephone calls, and if necessary, a certified letter to the participant/LAR'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, the participant will be considered as discontinued and/or lost to follow -up.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants assigned treatment, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- 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.
- If a participant fails to return to the clinic, or is otherwise unavailable, for a scheduled visit within the acceptable visit window, the site study staff must make a reasonable attempt to contact the participant to determine the reason for missing the appointment. The participant will be advised to return to the investigational site for evaluation, if an AE is suspected to have occurred. In this event, the investigational site will make a reasonable attempt to obtain all relevant medical records, and enter relevant data in the eCRF, as appropriate.
- Unscheduled visits that occur outside the protocol-specified visits are permitted at the discretion of the Investigator. Results for procedures, tests, and assessments conducted during unscheduled visits will be documented on the eCRF.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by Alexion or the Investigator, as per local health authority/ethics requirements.
- See Section 10.2 for a listing of clinical laboratory tests.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, can be found in the Laboratory Manual.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and General Procedures

8.1.1. Informed Consent

The Investigator, or qualified designee, must obtain a signed and dated informed consent/assent form from each participant prior to conducting any study procedures. All efforts will be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures.

8.1.2. Inclusion/Exclusion Criteria

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

8.1.3. Demographics

Demographic parameters, including age, sex, race, and ethnicity will be collected. All demographic information provided will be documented in the eCRF.

8.1.4. Medical History and PNH History

The participant's PNH medical history, including onset of first PNH symptom (Section 8.2.3) and date of diagnosis, will be documented at the Screening Visit. The participant's PNH medical history, including PNH-associated prior and concomitant conditions/disorders (aplastic anemia, myelodysplastic syndrome, hematuria or hemoglobinuria, renal failure, etc.), will be recorded at the Screening Visit.

Medical history including all relevant medical/surgical history will be recorded at the Screening Visit.

Medication use (prescription or over-the-counter, including vitamins and/or herbal supplements) within 28 days prior to the start of screening will also be recorded.

8.2. Efficacy Assessments

Blood will be collected according to the SoA (see Section 1.3) to assess the efficacy endpoints of LDH, transfusion requirements, change in Hgb, and other measures of hemolysis. Blood collection procedures are described in Section 8.3.5.

8.2.1. Hemolysis

The primary efficacy endpoint is the percent change in LDH from Baseline to Day 183 (Week 26).

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

8.2.2. Transfusion History and Transfusion Requirement Status

The number and units of transfusions prior to screening, during the Screening Period, and during the study will be documented on the eCRF for each participant at the timepoints specified in the SoA (Section 1.3). The information to be collected includes date of the transfusion and number of units of each blood component given.

Transfusion Guidelines:

It is recommended to administer RBC transfusion when a participant has the following:

1. Hemoglobin (Hgb) value of less than 7 g/dL regardless of presence of clinical signs or symptoms, or

2. Hgb value of less than 9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion.

In the event of life-threatening anemia, transfusion of ABO- and RhD-matched blood is appropriate. Further matching for Kell and JK antigens can be conducted if this does not delay availability of blood for emergent transfusion. The reason for transfusion as well as signs or symptoms associated with the participant's need for transfusion will be documented on the eCRF for each individual participant. Typical anemia-related symptoms warranting transfusions include angina, change in mental status, syncope, lightheadedness, confusion, shortness of breath, and fatigue.

The Investigator will determine whether a transfusion is needed and the appropriate number of units of RBCs to be transfused. Administration of transfusion including the date of the transfusion and the number of units of each blood component transfused will be documented in the eCRF.

8.2.3. PNH Symptomatology

The Investigator or designee will record the presence or absence of the following signs and symptoms of PNH for each participant: fatigue, chest pain, abdominal pain, dyspnea, dysphagia, erectile dysfunction, and red/dark urine or hemoglobinuria at the timepoints specified in the SoA (Section 1.3).

8.2.4. PNH Clone Size

WBC (granulocyte and monocyte) and RBC clone size measured by high-sensitivity flow cytometry will be recorded at the timepoints specified in the SoA (Section 1.3).

8.2.5. Other Disease-related Laboratory Parameters

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

The following disease-related laboratory parameters will be measured during the study:

- LDH normalization defined as LDH ≤ ULN
- Occult blood, urine
- Reticulocyte count
- PNH RBC clone size evaluated by high-sensitivity flow cytometry (Borowitz, 2010)
- Estimated glomerular filtration rate (calculated using the Modification of Diet in Renal Disease [MDRD] formula)
- Spot urine albumin: creatinine ratio
- C-reactive protein

8.2.6. FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale is a collection of QoL questionnaires pertaining to the management of fatigue symptoms due to a chronic illness. The FACIT-Fatigue scale is a 13-item questionnaire that assesses self-reported fatigue and its

impact upon daily activities and function over the preceding 7 days. Participants will score each item on a 5-point scale: 0 (Not at all) to 4 (Very much). Total scores range from 0 to 52, with higher score indicating better QoL.

The FACIT-Fatigue scale questionnaire is provided in Appendix 10.7.

8.2.7. Breakthrough Hemolysis

Breakthrough hemolysis 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], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy.

If a suspected event of breakthrough hemolysis occurs, LDH, PK, PD and other safety parameters (as determined by the Investigator) will be collected and analyzed at the central laboratory. If the suspected event of breakthrough hemolysis does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the participant and collection of the required LDH, PK, PD and other safety parameters.

If a participant experiences protocol-defined BTH due to complement-amplifying conditions (CAC), such as infection, trauma, and others, CAC should be recorded.

8.2.8. Major Adverse Vascular Events

MAVEs will be assessed as part of the planned evaluation for AEs during the study.

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 patient'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

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.9. Stabilized Hemoglobin

Participants achieving stabilized hemoglobin is one of exploratory endpoints. Stabilized hemoglobin is defined as avoidance of a ≥ 2g/dL decrease in hemoglobin level from baseline in the absence of transfusion.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the following organs/body systems: skin, head, ears, eyes, nose, throat, neck; lymph nodes, chest, heart, abdomen, extremities, musculoskeletal, respiratory, gastrointestinal, and neurological systems.
- Height will be measured at Screening for all participants. Body weight will be measured and recorded at every visit for all participants.
- An abbreviated physical examination will include a body-system relevant examination based upon Investigator's (or qualified designee) judgment and participant symptoms. At least 1 body system must be checked for an abbreviated examination.
- The Investigator should pay special attention to clinical signs related to previous serious illnesses. For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff.

8.3.2. Vital Signs

- Body temperature (°C or °F), heart rate, respiratory rate, and BP (mm Hg) will be recorded before blood collection for laboratory tests.
- BP and pulse measurements will be assessed in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.
- For BP measurements, 3 consecutive BP readings will be recorded at intervals of at least 1 minute. The average of the 3 BP readings will be recorded.
- On dosing days, vital sign measurements will be taken before study intervention administration.

8.3.3. Electrocardiograms

- Single 12-lead ECG(s) will be obtained as outlined in the SoA (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 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 indicated on the eCRF. For any clinically significant abnormal ECG results, the Investigator must contact the Medical Monitor to discuss the participant's continued eligibility to participate in this study.

8.3.4. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE in the AE section of the eCRF. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
    - If clinically significant 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 tests, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).
    - If laboratory values from non-protocol-specified laboratory tests 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 documented.

8.3.5. Blood Collection

Participants will be in a seated or supine position during the blood collection. Specific instructions for sample collection, processing, and shipping will be provided in a separate Laboratory Manual. If central laboratory tests results are not obtainable in a timely manner, samples may be collected at an unscheduled visit and analyzed locally. See the Laboratory Manual for additional information.

8.3.6. Pregnancy Testing

- Refer to Section 5.2 Exclusion Criteria for pregnancy testing exclusion criteria.
- Pregnancy testing (serum or urine) must be performed on all women of childbearing potential (WOCBP) at protocol-specified timepoints per SoA (Section 1.3).
- A negative pregnancy test is required for WOCBP before administration of study intervention.
- Any female participant who becomes pregnant while participating in the study will be discontinued from the study intervention.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- If a pregnancy is reported, the Investigator must immediately inform Alexion of the pregnancy and follow the procedures outlines in Section 8.4.6.

8.3.7. Participant Safety Card

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

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

8.3.8. Infusion-related Reactions

Local (infusion site reactions), systemic (infusion-associated/infusion-related reactions), and immune-mediated reactions as defined in Table 9 will be evaluated during the study period.

Table 9: Definitions for Infusion Reactions

Local Administration Reaction	Systemic Reaction	Immune-mediated Reactions
Infusion site reactions	Infusion-associated/ Infusion-related reactions	Hypersensitivity
AEs localized to the site of study intervention administration	Systemic AEs occurring during or within 24 hours of the start of infusion (eg, fever and/or shaking chills, flushing and/or itching, etc.)	AEs with Preferred Terms in the narrow SMQ of Anaphylactic reaction and the narrow SMQ of Hypersensitivity

Treatment of infusion-related reactions should be determined by the Investigator taking into consideration the participant's condition and local institutional guidelines.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

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

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 all AEs or SAEs, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, legal guardian, or the participant's LAR).

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

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

All AEs or SAEs will be collected from the signing of the ICF until the EOS visit at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to Alexion or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.4. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

The Investigator is not obligated to actively seek new information on 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 concluded participation in the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.4.7) 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.

8.4.4. Regulatory Reporting Requirements for SAEs and Other Events

- Prompt notification by the Investigator to Alexion of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and Investigators.
- Alexion is required to submit individual suspected unexpected serious adverse reaction (SUSAR) reports (defined in Section 10.3.4) in the format of MedWatch 3500 or CIOMS I Form to health authorities and Investigators as required.
- If the Investigator receives a safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion, they will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.
- Under the EU CTR 536/2014, events other than SAEs (eg, unexpected events) that may impact the benefit-risk balance should be reported. See definitions in Section 10.3.5.

8.4.5. Medication Error, Drug Abuse, and Drug Misuse

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

8.4.5.1. Timelines

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

The full definitions and examples of medication error, drug abuse, and drug misuse can be found in Section 10.4.

8.4.5.2. Medication Error

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

8.4.5.3. Drug Abuse

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

8.4.5.4. Drug Misuse

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

8.4.6. Pregnancy Reporting

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 8 months following the final dose of study intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form submit it to Alexion within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy by email ClinicalSAE@alexion.com or facsimile (+1-203-439-9347).
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The Investigator will collect follow-up information on the participant/pregnant partner, the pregnancy outcome, and the neonate, and the information will be forwarded to Alexion.
- Any poststudy pregnancy-related SAE in the mother or SAE in the newborn, if considered reasonably related to the study intervention by the Investigator, will be reported to Alexion as described above. While the Investigator is not obligated to actively seek this information in former study participants/pregnant partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.4.7. Adverse Events of Special Interest

An AESI is a serious or nonserious event of scientific or medical concern for a product or program (ICH-E2F, 2011). In this study, meningococcal infection is considered to be AESI.

8.5. Pharmacokinetics

- Blood samples will be collected for measurement of serum concentrations of ravulizumab as specified in the SoA (Section 1.3).
- Additional samples may be collected at additional timepoints during the study if warranted and agreed upon between the Investigator and sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided in a Laboratory Manual by sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. In the event of breakthrough hemolysis, a blood sample for PK analysis will be collected at any time that day.
- All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. PK samples collected out-of-window will be recorded as a protocol deviation.
- Samples will be used to evaluate the PK properties of ravulizumab. PK samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- For storage, handling, reuse, and destruction of biological samples, refer to Section 10.6 and/or the Laboratory Manual, as applicable.

8.6. Pharmacodynamics

- Serum samples will be collected for measurement of free C5 as specified in the SoA (Section 1.3).
- Additional samples may be collected at additional timepoints during the study if warranted and agreed upon between the Investigator and Alexion.
- Instructions for the collection and handling of biological samples will be provided in a Laboratory Manual by sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. In the event of breakthrough hemolysis, a blood sample for PD analysis will be collected at any time that day.
- All efforts will be made to obtain the PD samples at the exact nominal time relative to dosing. Out-of-window protocol deviation capture for PD samples follows that specified for PK sample collection (Section 8.5).
- Samples will be used to evaluate the PD of ravulizumab. PD samples may be used for research purposes or to evaluate safety or efficacy aspects during or after the study.

For storage, handling, reuse, and destruction of biological samples, refer to Section 10.6 and/or the Laboratory Manual, as applicable.

8.7. Genetics

Genetics is not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Serum samples for ADA and NAb analysis will be collected at timepoints according to SoA (Section 1.3), All efforts will be made to obtain the immunogenicity samples at the exact nominal time relative to dosing. Out-of-window protocol deviations captured for immunogenicity samples will follow the same approach as specified for PK sample collection (Section 8.5).

The detection and characterization of ADA or NAb to ravulizumab will be performed using a validated assay method by or under the supervision of Alexion. Antibodies to ravulizumab will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3).

ADA positive samples will be further characterized for antibody titer and presence of neutralizing antibodies (NAb). Samples may be stored for a maximum of 1 year (or according to local regulations) following the last participant's last visit for the study at a facility selected by Alexion. Additional analyses may be performed on collected ADA samples for further analysis or characterization.

For storage, handling, reuse, and destruction of biological samples, refer to Section 10.6 and/or the Laboratory Manual, as applicable.

8.10. Health Economics OR Medical Resource Utilization and Health Economics

Health economics and/or medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Details of the statistical analyses described below will be specified in a separate Statistical Analysis Plan (SAP). The first version of SAP will be signed off prior to first participant first visit and any subsequent amendments will be documented, with final amendments completed prior to database lock. It will include a more technical and detailed description of the statistical analyses described in this section.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes the primary endpoint 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 CSR. Additional exploratory analyses of the data may be conducted as deemed appropriate.

An interim CSR will be produced based on efficacy and safety data collected through the end of the 26-week Primary Treatment Period (Day 183). A final CSR to summarize long-term efficacy and safety data will be produced at study completion.

9.1. Statistical Hypothesis

The primary objective is to evaluate whether treatment with ravulizumab decreases LDH at Day 183 (Week 26). 1-sided hypothesis is planned to be tested whether mean percent change in LDH at Day 183 (Week 26) in single arm is less than 0.

$$H_o: \mu \geq 0 \text{ versus } H_a: \mu < 0$$

where μ represents the mean percent change in LDH at Day 183 (Week 26).

9.1.1. Multiplicity Adjustment

The Type I error for the testing of the primary endpoint will be controlled at a 1-sided significance level of 0.025. No multiplicity adjustments will be made for the analyses of secondary and exploratory endpoints.

9.2. Analysis Sets

Efficacy analyses will be performed on the Full Analysis Set (FAS). Safety analyses will be performed on the Safety Set. The populations are defined in Table 10.

Table 10: Analysis Sets

Participant Analysis Set	Description
Screened Set	All consented participants.
Safety Set (SS)	All enrolled participants who receive at least 1 dose (full or partial) of the study intervention.
Full Analysis Set (FAS)	All enrolled participants who receive at least 1 dose (full or partial) of the study intervention.
Pharmacokinetic Analysis Set (PKAS)	All ravulizumab treated participants with at least 1 post-baseline PK concentration available. All enrolled participants who receive at least 1 dose (full or partial) of the study intervention and who have at least 1 measurable concentration value.
Pharmacodynamic Analysis Set (PDAS)	All ravulizumab treated participants who have evaluable PD data. All enrolled participants who receive at least 1 dose (full or partial) of the study intervention and who have at least 1 measurable PD value.
Immunogenicity Analysis Set (IAS)	All enrolled participants who receive at least 1 dose (full or partial) of the ravulizumab and have at least 1 reportable post-dose result in the ADA assay.

For Primary Analysis at Data Cutoff (DCO) of Week 26:

The following data points sets are defined in Table 11:

Table 11: Data Point Set for the Primary Analysis at DCO of Week 26

Data Points Set	Description
DPS1: All data up to IE during Primary Treatment Period	All data points obtained at or after first dose up to the earliest date of last dose + 8 weeks or withdrawal from study or administration of disallowed medication or end of Primary Treatment Period at Week 26
DPS2: All data during Primary Treatment Period	All data points obtained at or after first dose up to the earliest date of withdrawal from study or end of Primary Treatment Period at Week 26
DPS3: All data on treatment during Primary Treatment Period	All data points obtained at or after first dose up to the earliest date of last dose + 8 weeks or withdrawal from study or end of Primary Treatment Period at Week 26

The participant analysis sets and DPSs for the Primary analysis at Week 26 will be used as follows (Table 12):

Table 12: Analysis Sets and Data Point Sets for the Primary Analysis at Week 26

Objective	Endpoint/Estimand	Participant Analysis Set	Data Points Set
Primary	Percentage change in LDH from baseline to Day 183 (Week 26)	FAS	DPS1
Secondary	LDH <1.5 ULN at Day 183 (Week 26)	FAS	DPS2
	TA through Week 26	FAS	DPS2
	Breakthrough hemolysis through Day 183 (Week 26)	FAS	DPS2
	Change in FACIT-Fatigue score from Baseline to Day 183 (Week 26)	FAS	DPS2
Safety	Incidence of TEAEs, SAEs, and TEAEs leading to discontinuation of study intervention during the Primary Treatment Period	SS	DPS3
PK	Change in serum ravulizumab concentration during the Primary Treatment Period	PKAS	DPS3
PD	Change in serum free C5 concentration during the Primary Treatment Period	PDAS	DPS3
Immunogenicity	ADA incidence, category of immune response, and titer, as well as NAb incidence during the Primary Treatment Period	IAS	DPS3

For Final Analysis at DCO of Week 58:

The following DPSs for final analysis at DCO of Week 58 are defined Table 13:

Table 13: Data Point Sets for the Final Analysis at DCO of Week 58

Data Points Set	Description
DPS4: All data on study	All data points obtained at or after first dose up to the earliest date of withdrawal from study or the end of study.
DPS5: All data on treatment	All data points obtained at or after first dose up to the earliest date of last dose+ 8 weeks or withdrawal from study or study completion

The participant analysis sets and DPSs for the Final analysis at Week 58 will be used as follows (Table 14):

Table 14: Analysis Sets and Data Point Sets for the Final Analysis at Week 58

Objective	Endpoint/Estimand	Participant Analysis Set	Data Points Set
Safety	Incidence of TEAEs, SAEs, and TEAEs leading to discontinuation of study intervention during the Primary Treatment Period	SS	DPS5
Exploratory	Exploratory endpoints	FAS	DPS4
PK	Change in serum ravulizumab concentration through end of study	PKAS	DPS5
PD	Change in serum free C5 concentration through end of study	PDAS	DPS5
Immunogenicity	ADA incidence, category of immune response, and titer, as well as NAb incidence for the duration of the study	IAS	DPS5

9.3. Statistical Analyses

9.3.1. General Considerations

Summary statistics will be computed and displayed by visit, where applicable. Descriptive statistics for continuous variables will minimally include the number of participants, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. Graphical displays will be provided as appropriate.

Baseline is defined as the last non-missing assessment prior to the first study intervention administration unless otherwise specified. In general, the baseline assessment will be the Day 1 assessment. If the Day 1 assessment is missing, the screening assessment, where available, will be used as the baseline assessment.

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

9.3.2. Primary Endpoint(s) Analysis

9.3.2.1. Derivation of Endpoint(s)

The primary endpoint is percentage change from Baseline in LDH at Week 26. The primary efficacy analysis will be based on the FAS.

Baseline LDH is defined as the average of all non-missing LDH assessments analyzed by the central laboratory prior to first study intervention administration.

The percent change in LDH at each nominal visit is defined as:

*(postbaseline LDH – baseline LDH) / baseline LDH * 100%*

9.3.2.2. Main Analytical Approach

The primary estimand will be conducted using the FAS for the primary endpoint (percent change from baseline in LDH at Week 26).

- Population: Adult participants with PNH who are naïve to complement inhibitor treatment and meet all of the inclusion criteria and none of the exclusion criteria in China
- Endpoint: Percentage change in LDH from baseline to Day 183 (Week 26)
- Treatment condition: ravulizumab
- Handling of intercurrent events (IEs): Discontinuation of study intervention and initiation of disallowed medication.
    - "Hypothetical strategy" will be used to handle the IEs (discontinuation of study intervention and initiation of disallowed medication). For the IE of discontinuation of study intervention, it is assumed that patients would have good treatment compliance (no discontinuation of study intervention), so measurements without treatment effect after discontinuation of study intervention will be excluded. For ravulizumab, measurements within 8 weeks after the last dose are considered to represent the efficacy. Hence, measurements after treatment discontinuation before last dose + 8 weeks will be included in the analysis. Only data before the occurrence of initiation of disallowed medication will be included in the analysis.

      A mixed-effect model for repeated-measures (MMRM) will be used for primary analysis which assumes MAR for missing data mechanism. Through the MMRM, the potential efficacy measures (after the IEs) will be implicitly imputed which assume participants would not have intercurrent events.
- Population-level summary: Mean percentage change in LDH from baseline to Day 183 (Week 26)

The MMRM will be used to test whether mean percent change in LDH at Week 26 is less than zero. The model will include percent change from baseline in LDH as the response variable and fixed, categorical effects of visit, and continuous effect of baseline LDH as covariates. An unstructured covariance matrix will be used to model the within-patient variability. If this analysis model fails to converge, the covariance matrix structures will be evaluated in the following order until model convergence is met: Toeplitz, first-order autoregressive, and compound symmetry. The order is specified according to decreasing number of covariance parameters in the structure. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The point estimate and 2-sided 95% confidence interval (CI) for the mean percent change in LDH at Week 26 and p-value will be provided.

9.3.2.3. Sensitivity Analyses and Supplementary Analyses

Sensitivity analyses and supplementary analyses will be specified in the SAP as needed.

9.3.3. Secondary Endpoint(s) Analyses

9.3.3.1. Derivation of Endpoint(s)

The secondary efficacy endpoints will include the following:

- Participants achieving LDH < 1.5 × ULN at Day 183 (Week 26)
- Participants achieving TA through Week 26, defined as remaining transfusion free (i.e., have not received any transfusion) and not requiring transfusion as per protocol-specified guidelines between Week 2 and Week 26
- Participants experiencing breakthrough hemolysis through Day 183 (Week 26), defined as at least 1 new or worsening symptom or sign of hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [Hgb < 10.5 g/dL], MAVE [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN after LDH < 1.5 × ULN on therapy during the primary treatment period.
- Change in FACIT-Fatigue score from baseline to Day 183 (Week 26)
- Change in Hgb from baseline to Day 183 (Week 26)

9.3.3.2 Main Analytical Approach

There is no formal statistical testing for all secondary endpoints. All secondary efficacy analyses will be based on the FAS.

For continuous endpoints of change from baseline, such as FACIT-Fatigue score and Hgb, observed mean values and 95% CIs will be summarized.

For categorical endpoints of LDH < 1.5× ULN at Day 183, TA and BTH through Day 183, the observed proportions of participants will be summarized along with 95% 2-sided Clopper-Pearson exact CIs.

Details of the analyses will be provided in the SAP.

9.3.4. Exploratory Endpoint(s) Analysis

The exploratory analyses will be descriptive in nature and will be based on the FAS. Details of these analyses will be presented in the SAP.

9.3.5. Safety Analyses

All safety analyses will be made on the Safety Set.

The safety and tolerability of ravulizumab will be assessed based on treatment-emergent adverse events (TEAEs), clinical laboratory findings, vital sign findings, electrocardiogram (ECG) abnormalities, and physical examination.

The incidence of TEAEs, TEAEs leading to treatment discontinuation, and treatment emergent serious adverse events (TESAEs) will be summarized. All TEAEs will be coded using MedDRA

version 26.1 or higher and will be summarized by System Organ Class (SOC) and Preferred Term overall, by severity, and by relationship to treatment. Detailed by-participant listings of TEAEs, TESAEs, related TEAEs, and TEAEs leading to treatment discontinuation will be provided.

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

Observed values and changes from baseline in clinical chemistry, hematology, and urinalysis will be summarized descriptively at baseline and each postbaseline timepoint. For laboratory results that can be classified as normal, low, or high based on normal range values, shifts from baseline in classification will be summarized for all study visits.

Electrocardiograms will be evaluated and summarized as normal, abnormal not clinically significant, or abnormal clinically significant. A shift from baseline to worst on-study ECG table will be presented for ECG results. Observed values and change from baseline in ECG intervals (PR, RR, interval between the start of the Q wave and the end of the T wave in an ECG [QT], and QTc) will be summarized descriptively at baseline and each postbaseline timepoint. QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

9.3.6. PK/PD Analyses

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

During PK analysis, graphs of mean and individual serum concentration-time profiles will be provided. Descriptive statistics will be calculated for serum drug concentration data at each sampling time, as appropriate. PK parameters such as peak and trough serum ravulizumab concentrations will be reported and summarized.

9.3.7. Immunogenicity Analysis

All immunogenicity analyses will be performed on the Immunogenicity Analysis Set.

Immunogenicity variables include ADA status, ADA response category, ADA titers and NAb status over the duration of the study. Definitions of the ADA status, and response categories will be provided in the SAP. ADA status and ADA response categories will be summarized as absolute occurrence (n) and percentage of all participants.

ADA status categories:

- ADA negative
- ADA positive

Participants who are ADA positive will be further categorized into ADA response categories as follows:

- Pre-existing immunogenicity
- Treatment-emergent ADA responses
- Treatment-boosted ADA responses

Participants with treatment-emergent or treatment-boosted ADA responses will be further categorized as:

- −Persistent responses
- −Indeterminate responses
- −Transient responses

ADA positive samples will be further characterized for neutralizing activity in a NAb assay. NAb status categories are as follows:

- NAb positive
- NAb negative

NAb status will be summarized as absolute occurrence (n) and percentage of all participants.

9.4. Interim Analysis

An interim efficacy and safety assessment will be conducted as Primary Analysis when all participants have completed 26-week Primary Treatment Period or withdrawn from the 26-week Primary Treatment Period. A CSR will be developed based on efficacy and safety data collected through the end of the 26-week Primary Treatment Period. It will be utilized for the submission of the NDA in China.

The final analysis will be performed upon the completion of the study at Week 58. A final CSR to summarize long-term efficacy and safety data will be developed at study completion.

9.5. Sample Size Determination

Approximately 18 participants will be enrolled. The sample size calculation is based on the primary efficacy endpoint - percent change in LDH at Week 26. It is assumed that a mean percent decrease in LDH at Week 26 is 30% and an associated SD is 30%. The total sample size of 18 participants will have > 90% power to detect a statistically significant treatment effect on whether the percentage change in LDH at Week 26 is less than 0, assuming a 10% dropout rate. This is based on a one sample t-test at a one-sided type I error rate of 2.5%.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments (ie, modifications), ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - 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 per local regulations
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU CTR 536/2014 for clinical studies, EU MDR 2017/745 for clinical device research, and all other applicable local regulations
  - Promptly notifying Alexion of any (potential) serious breach of the protocol or regulations (including if a data breach compromises the integrity, confidentiality, or availability of the personal data of participants) so that legal and ethical obligations are met. A "serious breach" means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- The Investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach, including personal data breaches.
- A (potential) serious breach is promptly reported to Alexion or delegated party, through the contacts (email address or telephone number) provided by Alexion.
- Alexion and the site have taken all necessary steps to avoid personal data breaches and have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and information technology security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- Both Alexion and the study site have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- In compliance with applicable laws, the data controller for the processing activity where the personal data breach occurred (Alexion or respectively the study site) will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- If the personal data breach needs to be notified to participants, the notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the data controller and for data breaches occurred within the processing activities of Alexion as the data controller, the notification is done in collaboration with the site and is performed by the site and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the participants. The site and/or Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by Alexion, the processor under contractual obligations with Alexion promptly and in due course after discovering the breach notifies Alexion and provides full cooperation with the investigation. In these cases, to the extent Alexion is the data controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the participants.
- Where a personal data breach is suffered by the Study Monitor, the latter will provide Alexion with all of the information needed for notification of the breach, without disclosing data that allows Alexion directly or indirectly to identify the participants. The notification will be done by Alexion solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of reidentification of the participants. If the data breach must be

notified to the data participants, the notification will be done directly by the Study Monitor in collaboration with the site and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the participants. The contract between Alexion and the Study Monitor shall expressly specify these conditions.

- The contract between the study site and Alexion for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

- The Coordinating Investigator will be identified among the enrolling Investigators during the course of the study and will be responsible for reviewing the CSR and confirming that it accurately describes the conduct and results of the study.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator or designee to obtain signed informed consent from all study participants, or the participant's LAR, prior to performing any study-related procedures including screening assessments.
- The Investigator or designee will explain the nature of the study (including but not limited to the study objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or his/her LAR, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Potential participants and their LAR must be informed that their participation is voluntary. Participants or their LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must include a statement that signed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF form(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant

or their LAR, as applicable. This document will require translation into the local language. Original signed consent forms must remain in each participant's study file and must be available for verification at any time.

Participants who are rescreened outside of the screening window (SoA Table 3) are required to sign a new ICF (Section 5.4).

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, date of birth, or any information which would make the participant identifiable will not be transferred.
- Participants must be informed about the uses of their personal study-related and coded (pseudonymized) data, who will have access to their personal data, how and how long it will be used and that it will be used by Alexion in accordance with local data protection law. In addition, multiple local laws require that participants must also be informed of any individuals rights they may have with regard to their personal data. Participants will be informed about how their personal study-related data will be disclosed and are provided with the appropriate legal basis for which a controller processes their personal data. The level of disclosure, the security controls use to protect their data and information regarding any transfer of their personal data outside of their country or region must also be explained to the participant.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, any third parties acting on behalf of Alexion, and by inspectors from regulatory authorities.
- Sponsor and the site as a data controller has implemented privacy and security controls designed to help protect participant personal data, including information security controls, firewalls, incident detection, and secure transfer measures.
- The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- The EU GDPR defines pseudonymization as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.
- Appropriate safeguards will be implemented to protect coded data during and after the study that include:

- Access to the coded data will be limited to specific individuals subject to confidentiality obligations (including the obligation to not attempt to re-identify individuals/decode the clinical data).
- The coded data will be protected with security measures to avoid data alteration, loss, and unauthorized accesses and further de-identification techniques may be applied.
- A data protection impact assessment, where required, will apply to identify and mitigate privacy risks, if any, associated with each scientific research.
- The coded data will not be shared for direct marketing purposes or other purposes that are not legal duties or are not considered scientific research according to the applicable data protection legislation. In particular, they will not be used to make decisions about future services available to the participant, such as insurance.

- In addition to having the participants' data and biosamples coded, the data are also protected by high-standard technical security means, such as strong access control and encryption.
- Participants are also protected legally by the following means if the level of disclosure of the coded data includes sharing of the latter with other third parties, as the participants will be explained in the ICF:

  − The participants' coded data are protected by contractual arrangements, Codes of Conduct, or certifications that set the rules for personal information protection to those available in European countries or other alternatives set forth in the law, as well as any supplementary technical and organizational measures that may results out of conducted transfer impact assessments.

10.1.5. 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. However, posting of study results per local regulations may be deferred to a later date for one of the following reasons:

- Study is still ongoing in other countries or regions
- Study is part of an ongoing review for approval by Health Authorities; study result data deferral request can be submitted.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on the 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 eCRF.

- Guidance on completion of eCRFs will be provided in the electronic case report form (eCRF) completion guidelines.
- 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 documents.
- Quality tolerance limits (QTLs) will be predefined in the IQRMP to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- Alexion or designee is responsible for the data management of this study, including quality checking of the data.
- Alexion assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Sponsor. No records may be transferred to another location or party without written notification to Sponsor. Clinical study documents and records required as part of the TMF are archived and stored by Sponsor for at least 30 years.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. CRFs must be completed by the Investigator or designee as indicated in the site delegation log. Source documents are filed at the investigational site. The Investigator may need to request previous medical records or transfer records, depending on the study and per local regulations, if applicable. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in source data agreement.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Alexion or designee will perform monitoring 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.
- Per ICH E6 (R2) guidelines and good documentation practice requirements, source documents and study records in all media (eg, paper, electronic) must be Attributable, Legible, Contemporaneous, Original, Accurate, and Complete.

10.1.8. Study and Site Start and Termination/Closure

Study Start

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 activation and will be the study start date.

Study/Site Termination

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 ICH GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected
- Discontinuation of further study intervention development.

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

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

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

10.1.9. Publication Policy

- Alexion strives to publish results from all research studies regardless of whether the findings are positive, negative, or inconclusive, or whether the product is investigational, licensed, or has been discontinued or withdrawn from the market. The minimum commitment is to all Phase 2 and Phase 3 clinical studies. Alexion also commits to publish other studies of significant scientific or medical importance including, but not limited to Phase 1 clinical studies, discovery, research, epidemiology, and health economics and outcomes research.
- For registration studies, journal submission of primary manuscripts must be within 12 to 18 months of study completion. Study completion is defined as data availability for primary endpoints following completion of the clinical study as defined in the protocol. In the case of early phase studies and research studies involving investigational products, submission may be delayed to protect intellectual property. In the case of discontinued investigational programs, study completion is defined as the time of data availability following termination of the program.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol specified endpoints) to Sponsor for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Sponsor to protect proprietary information and provide comments.
    - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property (IP). All publications describing the results of Alexion sponsored studies (including Investigator-led analyses, as well as Investigatorinitiated studies) shall be reviewed by the IP team at advanced draft stage in order to ensure IP protection.
- Primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Sponsor’s policy prohibits duplicate publication, whereby the same results must not be published in multiple peerreviewed journal manuscripts.
    - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.
- Sponsor will comply with the requirements for publication of study results as defined by the Pharmaceutical Research and Manufacturers of America, the International Committee of Medical Journal Editors (ICMJE; www.icmje.org) recommendations,

and per the Alexion/AstraZeneca Publication Policy. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with ICMJE authorship guidelines as well as journal- and congress-specific guidelines and requirements (as applicable) and per the Alexion/AstraZeneca Publication Policy. Authors must meet all four ICMJE authorship criteria to qualify for authorship. The relative order of Authors will be determined by consensus among the authors.
- Sponsor will make reasonable efforts to publish Plain Language Summaries of abstracts of selected manuscripts and poster presentations based upon accepted criteria, and include participants and/or caregivers as reviewers for readability and understanding of lay person language.
- No compensation shall be provided to external Authors for authorship of publication, including drafting or revising a publication. Sponsor may reimburse the presenting Author of an Alexion-supported publication for travel, lodging, and registration to present a poster or oral presentation at scientific meeting, consistent with the Alexion Global Procurement and Sourcing Procedure, the Sponsor Antibribery Anticorruption Policy, and the Alexion Global Travel and Expense Policy.
- Fair market value compensation may be provided for needed preidentified services, such as statistical analyses, additional research or professional medical writing support, provided by Alexion pursuant to an executed contract.
- Authors must disclose financial or personal affiliations that could be considered a conflict of interest in the publication.
  - Investigators who participate as authors in manuscripts derived from Alexion sponsored studies will agree to the prerequisites as outlined in the Alexion Author Letter of Agreement prior to engaging in manuscript development.
- More details are provided in the Alexion/AstraZeneca Publication Policy.
- Medical publications are developed free of commercial influence. Publications cannot be developed with the intent to promote off-label use of a product or to unduly influence prescribers.
- Proposed publications should not be duplicative or redundant with prior publications unless there is a compelling medical/scientific need to reanalyze, reinterpret, or translate the prior publication.

10.2. Clinical Laboratory Tests

- The tests detailed in Table 15 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. 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 intervention decision or response evaluation, the results must be recorded.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional laboratory tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: WOCBP should only be enrolled after a negative serum or urine pregnancy test result at Screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB/IEC and should be performed per the timepoints specified in the SoA (Section 1.3).

Investigators must document their review of each laboratory safety report.

Table 15: Protocol-required Laboratory Tests

Laboratory Tests	Parameters	
Hematology	Platelet count	
	RBC count	
	RBC indices	• Distribution width • Mean corpuscular volume • Mean corpuscular hemoglobin • Reticulocyte count
	• WBC count with differential:	• Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Hemoglobin	
	Free hemoglobin	
	Hematocrit	
	Haptoglobin	
	Coagulation panel	• D-dimer • International normalized ratio • Prothrombin time • Partial thromboplastin time

Table 15: Protocol-required Laboratory Tests

Laboratory Tests	Parameters	
Clinical chemistry	• Alanine aminotransferase • Albumin • Alkaline phosphatase • Aspartate aminotransferase • Bicarbonate • Blood urea nitrogen • Calcium • Chloride • C-reactive protein • Creatinine • Gamma-glutamyltransferase	• Glucose [fasting] • Lactate dehydrogenase • Magnesium • Phosphorus • Potassium • Sodium • Total bilirubin (direct and indirect) • Total protein • Uric acid
Routine urinalysis	• Albumin • Appearance • Bilirubin • Blood • Color • Creatinine • Glucose • Ketones	• Nitrite • pH • Protein • Specific gravity • Urobilinogen
PK/PD and immunogenicity	• Serum PK • Serum PD (free C5) • Immunogenicity (ADA and/or NAb)	
Other study specific tests	• HIV-1 • HIV-2 • PNH clone size • Beta human chorionic gonadotropin (as needed for WOCBP) • Serum Follicle-stimulating hormone (as needed in women of non-childbearing potential only)	

10.3. AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience).
- A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error.
- Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- 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.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (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.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of drug dependency or drug abuse.

Definition of SUSAR

A suspected unexpected serious adverse reaction (SUSAR) is defined as:

An event that is serious, that has at least a reasonable possibility as being related to the IMP as assessed by the Investigator and/or Alexion, and is not listed in the appropriate Reference Safety Information (IB).

Alexion has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents.

Suspected unexpected serious adverse reactions will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following regional, national and local regulatory reporting requirements, as applicable.

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

10.3.3.1. AE and SAE 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/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 Alexion AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.3.2. Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the 5 categories from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening
- Grade 5: Fatal

10.3.3.3. Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship as either "related" or "not related."
  - **Related:** Causality of "related" is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.
  - **Not related**: The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as "not related."

- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Alexion. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.3.4. Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Alexion via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Alexion will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE Report Form to report the event to Alexion GPS within 24 hours.
    - The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source

documents, and send a copy via email or facsimile to the contact information provided below.

- All paper forms and follow-up information submitted to Alexion must be accompanied by a cover page signed by the Investigator.
- Contacts for paper SAE reporting:

  Email: clinicalSAE@alexion.com or facsimile: + 1.203.439.9347

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Alexion GPS by telephone.

10.3.5. Unexpected Events

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

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

10.4. Medication Error, Drug Abuse, and Drug Misuse

Medication Error

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

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

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

Medication error includes situations where an error:

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

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

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

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

- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose [refer to Section 6.8 for information on overdose])
- Participant failed to return unused medication or empty packaging

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

Drug Abuse

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

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

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)

- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

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

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

Examples of drug misuse include but are not limited to:

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

10.5. Contraceptive and Barrier Guidance

10.5.1. Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
    - 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 1 FSH measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen 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.
    - Permanent sterilization methods (for the purpose of this study) include:
        - 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, gonadal dysgenesis), 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.

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

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy

d. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), 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.

2. Postmenopausal female

   a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

      - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
      - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency: *Failure rate of < 1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a to medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods That Are User Dependent: *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal • Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c]

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• Oral • Injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

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

[b] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

10.6. Handling of Human Biological Samples

All research and biological samples, including those for possible future research, are subject to national regulations and will only be conducted in a specified country if approved in that country.

Handling, storage, and shipment of biological samples are detailed in the Laboratory Manual.

10.6.1. Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each site keeps full traceability of collected biological samples from the participants while in storage at the site until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

Alexion or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

All appropriately consented samples will be retained for a maximum of one year from final CSR publication.

If required, Alexion will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is sooner.

10.6.2. Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, Alexion is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures the participant's withdrawal of informed consent to the use of donated samples is communicated immediately to Alexion or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and Alexion are informed about the sample disposal.

Alexion ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, the action is documented, and study site is notified.

10.7. Participant-Reported Outcome Instruments

FACIT Fatigue Scale (Version 4)

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

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

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