TITLE PAGE

Protocol Title: Open-label, Multicenter Study to Assess the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Eculizumab in Complement Inhibitor Treatment Naïve Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH) in China

Protocol Number: ECU-PNH-301

Compound: Eculizumab

Study Phase: 3b

Short Title: Open-label Study of Eculizumab in Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH) in China

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address: 121 Seaport Blvd Boston, MA 02210

Regulatory Agency Identifier Number(s): Not assigned

Original Protocol: 30 Nov 2021

Protocol Amendment 1: 06 Nov 2023

Sponsor Signatory:

[redacted]

15-NOV-2023

Date

Alexion Pharmaceuticals, Inc.

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

INVESTIGATOR'S AGREEMENT

I have read the study protocol amendment and agree to conduct the study in accordance with this protocol amendment, 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 (GCP), 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 amendment.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 1

Overall Rationale for the Amendment:

The primary reason for this substantial amendment change was to update 2 additional secondary endpoints that evaluates efficacy of eculizumab in participants with PNH, and to analyze TEAEs by Primary Treatment Period, Long-term Extension, and Overall Period.

Additionally, updates to estimand descriptions for endpoints, nonserious adverse drug reaction (ADR) reporting, medication error description, and other key administrative clarifications were made.

Section # and Name	Description of Change	Brief Rationale
Title Page	Added original protocol and protocol amendment details.	Administrative.
1.1. Synopsis (Objectives, Estimands, and Endpoints) 3. Objectives, Estimands, and Endpoints (Table 5) 3.1. Primary Estimand 3.2. Secondary Estimands	Updated definition of "Population" and removed mention of FAS: **Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria**.	To align the definition of population with ICH E9 (R1).
1.1. Synopsis (Objectives, Estimands, and Endpoints) 3. Objectives, Estimands, and Endpoints (Table 5, secondary estimands and endpoints) 3.2. Secondary Estimands (summary measures)	• Updated variables, and/or summary measures for PK, PD, immunogenicity assessments as follows: **PK:** Summary measure: **Mean** ~~**S**~~serum eculizumab concentrations at all ~~available study~~ **scheduled** visits. **PD:** Summary measure: Mean change**s** in serum free and total C5 concentrations ~~from baseline over time~~ at all ~~study~~**scheduled** visits. **Immunogenicity:** Variable: **ADA response category** ~~Proportion of participants with ADA positive and titer of ADAs and titer of ADSs if participants are ADA positive.~~. Summary measure: Proportion of ~~participants at all study visits with ADA positive and titer of ADAs for participants who are confirmed ADA positive~~ **treatment-emergent ADA positive participants.**	To align the definition of population with ICH E9 (R1).

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis (Objectives, Estimands, and Endpoints) 3. Objectives, estimands and endpoints (Table 5, additional secondary estimands and endpoints)	• Added estimands framework for all the additional secondary efficacy endpoints. • Changed the timepoint for assessment from "all scheduled visits" to "Week 12" for the variables FACIT-Fatigue and LDH normalization • Proportion of participants with breakthrough hemolysis **during the Primary Treatment Period** • Revised text in the additional secondary endpoint on transfusion avoidance as follows: ~~Number (%) of participants who need blood transfusion and units transfused at all scheduled visits.~~ **Proportion of participants achieving transfusion avoidance during the Primary Treatment Period**	To align with ICH E9 (R1).
	Added following additional secondary endpoint: "**Number (%) of participants achieving LDH ≤ 1.5 × ULN at Week 12**"	
1.1. Synopsis (Overall Design) 1.3. Schedule of Activities (Table 1 through Table 3) 4.1. Overall Design	Updated definition of ED Visit to early discontinuation from the study.	For clarity.
1.1. Synopsis (Overall Design) 4.1. Overall Design 5.1. Inclusion Criteria	Revised 14 days to 2 weeks and "antibiotics" to "**prophylactic** antibiotics"	For clarity and internal document consistency.
1.3. Schedule of Activities (Table 1 through Table 3)	Table and footnote for PK/PD sampling was updated to include ADA sampling, and the footnotes updated to specify peak are for PK samples.	Added for clarity.
2.1. Study Rationale	Updated to add date as follows: Eculizumab is approved in China for the treatment of PNH in children and adults **since Sep 2018**.	Added for updated information.
3.1. Primary Estimand	Added the use of hypothetical strategy for handling intercurrent events.	Added for clarity.
3.2. Secondary Estimands	Reference to SAP is added for details on the estimands.	Added for clarity.

Section # and Name	Description of Change	Brief Rationale
4.4. End of Study Definition	Added as follows: "…is considered to early terminate from the Long-term Extension Period if the participant discontinues **from the study** during…"	For clarity.
5.2. Exclusion Criteria 8.10.5. Prior and Concomitant Medications (Prior Medications)	Updated the timeframe for usage of prior medications, investigational drug or device before the start of Screening or during the Screening Period before the first dose of eculizumab from 30 days to 28 days.	For consistency.
6.5. Prior and Concomitant Therapy	• Updated the heading as follows: **Prior and** Concomitant Therapy • Updated that concomitant medications will be recorded per the SOA.	For accuracy
6.8. Treatment of Overdose	Moved from Section 8.4 to Section 6 as a new sub-section, Section 6.8.	Updated to align with the latest Alexion CPT.
7.1. Discontinuation of Study Intervention	The text was updated as follows: If the study intervention is ~~definitively~~**permanently** discontinued, the participant should**, if at all possible,** remain in the study to be evaluated **for all assessments** at the ~~8-week Safety Follow-up Phone Call as specified~~**scheduled visits described** in the SoA (Section 1.3)	For clarity.
8.1.4. Breakthrough Hemolysis	Text to define MAVE was added.	For clarity.
8.1.5. Transfusion History and Transfusion Requirement Status	Text on transfusion guidelines was added.	For clarity.
8.2.6. Participant Safety Card	Updated the timepoint of "3 months" to "8 weeks" to align with Safety Follow-up.	For consistency.
8.3. Adverse Events, Serious Adverse Events and Other Safety Reporting	Section heading updated as follows: Adverse Events, ~~and~~ Serious Adverse Events **and Other Safety Reporting**	Updated to align with the latest Alexion CPT.
8.3.4. Regulatory Reporting Requirements for SAEs and Other Events	• Section heading updated as follows: Regulatory Reporting Requirements for SAEs **and Other Events** • Text was added on ADR, and on reporting and recording of nonserious ADRs.	Updated section heading to align with the latest Alexion CPT and added text on ADR for clarity.

Section # and Name	Description of Change	Brief Rationale
8.3.6. Medication Error, Drug Abuse, and Drug Misuse	Added new sub-section on Medication Error, Drug Abuse, and Drug Misuse	Updated to align with the latest Alexion CPT.
8.4. Pharmacokinetics 8.5. Pharmacodynamics 8.8. Immunogenicity Assessments	Text was added for: • Storage, handling, reuse, and destruction of biological samples • Storage and disposal of PK and PD samples • Retention of the samples collected in China	Added sample storage information in relevant sections for clarity.
8.10.4. Medical History and PNH History	Text was added to list the concomitant indications or disorders and reference to Section 8.11.5 was added for more information.	Added for clarity.
8.10.5. Prior and Concomitant Medications	• Updated the section heading to: Prior and Concomitant Medications ~~Review~~ • Removed sub-section numberings (Section 8.11.5.1 and Section 8.11.5.2) and changed the sub-heading to bold.	Updated for clarity.
8.10.6. Study Intervention Administration	Added “total C5” to list of PD data collected.	For clarity and consistency.
9.4.1.1. Analyses of Primary Efficacy Estimand and/or Endpoint	Removed “random effect” and added mixed model repeated measures (MMRM) will be used for analyses.	For clarity and consistency.
9.4.1.2. Analyses of Secondary Efficacy Estimand(s) and/or Endpoint(s)	Text was revised to include the newly added estimands and to define transfusion avoidance.	For consistency and clarity.
9.4.2. Safety Analyses	• Timepoints for analyses of TEAEs in different phases were added as follows: **For the Primary Treatment Period, TEAEs through Day 99 (Week 12) will be tabulated and presented separately. For the Long term Extension Period, TEAEs will be summarized starting from Week 12 through the end of study (EOS). TEAEs will also be summarized for the Overall Period.** • Vitals signs were added to the list of variables.	For clarity.

Section # and Name	Description of Change	Brief Rationale
9.4.3.1. PK/PD	Updated the following text: The PK data in this study might be pooled with other studies to conduct a population PK modelling analyses**, which may be described in a separate SAP**. The potential impact of participant characteristics (covariates) on PK ~~will~~ **may** be evaluated. The relationship between PK exposure and ~~PD (free C5 concentration) will~~**response may** be explored. The ~~population PK analysis will be described in a separate SAP. The~~ **potential** results of population PK **and exposure-response** analysis ~~will~~ **may** be reported in a separate report.	For clarity.
9.4.3.2. Immunogenicity	Revised as follows: ~~For assessment of immunogenicity, the presence of confirmed~~ **ADA** positive ~~ADAs will be summarized. Additionally, following confirmation of positive ADAs,~~ samples will be ~~assessed~~**further characterized** for ~~ADA~~**antibody** titer and presence of neutralizing antibodies. **Samples may be stored for a maximum of 1 year of the final CSR (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.**	To align with the latest Alexion CPT and for clarity.
10.3. AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Updated the heading to add SAEs.	To align with the latest Alexion CPT.
10.3.1. Definition of AE (Events Not Meeting the AE Definition)	Added reference to Section 10.4.	For more details.
10.3.5. Unexpected Events	Added a new section on unexpected events.	To align with the latest Alexion CPT.
10.4. Medication Error, Drug Abuse and Drug Misuse	This section is newly added.	To align with the latest Alexion CPT and for clarity in reporting medication error, drug abuse and drug misuse including overdose.
10.8. Protocol Amendment History	Added details on Protocol Amendment 1.	Administrative.

Section # and Name	Description of Change	Brief Rationale
Throughout	Headers updated with amendment number and date.	Administrative.
Throughout	Corrected grammar, syntax, abbreviations, style, and formatting. Updated sub-section numbering in Section 8.3 and Section 10 due to addition of a new sub-section (Section 8.3.6 and Section 10.4, respectively).	For clarity and to maintain internal document consistency.

Note: […] indicates additional unchanged text; ~~strikethrough~~ indicates deleted text; **bold** indicates added text
Abbreviations: ADA = antidrug antibody; ADR = adverse drug reaction; AE = adverse event; C5 = complement component 5; CPT = common protocol template; CSR = clinical study report; ED = early discontinuation from the study; EOS = end of study; FACIT = ; FAS = Full Analysis Set; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; LDH = lactate dehydrogenase; MAVE = major adverse vascular event; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PNH = paroxysmal nocturnal hemoglobinuria; SAE = serious adverse event; SAP = statistical analysis plan; SoA = Schedule of Activities; TEAE = treatment emergent adverse event; ULN = upper limit of normal

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

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

Short Title:

Open-label Study of Eculizumab in Adult Participants with Paroxysmal Nocturnal Hemoglobinuria (PNH) in China

Rationale:

Paroxysmal nocturnal hemoglobinuria (PNH) is a progressive and life-threatening disease characterized by complement-mediated hemolysis, resulting in serious life-threatening complications and early mortality. Eculizumab (SOLIRIS®), a recombinant humanized monoclonal antibody, specifically binds to human complement protein, complement component 5 (C5) to inhibit terminal complement activation and prevent cell lysis caused by terminal complement complex (C5b-9), thereby improving intravascular hemolysis that is the primary clinical manifestation of PNH.

Eculizumab was approved for the treatment of PNH in the United States and European Union in 2007, and data have since supported approval of eculizumab for the treatment of patients with PNH in more than 50 countries worldwide, including Canada, Australia, Japan, South Korea, and China.

The objective of this postapproval study is to assess the efficacy and safety of eculizumab in participants with PNH in China.

Objectives, Estimands, and Endpoints

Objectives	Estimands and Endpoints
Primary	
To assess efficacy of eculizumab in participants with PNH	• Population: Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Percentage change from Baseline in LDH at Week 12 (Section 3.1). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will not be used. • Summary measure: Mean percent change from Baseline in LDH at Week 12.

Objectives	Estimands and Endpoints
Secondary	
To assess the safety and tolerability of eculizumab in participants with PNH	• Population: Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Incidence of TEAEs and SAEs. • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be included. • Summary measure: Number and percentage of participants with TEAEs and SAEs and number of events by System Organ Class and Preferred Term.
To characterize the pharmacokinetics of eculizumab in participants with PNH	• Population: Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Serum eculizumab concentrations over time (Section 3.1). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Mean serum eculizumab concentrations at all scheduled visits.
To characterize the pharmacodynamics of eculizumab in participants with PNH	• Population: Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Changes in serum free and total C5 concentrations from Baseline over time (Section 3.1). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Mean changes in serum free and total C5 concentrations at all scheduled visits.

Objectives	Estimands and Endpoints
To characterize the immunogenicity of eculizumab in participants with PNH	• Population: Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: ADA response category. • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Proportion of treatment-emergent ADA positive participants.
Additional Secondary	
To evaluate the efficacy of eculizumab in participants with PNH by additional measures	• Change from Baseline in participant-reported fatigue, assessed via Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at Week 12. Variable: Change from Baseline in FACIT-Fatigue score at Week 12 Treatment: Eculizumab ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. Summary measure: Mean change from Baseline in FACIT-Fatigue at Week 12.
	• Proportion of participants with breakthrough hemolysis during the Primary Treatment Period. Variable: Breakthrough hemolysis during the Primary Treatment Period Treatment: Eculizumab ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. Summary measure: Proportion of participants with breakthrough hemolysis during the Primary Treatment Period.

Objectives	Estimands and Endpoints
	Number (%) of participants achieving LDH normalization at Week 12. Variable: LDH normalization response at Week 12 Treatment: Eculizumab ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. Summary measure: Proportion of participants achieving LDH normalization at Week 12.
	• Proportion of participants achieving transfusion avoidance during the Primary Treatment Period. Variable: Transfusion avoidance during the Primary Treatment Period. Treatment: Eculizumab ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. Summary measure: Proportion of participants achieving transfusion avoidance during the Primary Treatment Period.
	• Number (%) of participants achieving LDH ≤ 1.5 × ULN at Week 12 Variable: LDH ≤ 1.5 × ULN at Week 12 ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. Summary measure: Proportion of participants with LDH ≤ 1.5 ULN at Week 12
To characterize the safety profile of eculizumab in participants with PNH by additional safety measures	• Changes from Baseline in vital signs and laboratory parameters at all scheduled visits.

Abbreviations: ADA = antidrug antibody; C5 = complement component 5; FACIT = Functional Assessment of Chronic Illness Therapy; FAS = Full Analysis Set; ICE = intercurrent event; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; SAE = serious adverse event; TEAE = treatment-emergent adverse event; ULN = upper limit of normal

Overall Design

This is a Phase 3b, single-arm, open-label, multicenter study to evaluate the efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of eculizumab in adult participants with PNH in China who previously have not been treated with complement inhibitors. Approximately 25 eligible participants in China will be enrolled.

The study consists of 4 periods: Screening Period, Primary Treatment Period, Long-term Extension Period, and Safety Follow-up Period (phone call) that will be required only for participants who discontinue eculizumab treatment during the Primary Treatment Period or Long-term Extension Period, or for participants who will not receive continued access to eculizumab after completing study treatment.

After providing informed consent, participants will be screened for eligibility for the study during the 4-week Screening Period. If all inclusion criteria and none of the exclusion criteria are met, participants will be enrolled and vaccinated against *Neisseria 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 eculizumab will receive treatment with appropriate prophylactic antibiotics until 2 weeks after the vaccination.

During the 12-week Primary Treatment Period, all participants will receive eculizumab 600 mg intravenously (IV) weekly on Day 1, Day 8, Day 15, and Day 22 and 900 mg IV at Day 29 and every 2 weeks thereafter. Participants will be required to complete all study visits in the Primary Treatment Period to be eligible for the Long-term Extension Period. During the Long-term Extension Period, all participants will continue to receive eculizumab for an additional 52 weeks.

Participants who discontinue eculizumab treatment at any time during the study will have an Early Discontinuation (ED) Visit at the time of discontinuation from the study and a Safety Follow-up Phone Call 8 weeks after the last dose.

Participants who will not receive continued access to eculizumab after completing study treatment will also have a Safety Follow-up Phone Call 8 weeks after the last dose.

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

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

Number of Participants:

Approximately 25 participants will be enrolled and treated.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and satisfying inclusion/exclusion criteria. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

Eculizumab 600 mg or 900 mg will be administered by IV infusion over approximately 35 minutes (range of 25 to 45 minutes) according to the following regimen:

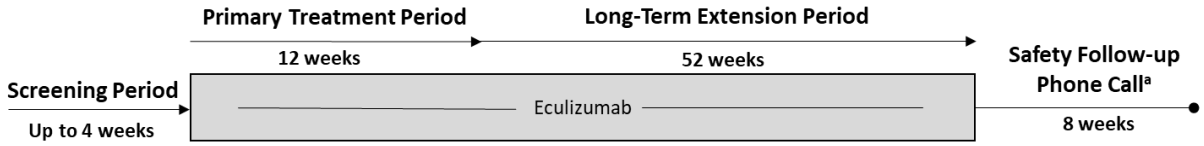
- Induction dosing: 600 mg once a week (every 7 ± 1 days) × 4 doses (Day 1, Day 8, Day 15, and Day 22).
- Maintenance dosing: 900 mg every 2 weeks (every 14 ± 2 days) starting at Day 29.

The total duration of study participation for each participant will be up to 76 weeks, including the Screening Period (up to 4 weeks), Primary Treatment Period (12 weeks), Long-term Extension Period (52 weeks), and Safety Follow-up Phone Call (8 weeks after last dose for any participant who discontinues eculizumab treatment or for any participant who will not receive continued access to eculizumab after completing study treatment).

Data Monitoring Committee: No

1.2. Schema

Figure 1: ECU-PNH-301 Study Design Schematic



[a] The Safety Follow-up Phone Call is required for any participant who discontinues eculizumab early, either during the Primary Treatment Period or Long-term Extension Period, or for any participant who will not receive continued access to eculizumab after completing study treatment.

1.3. Schedule of Activities

Table 1: Schedule of Activities: Screening Through the Primary Treatment Period

Period	Screening	Primary Treatment Period[a]									Notes
Study Day Visit Window (days)	**-28 to -1**	**1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 1**	**43 ± 2**	**57 ± 2**	**71 ± 2**	**85[b] ± 2**	
End of Week	**-4 to 0**	**Day 1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	
General Assessments/Procedures											
Informed consent	X										Refer to Section 8.10.1.
Inclusion and exclusion criteria	X										Refer to Section 8.10.3.
Demography	X										Refer to Section 8.10.2.
Medical history	X										Refer to Section 8.10.4.
PNH medical history	X										Refer to Section 8.10.4.
Confirmation or administration of meningococcal vaccination	X										Participants must be vaccinated against meningococcal infection and revaccinated during the study if needed (Section 6.5.3).
HIV testing	X										Test includes HIV-1 and HIV-2. Refer to Section 8.2.4.
Serum or urine pregnancy test[c]	X	X				X		X		X	Female participants of childbearing potential only (Section 8.2.5).
Follicle-stimulating hormone	X										Postmenopausal females only (Section 8.2.4 and Section 10.5.1)
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	
Safety and Efficacy Assessments											
Physical examination	X										Refer to Section 8.2.1.
Abbreviated physical examination		X	X	X	X	X	X	X	X	X	Refer to Section 8.2.1. May be performed at any visit as deemed necessary by the Investigator.

Table 1: Schedule of Activities: Screening Through the Primary Treatment Period

Period	**Screening**	**Primary Treatment Period**[a]									**Notes**
Study Day **Visit Window (days)**	**-28 to -1**	**1**	**8** **± 1**	**15** **± 1**	**22** **± 1**	**29** **± 1**	**43** **± 2**	**57** **± 2**	**71** **± 2**	**85**[b] **± 2**	
End of Week	**-4 to 0**	**Day 1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	
Vital signs	X	X	X	X	X	X	X	X	X	X	Refer to Section 8.2.2.
Safety 12-Lead ECG	X									X	Refer to Section 8.2.3.
Record transfusions and transfusion parameters	X	X	X	X	X	X	X	X	X	X	Transfusions given during and between visits will be recorded (Section 8.1.5).
PNH symptomatology	X	X	X	X	X	X	X	X	X	X	Refer to Section 8.1.6.
FACIT-Fatigue	X	X	X	X	X	X	X	X	X	X	Refer to Section 8.1.3.
Chemistry including LDH	X	X	X	X	X	X	X	X	X	X	Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line (Section 8.2.4).
Hematology including coagulation	X	X	X	X	X	X	X	X	X	X	Refer to Section 8.2.4.
Urinalysis and urine chemistry	X									X	Refer to Section 8.2.4.
PNH clone size	X	X				X		X		X	Refer to Section 8.1.7.
Review safety card		X	X	X	X	X	X	X	X	X	Refer to Section 8.2.6.
Breakthrough hemolysis	←Monitor continuously→										Refer to Section 8.1.4.
Concomitant medications	←Monitor continuously→										Refer to Section 8.10.5.
Adverse events	←Monitor continuously→										Refer to Section 8.3.
PK/PD/ADA Assessments											
PK/PD sampling[d]		B/P				T/P				T/P[e]	Refer to Section 8.4 and Section 8.5.
Immunogenicity (ADA)[d]		B				T				T	Samples will be collected predose (Section 8.8).

Table 1: Schedule of Activities: Screening Through the Primary Treatment Period

Period	Screening	Primary Treatment Period[a]									Notes
Study Day **Visit Window (days)**	**-28 to -1**	**1**	**8** **± 1**	**15** **± 1**	**22** **± 1**	**29** **± 1**	**43** **± 2**	**57** **± 2**	**71** **± 2**	**85[b]** **± 2**	
End of Week	**-4 to 0**	**Day 1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	
Administration of Study Intervention											
Eculizumab administration		X	X	X	X	X	X	X	X	X[e]	Administered after all other required tests/procedures. Refer to Section 8.10.6.

[a] An ED Visit and Safety Follow-up Phone Call are required for any participant who discontinues from the study. Refer to Table 3 for assessments at the ED Visit and Safety Follow-up Phone Call.

[b] Participants who complete the Primary Treatment Period who will not continue to the Long-term Extension Period and who will not receive continued access to eculizumab after study participation must have a Safety Follow-up Phone Call (Table 3).

[c] For female participants of childbearing potential, a serum pregnancy test should be performed at Screening and the last study visit, and at other timepoints as determined by the Investigator. A urine pregnancy test should be performed at all other timepoints.

[d] PK/PD and ADA baseline (B) and trough (T) samples are to be taken within 90 minutes before eculizumab administration. Peak (P) for PK samples are to be taken within 90 minutes after completion of eculizumab administration.

[e] Eculizumab administration and postdose PK/PD sample collection on Day 85 is considered to be part of the Long-term Extension Period.

Abbreviations: ADA = antidrug antibody; B = baseline; ECG = electrocardiogram; ED = early discontinuation from the study; FACIT = Functional Assessment of Chronic Illness Therapy; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; P = peak; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; T = trough

Table 2: Schedule of Activities: Long-term Extension Period

Period	Long-term Extension Period[a]																Notes
Study Day Visit Window (days)	**99 ± 2**	**113 ± 2**	**127 ± 2**	**141 ± 2**	**155 ± 2**	**169 ± 2**	**183 ± 2**	**197 ± 2**	**211 ± 2**	**225 ± 2**	**239 ± 2**	**253 ± 2**	**267 ± 2**	**281 ± 2**	**295 ± 2**	**309 ± 2**	
End of Week	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	
General Assessments/Procedures																	
Serum or urine pregnancy test[b]		X		X		X		X		X		X		X		X	Female participants of childbearing potential only (Section 8.2.5).
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety and Efficacy Assessments																	
Abbreviated physical examination						X						X					Perform when deemed necessary by the Investigator (Section 8.2.1).
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Refer to Section 8.2.2.
Safety 12-Lead ECG							X										Refer to Section 8.2.3.
Record transfusions and transfusion parameters	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Transfusions given during and between visits will be recorded (Section 8.1.5).
PNH symptomatology						X						X					Refer to Section 8.1.6.
FACIT-Fatigue						X						X					Refer to Section 8.1.3.
Chemistry including LDH						X						X					Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line (Section 8.2.4).
Hematology including coagulation						X						X					Refer to Section 8.2.4.
Urinalysis and urine chemistry						X						X					Refer to Section 8.2.4.
PNH clone size													X				Refer to Section 8.1.7.
Review safety card	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Refer to Section 8.2.6.
Breakthrough hemolysis	←Monitor continuously→																Refer to Section 8.1.4.

Table 2: Schedule of Activities: Long-term Extension Period

Period	Long-term Extension Period[a]																Notes
Study Day Visit Window (days)	**99 ± 2**	**113 ± 2**	**127 ± 2**	**141 ± 2**	**155 ± 2**	**169 ± 2**	**183 ± 2**	**197 ± 2**	**211 ± 2**	**225 ± 2**	**239 ± 2**	**253 ± 2**	**267 ± 2**	**281 ± 2**	**295 ± 2**	**309 ± 2**	
End of Week	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	
Concomitant medications	←Monitor continuously→																Refer to Section 8.10.5.
Adverse events	←Monitor continuously→																Refer to Section 8.3.
PK/PD/ADA Assessments																	
PK/PD sampling[c]						T/P						T/P					Refer to Section 8.4 and Section 8.5.
Immunogenicity (ADA)[c]						T						T					Samples will be collected predose (Section 8.8).
Administration of Study Intervention																	
Eculizumab administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Administered after all other required tests/procedures. Refer to Section 8.10.6.

[a] An ED Visit and Safety Follow-up Phone Call are required for any participant who discontinues from the study. Refer to Table 3 for assessments at the ED Visit and Safety Follow-up Phone Call.

[b] For female participants of childbearing potential, a serum pregnancy test should be performed at Screening and the last study visit, and at other timepoints as determined by the Investigator. A urine pregnancy test should be performed at all other timepoints.

[c] PK/PD and ADA trough (T) samples are to be taken within 90 minutes before eculizumab administration. Peak (P) for PK samples are to be taken within 90 minutes after completion of eculizumab administration.

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ED = early discontinuation from the study; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; P = peak; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; T = trough

Table 3: Schedule of Activities: Long-term Extension Period (Continued), Early Discontinuation, and Safety Follow-up

Period or Visit	Long-term Extension Period												Notes
Study Day Visit Window (days)	323 ± 2	337 ± 2	351 ± 2	365 ± 2	379 ± 2	393 ± 2	407 ± 2	421 ± 2	435/ EOT ± 2	449[a] ± 2	ED[b]	Safety Follow-up Phone Call[c] (8 weeks after last dose) ± 3	
End of Week	46	48	50	52	54	56	58	60	62	64			
General Assessments/Procedures													
Serum or urine pregnancy test[d]		X		X		X		X		X	X		Female participants of childbearing potential only. (Section 8.2.5).
Weight	X	X	X	X	X	X	X	X	X	X	X		
Safety and Efficacy Assessments													
Abbreviated physical examination		X						X		X	X		Perform when deemed necessary by the Investigator (Section 8.2.1).
Vital signs	X	X	X	X	X	X	X	X	X	X	X		Refer to Section 8.2.2.
Safety 12-Lead ECG				X						X	X		Refer to Section 8.2.3.
Record transfusions and transfusion parameters	X	X	X	X	X	X	X	X	X	X	X	X	Transfusions given during and between visits will be recorded (Section 8.1.5).
PNH symptomatology		X						X	X	X	X		Refer to Section 8.1.6.
FACIT-Fatigue		X						X	X	X	X		Refer to Section 8.1.3.
Chemistry including LDH		X						X		X	X		Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line (Section 8.2.4).
Hematology including coagulation		X						X		X	X		Refer to Section 8.2.4.
Urinalysis and urine chemistry		X								X	X		Refer to Section 8.2.4.

Table 3: Schedule of Activities: Long-term Extension Period (Continued), Early Discontinuation, and Safety Follow-up

Period or Visit	**Long-term Extension Period**												**Notes**
Study Day Visit Window (days)	**323 ± 2**	**337 ± 2**	**351 ± 2**	**365 ± 2**	**379 ± 2**	**393 ± 2**	**407 ± 2**	**421 ± 2**	**435/ EOT ± 2**	**449[a] ± 2**	**ED[b]**	**Safety Follow-up Phone Call[c] (8 weeks after last dose) ± 3**	
End of Week	**46**	**48**	**50**	**52**	**54**	**56**	**58**	**60**	**62**	**64**			
PNH clone size										X	X		Refer to Section 8.1.7.
Review safety card	X	X	X	X	X	X	X	X	X	X	X	X	Refer to Section 8.2.6.
Breakthrough hemolysis	←Monitor continuously→										X	X	Refer to Section 8.1.4.
Concomitant medications	←Monitor continuously→										X	X	Refer to Section 8.10.5.
Adverse events	←Monitor continuously→										X	X	Refer to Section 8.3.
PK/PD/ADA Assessments													
PK/PD sampling[e]		T/P						T/P		T	X		Refer to Section 8.4 and Section 8.5. PK/PD sample at an ED Visit may be collected at any time.
Immunogenicity (ADA)[e]		T						T		T	X		Samples will be collected predose (Section 8.8). ADA sample at an ED Visit may be collected at any time.
Administration of Study Intervention													
Eculizumab administration	X	X	X	X	X	X	X	X	X				Administered after all other required tests/procedures. Refer to Section 8.10.6.

[a] The Day 449 Visit will be the last study visit for participants who complete study treatment in the Long-term Extension and who will receive continued access to eculizumab after the study. Refer to the Safety Follow-up Phone Call (footnote c) for participants who complete study treatment but who will not receive continued access to eculizumab after the study.

[b] An ED Visit is required at the time of withdrawal for any participant who discontinues from the study. Also refer to the Safety Follow-up Phone Call (footnote c).

[c] The Safety Follow-up Phone Call is required for any participant who discontinues from the study, either during the Primary Treatment Period or Long-term Extension Period; the Safety Follow-up Phone Call will be the last study visit for participants who discontinue from the study. The Safety Follow-up Phone Call is also required for any participant who completes study treatment in either the Primary Treatment Period or Long-term Extension Period but who will not receive continued access to eculizumab after study participation; the Safety Follow-up Phone Call will be the last study visit for these participants. The Safety Follow-up Phone Call should occur 8 weeks after the last dose of eculizumab. Other means of verbal communication, such as videoconferencing, are acceptable for the Safety Follow-up Phone Call.

Table 3: Schedule of Activities: Long-term Extension Period (Continued), Early Discontinuation, and Safety Follow-up

[d] For female participants of childbearing potential, a serum pregnancy test should be performed at Screening and the last study visit, and at other timepoints as determined by the Investigator. A urine pregnancy test should be performed at all other timepoints.
[e] PK/PD and ADA trough (T) samples are to be taken within 90 minutes before eculizumab administration. Peak (P) for PK samples are to be taken within 90 minutes after completion of eculizumab administration.
Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ED = early discontinuation from the study; EOT = end of treatment; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; P = peak; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; T = trough

2. INTRODUCTION

2.1. Study Rationale

PNH is a progressive and life-threatening disease characterized by complement-mediated hemolysis, resulting in serious life-threatening complications and early mortality. Eculizumab, a recombinant humanized monoclonal antibody, specifically binds to human complement protein C5 to inhibit terminal complement activation, and prevent cell lysis caused by C5b-9, thereby improving intravascular hemolysis that is the primary clinical manifestation of PNH. Extensive clinical trials in PNH have shown that eculizumab significantly reduces hemolysis in patients with PNH, leading to an improvement in symptoms and a reduction in major health problems associated with the disease (Brodsky 2008; Hillmen 2004; Hillmen 2006; Kanakura 2011).

Eculizumab is approved in China for the treatment of PNH in children and adults since Sep 2018. The therapeutic efficacy and safety of eculizumab have been demonstrated in clinical trials for registration and supported by subsequent postmarketing evidence. This postapproval study will be conducted in adult participants with PNH being treated in China to support continued registration in China.

In addition to evaluation of safety and efficacy, the study is designed to characterize the PK, PD, and immunogenicity of eculizumab in this patient population. Drug safety information will be collected continuously to support the safety profile.

2.2. Background

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

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

The signs and symptoms of PNH can be attributed to chronic, uncontrolled complement C5 cleavage and release of C5a and C5b-9 leading to RBC hemolysis, which together result in the release of intracellular free hemoglobin and lactate dehydrogenase (LDH) into circulation; irreversible binding to and inactivation of nitric oxide (NO) by hemoglobin and inhibition of NO

synthesis; vasoconstriction and tissue-bed ischemia due to absence of vasodilatory NO, as well as possible microthrombi manifesting as abdominal pain, dysphagia, and erectile dysfunction; platelet activation; and a proinflammatory and prothrombotic state (Brodsky, 2014; Hill, 2013). A substantial proportion of patients with PNH experience renal dysfunction and pulmonary hypertension (Hill, 2012; Hill, 2013; Hillmen, 2010). Patients also experience venous or arterial thrombosis in diverse sites, including the abdomen or central nervous system (Brodsky, 2014).

Eculizumab is a humanized monoclonal antibody that specifically binds to the complement protein C5 with high affinity. It has no known off-target interactions with other proteins in vitro or in vivo. In addition, eculizumab is predicted to be effectorless, having no detectable binding to complement C1q or most Fcγ receptors (FcγR I, IIb/c IIIa, IIIb) and more than 10-fold weaker binding than an IgG1 isotype to FcγR IIa. These attributes underlie the established safety and therapeutic efficacy profile of eculizumab demonstrated in 3 pivotal Phase 3 clinical studies and supported by subsequent postmarketing experience in the treatment of PNH.

A detailed description of the chemistry, pharmacology, and toxicology data available for eculizumab is provided in the Investigator Brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of eculizumab may be found in the Soliris Package Insert.

2.3.1. Risk Assessment

Table 4: Risk Assessment

Identified and Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Identified Risks		
Meningococcal infection	The use of eculizumab is known to increase the patient's susceptibility to *Neisseria meningitidis* infection.	Participants must be vaccinated against all available serotypes of *N meningitidis* (A, C, Y, W 135, and B if available). Prophylactic antibiotics will be required for participants (if initiated on eculizumab less than 2 weeks after the start of vaccination series). 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 (Schedule of Activities, Section 1.3.

Table 4: Risk Assessment

Identified and Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infusion-related reaction	As with all therapeutic proteins, administration of eculizumab may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. Most infusion reactions that occurred in patients receiving eculizumab were nonserious and did not required discontinuation of eculizumab.	Participants with known hypersensitivity to eculizumab, murine proteins, or to any of the excipients will be excluded. Treatment with eculizumab will be discontinued in participants who experience serious hypersensitivity reactions (see Section 7).
Potential Risks		
Immunogenicity	Therapeutic proteins, including humanized monoclonal antibodies like eculizumab, may be associated with immunogenicity responses. Infrequent antibody responses have been detected in eculizumab-treated patients across all clinical studies. In paroxysmal nocturnal hemoglobinuria placebo-controlled studies, low antibody responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%).	Presence of antidrug antibodies will be assessed. Blood samples will be collected to test for presence and titer of antidrug antibodies to eculizumab in serum prior to study intervention administration as indicated in the Schedule of Activities (Section 1.3).
Serious intravascular hemolysis	A participant who discontinues treatment with eculizumab should be closely monitored for signs and symptoms of serious intravascular hemolysis described in Section 7.1.	If serious hemolysis occurs after eculizumab discontinuation, consider the following procedures/treatments: blood transfusion (packed red blood cells [RBCs]) or exchange transfusion if the PNH RBCs are > 50% of the total RCs by flow cytometry; anticoagulants; corticosteroids; or reinstitution of eculizumab.

2.3.1.1. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of this original protocol. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19 (see Section 10.7).

2.3.2. Benefit Assessment

Eculizumab is a recombinant, humanized monoclonal antibody that binds to complement protein C5 and delivers rapid, sustained, and specific inhibition of C5 activation and the terminal complement cascade.

The safety and efficacy of eculizumab in patients with PNH with hemolysis were assessed in a randomized, double-blind, placebo-controlled, 26-week study, a single arm 52-week study, and a long-term extension study. Hemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH RBCs was monitored by flow cytometry. A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBC transfusion and less fatigue. The efficacy and safety of eculizumab is further supported by more than 10 years of postmarketing experience in the treatment of PNH.

2.3.3. Overall Benefit: Risk Conclusion

Eculizumab has a cumulative patient-year exposure of 62341 at the time of this original protocol and has been well tolerated. Considering the measures taken to minimize risk to participants who will take part in this study, the potential risks identified in association with eculizumab are justified by the anticipated benefits that may be afforded to participants with PNH.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Mapping of objectives to estimands and endpoints is provided in Table 5.

Table 5: Mapping of Objectives to Estimands and Endpoints

Objectives	Estimands and Endpoints
Primary	
To assess efficacy of eculizumab in participants with PNH	• Population: Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Percentage change from Baseline in LDH at Week 12 (Section 3.1). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will not be used. • Summary measure: Mean percent change from Baseline in LDH at Week 12.
Secondary	
To assess the safety and tolerability of eculizumab in participants with PNH	• Population: Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Incidence of TEAEs and SAEs. • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be included. • Summary measure: Number and percentage of participants with TEAEs and SAEs and number of events by System Organ Class and Preferred Term

Table 5: Mapping of Objectives to Estimands and Endpoints

Objectives	Estimands and Endpoints
To characterize the pharmacokinetics of eculizumab in participants with PNH	• Population: Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Serum eculizumab concentrations over time (Section 3.1). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Mean serum eculizumab concentrations at all scheduled visits.
To characterize the pharmacodynamics of eculizumab in participants with PNH	• Population: Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Changes in serum free and total C5 concentrations from Baseline over time (Section 3.1). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Mean changes in serum free and total C5 concentrations at all scheduled visits.
To characterize the immunogenicity of eculizumab in participants with PNH	• Population: Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: ADA response category. • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Proportion of treatment-emergent ADA positive participants.

Table 5: Mapping of Objectives to Estimands and Endpoints

Objectives	Estimands and Endpoints
Additional Secondary	
To evaluate the efficacy of eculizumab in participants with PNH by additional measures	• Change from Baseline in participant-reported fatigue, assessed via Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at Week 12. Variable: Change from Baseline in FACIT-Fatigue score at Week 12 Treatment: Eculizumab ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. Summary measure: Mean change from Baseline in FACIT-Fatigue at Week 12.
	• Proportion of participants with breakthrough hemolysis during the Primary Treatment Period. Variable: Breakthrough hemolysis during the Primary Treatment Period Treatment: Eculizumab ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. Summary measure: Proportion of participants with breakthrough hemolysis during the Primary Treatment Period.
	Number (%) of participants achieving LDH normalization at Week 12. Variable: LDH normalization response at Week 12 Treatment: Eculizumab ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. Summary measure: Proportion of participants achieving LDH normalization at Week 12.

Table 5: Mapping of Objectives to Estimands and Endpoints

Objectives	Estimands and Endpoints
	• Proportion of participants achieving transfusion avoidance during the Primary Treatment Period. Variable: Transfusion avoidance during the Primary Treatment Period. Treatment: Eculizumab ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. Summary measure: Proportion of participants achieving transfusion avoidance during the Primary Treatment Period.
	• Number (%) of participants achieving LDH ≤ 1.5 × ULN at Week 12 Variable: LDH ≤ 1.5 × ULN at Week 12 ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. Summary measure: Proportion of participants with LDH ≤ 1.5 ULN at Week 12
To characterize the safety profile of eculizumab in participants with PNH by additional safety measures	• Changes from Baseline in vital signs and laboratory parameters at all scheduled visits.

Abbreviations: ADA = antidrug antibody; C5 = complement component 5; FACIT = Functional Assessment of Chronic Illness Therapy; FAS = Full Analysis Set; ICE = intercurrent event; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; SAE = serious adverse event; TEAE = treatment-emergent adverse event; ULN = upper limit of normal

3.1. Primary Estimand

The primary objective of the study is to assess the efficacy of eculizumab characterized by the reduction in hemolysis as evaluated by percentage change from Baseline in LDH at Week 12.

The estimand corresponding to the primary objective is defined as follows:

The percent change from Baseline to Week 12 in LDH without premature discontinuation of study intervention treatment or the initiation of disallowed therapy of medicine. Population for this analysis includes Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. For main analysis, a hypothetical strategy will be used to handle intercurrent events where all LDH measurement after the premature

discontinuation of study intervention and initiation of disallowed therapy or medicine will be excluded (refer ICH E9 [R1] 2017, page 18).

3.2. Secondary Estimands

Secondary objectives of the study are to characterize the safety and tolerability of eculizumab, characterize the PK and PD of eculizumab, and characterize the immunogenicity of eculizumab in participants with PNH in China during the entire study period.

The estimands corresponding to these secondary objectives are as follows. Populations for analysis are Chinese participants with PNH who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria.

- Number and percentage of participants in the Safety Set with treatment-emergent adverse event (TEAEs) and serious adverse events (SAEs) and number of events.
- Mean serum eculizumab concentration at all scheduled visits.
- Mean changes in serum free and total C5 concentrations at all scheduled visits.
- Proportion of treatment-emergent ADA positive participants.

Additional secondary objectives are presented in Table 5. For details of estimands, refer to the SAP.

3.3. Tertiary/Exploratory Estimands

Not applicable.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3b, single-arm, open-label, multicenter study to evaluate the efficacy, safety, PK, PD, and immunogenicity of eculizumab in adult participants with PNH in China who previously have not been treated with complement inhibitors. Approximately 25 eligible participants in China will be enrolled.

The study consists of 4 periods: Screening Period, Primary Treatment Period, Long-term Extension Period, and Safety Follow-up Period (phone call). The Safety Follow-up Period will be required only for participants who discontinue eculizumab treatment during the Primary Treatment Period or Long-term Extension Period, or for participants who will not receive continued access to eculizumab after completing study treatment. The study schematic is provided in Section 1.2.

After providing informed consent, participants will be screened for eligibility for the study during the 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 eculizumab will receive treatment with appropriate prophylactic antibiotics until 2 weeks after the vaccination.

During the 12-week Primary Treatment Period, all participants will receive eculizumab 600 mg IV weekly on Day 1, Day 8, Day 15, and Day 22 and 900 mg IV every 2 weeks starting at Day 29. Participants will be required to complete all study visits in the Primary Treatment Period to be eligible for the Long-term Extension Period. During the Long-term Extension Period, all participants will continue to receive eculizumab for an additional 52 weeks.

Participants who discontinue eculizumab 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 8 weeks after the last dose.

Participants who will not receive continued access to eculizumab after completing study treatment (see Section 6.7) will also have a Safety Follow-up Phone Call 8 weeks after the last dose.

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

4.2. Scientific Rationale for Study Design

4.2.1. Single Arm, Open-label Design

This study is designed to assess the efficacy and safety of eculizumab in adult participants with PNH in China. The safety and efficacy of eculizumab to reduce hemolysis in patients with PNH has been demonstrated in a global 26-week placebo-controlled study, 52-week single-arm study, and a long-term extension study. Eculizumab is currently the standard of care for PNH, and a

single-arm study will provide sufficient data to support continued treatment with eculizumab in this patient population.

4.2.2. Rationale for Selected Endpoints

Data support LDH as a reliable, objective, and direct measure of intravascular hemolysis in patients with PNH and is considered by experts as the best measure of complement-mediated hemolysis, the hallmark of PNH disease activity (Canalejo, 2014; Dale, 1972; Parker, 2006). Results from 3 eculizumab clinical studies showed that LDH concentrations remained markedly elevated and unchanged in untreated patients, while eculizumab-treated patients had immediate reductions in LDH concentrations (Soliris® product labeling). This reduction mirrored a rapid reduction in symptoms (Brodsky 2008; Hillmen, 2007).

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

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 12. In previous studies, the reduction of intravascular hemolysis as measured by LDH occurred as soon as 1 week after the first eculizumab dose, and the reduction was sustained during the treatment period. A Primary Treatment Period of 12 weeks is sufficient to reach the nadir of LDH reduction.

4.3. Justification for Dose

The dosages of eculizumab intended for administration in this study are the approved dosages and have been well established in global pivotal Phase 3 studies. Full details are available in the eculizumab Package Insert.

4.4. End of Study Definition

A participant is considered to have completed the Primary Treatment Period if the participant has completed the Day 85 (Week 12) Visit shown in the Schedule of Activities (SoA; Section 1.3). A participant is considered to have completed the Long-term Extension Period if the participant completes the Day 449 (Week 64) Visit shown in the SoA or transitions to receive continued access to eculizumab during the Long-term Extension Period.

A participant is considered to early terminate from the study if the participant is discontinued from the study during the Primary Treatment Period. A participant who enters the Long-term Extension Period is considered to early terminate from the Long-term Extension Period if the participant discontinues from the study during the Long-term Extension Period and will not receive continued access to eculizumab after study participation.

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

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. Must be ≥ 18 years of age at the time of signing the informed consent form (ICF).

Type of Patient and Disease Characteristics

2. Documented diagnosis of PNH, confirmed by flow cytometry evaluation of white blood cells and RBCs, with granulocyte or monocyte clone size of ≥ 10% at Screening.
3. LDH level ≥ 1.5 × the upper limit of normal (ULN) at Screening (central laboratory test result).
4. To reduce the risk of meningococcal infection (*N meningitidis*), all participants must be vaccinated against *N meningitidis* if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer. Participants must be vaccinated at least 2 weeks prior to receiving the first dose of eculizumab or be vaccinated and receive treatment with appropriate prophylactic antibiotics until 2 weeks after the vaccination.

Sex

5. Male and/or female.
6. Female participants of childbearing potential and male participants must follow protocol-specified contraception guidance as described in Section 10.5.

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. History of *N meningitidis* infection or unresolved meningococcal disease.
2. Active systemic bacterial, viral, or fungal infection within 7 days prior to Screening.
3. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study intervention administration on Day 1.
4. 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.

5. History of or ongoing major cardiac, pulmonary, renal, endocrine, hepatic disease (eg, active hepatitis), coexisting chronic anemia unrelated to PNH or anticipated need for major surgery within 6 months of study entry, that in the opinion of the Investigator or Alexion, precludes the participant's participation in an investigational clinical study.

Prior/Concomitant Therapy

6. Has received eculizumab or other complement inhibitor treatment previously.
7. History of hematopoietic stem cell transplantation.
8. 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

9. Has participated in any other investigational drug study or was exposed to an investigational drug or device within 28 days or 5 half-lives (whichever is longer) of Screening.

Diagnostic Assessments

10. Absolute neutrophil count ≤ 500/μL at Screening.
11. Platelet count < 30000/mm^3 at Screening.

Other Exclusions

12. Hypersensitivity to murine proteins or to one of the excipients of eculizumab.
13. Pregnant, breastfeeding, or intending to conceive during the course of the study.
14. Any medical condition that, in the opinion of the Investigator, might interfere with the participant's participation in the study, poses an added risk for the participant, or confounds the assessment of the participant.

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials 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 based on discussion and agreement between the Investigator and the Medical Monitor.

6. STUDY INTERVENTION

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

6.1. Study Intervention Administered

In this study, participants will receive open-label eculizumab during the Primary Treatment Period and Long-term Extension Period. Specific details of the study intervention are provided in Table 6.

Table 6: Study Intervention

Study Intervention Name	Eculizumab
Type	Monoclonal antibody
Dose Formulation	Sterile liquid
Unit Dose Strength(s)	300 mg/30 mL (10 mg/mL) as a clear, colorless solution in a single-dose vial
Dosage Level(s)	600 mg once a week on Day 1, Day 8, Day 15, and Day 22, and 900 mg every 2 weeks from Day 29 to Day 435
Route of Administration	Intravenous infusion
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by Alexion or contracted manufacturing organization
Packaging and Labeling	Eculizumab will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Eculizumab will be supplied in kits and labeled as required per country requirement.

Abbreviations: IMP = investigational medicinal product; NIMP = noninvestigational medicinal product

6.1.1. Study Intervention Packaging and Labeling

Study intervention will be labeled according to the country's regulatory requirements. At a minimum, the container will be labeled with:

- The protocol number
- Lot number/expiry date
- Alexion name and address
- Instructions for use and storage

6.2. Preparation/Handling/Storage/Accountability

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

Prior to administration, the study intervention solution should be visually inspected for particulate matter and discoloration. The study intervention solution should be clear and colorless.

Infusions of study intervention should be prepared using aseptic technique.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any 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.
4. Further guidance regarding preparation, handling, storage, and accountability and information for the final disposition of unused study intervention is provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. All participants, site personnel, and Alexion staff will be unblinded to participant treatment.

6.4. 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 electronic case report form (eCRF).

6.5. 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 should be contacted with 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 packed RBCs 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.

6.5.1. Allowed Medicine and Therapy

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

- Erythropoietin, if the participant has been receiving a stable dose for at least 8 weeks before Screening.
- Immunosuppressants, if the participant has been receiving a stable dose for at least 8 weeks before Screening.
- Corticosteroids, if the participant has been receiving a stable dose for at least 4 weeks before Screening.
- Vitamin K antagonists (eg, warfarin), if the participant has had a stable international normalized ratio (INR) level (per Investigator's discretion) for at least 4 weeks before Screening.

- Iron supplements or folic acid, if the participant has been receiving a stable dose for at least 4 weeks before Screening.

Adjustments in the frequency or dose level in any of the above medications can be made if the 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.

6.5.2. Disallowed Medicine and Therapy

- Whole blood
- Traditional Chinese herbal preparations that in the opinion of the Investigator or Alexion might confound the assessment of the participant
- Chemotherapy
- Any other investigational drug or device

6.5.3. Vaccination

The use of eculizumab increases a participant's susceptibility to meningococcal infection (*N meningitidis*). To reduce the risk of meningococcal infection, all participants must be vaccinated against meningococcal infections if not already vaccinated within the period of active coverage specified by the vaccine manufacturer.

- Participants who initiate study intervention less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
- Participants must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, eculizumab).
- Vaccines against serotypes A, C, Y, W135 are required, plus B where available, to prevent common pathogenic meningococcal serotypes.
- 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).

6.6. Dose Modification

Dose modification is not permitted.

6.7. Intervention After the End of the Study

Participants who complete the study and show clinical benefit will be offered continued access to eculizumab as permitted by regulations until eculizumab is commercially available.

6.8. Treatment of Overdose

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.

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

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

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

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study intervention. If the study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for all assessments at the scheduled visits described in the SoA (Section 1.3).

Participants must be considered for discontinuation from study intervention if any of the following occur during the study:

- Serious hypersensitivity reaction
- Pregnancy or planned pregnancy (Section 10.5.3)
- Severe uncontrolled infection
- Use of disallowed medication (defined in Section 6.5.2)
- Alexion or Investigator deems it necessary for the participant
- Other safety criteria (eg, AE, PK criteria)

A participant who discontinues treatment with eculizumab should be closely monitored for signs and symptoms of serious intravascular hemolysis. Serious hemolysis is identified by serum LDH levels greater than the pretreatment level, along with any of the following: greater than 25% absolute decrease in PNH clone size (in the absence of dilution due to transfusion) in 1 week or less; a hemoglobin level < 5 g/dL or a decrease of > 4 g/dL in 1 week or less; angina; change in mental status; a 50% increase in serum creatinine level; or thrombosis. Monitor any participant who discontinues eculizumab for at least 8 weeks to detect serious hemolysis and other reactions.

Data collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed are provided in the SoA (Section 1.3).

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 Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and eCRF.
- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This activity is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an ED Visit should be conducted, as shown in the SoA (Section 1.3). Refer to the 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.

  - The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant 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 to reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- See Section 10.2 for the list of clinical laboratory tests.

8.1. Efficacy Assessments

8.1.1. Hemolysis

The primary efficacy endpoint is the percent change from Baseline in LDH at Week 12.

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

8.1.2. Other Disease-related Laboratory Parameters

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

The following disease-related laboratory parameters will be measured during the study (refer to Section 8.4 for PK assessments):

- 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

8.1.3. FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale is a collection of quality of life (QoL) questionnaires pertaining to the management of fatigue symptoms due to a chronic illness. The FACIT-Fatigue 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.

8.1.4. 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.

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

If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD samples 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, and PD samples.

8.1.5. 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 CRF 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 CRF.

8.1.6. 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).

8.1.7. PNH Clone Size

White blood cell (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. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of general appearance; skin; head, ear, eye, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limb; central nervous system; and musculoskeletal system. Height and weight will also be measured and recorded.

- An abbreviated physical examination will include a body-system relevant examination based on Investigator judgment and participant symptoms.
- Height will be measured recorded at Screening for all participants. Weight will be measured and recorded at every visit for all participants.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Body temperature (°C or °F), pulse rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg) will be assessed.
- Blood pressure and pulse measurements will be assessed seated with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure 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.
- On dosing days, vital sign measurements will be taken before study intervention administration.

8.2.3. Electrocardiograms

- Single 12-lead electrocardiogram (ECG) will be conducted as outlined in the SoA (Section 1.3) to obtain heart rate, 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 CRF. 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 protocol.

8.2.4. Clinical Safety Laboratory Assessments

- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the final dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be collected in accordance with the Laboratory Manual and the SoA (Section 1.3).
- Laboratory assessments performed at the institution's local laboratory that require a change in participant management or are considered clinically significant by the Investigator must be recorded in the AE or SAE eCRF. When possible, parameter value outside of the reference range should be entered in a free-text field.

8.2.5. Pregnancy

- Pregnancy data from female participants of childbearing potential and female spouses/partners of male participants will be collected from the first dose of study intervention and at the timepoints specified in the SoA (Section 1.3). Any female participant who becomes pregnant during the study should be considered for discontinuation from the study intervention and withdrawn from the study. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.5.3.

8.2.6. Participant Safety Card

Before the first dose of study intervention, a Participant Safety Card will be provided to participants to carry with them at all times until 8 weeks 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 that the participant has the Participant Safety Card.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

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

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

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

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

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

All SAEs will be recorded and reported to Alexion immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of the date the investigational site became aware of the event.

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow-up on each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs and Other Events

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.
- Alexion is required to submit individual suspected unexpected serious adverse reaction (SUSAR) reports (defined in Section 10.3.2) in the format of MedWatch 3500 or Council for International Organizations of Medical Sciences (CIOMS) I Form to health authorities and Investigators as required.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will

review and then file it along with the Investigator's Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

- An ADR is an AE suspected to be causally related to the investigational medicinal product (IMP). All nonserious ADRs (ie, AEs suspected to be causally related to Alexion IMP) should be reported to Alexion Global Patient Safety (GPS). If any nonserious ADR occurs during the study, the Investigator should inform Alexion GPS within 5 calendar days of awareness. The Investigator or other site personnel should record the AE in the appropriate eCRF in the EDC system, complete the paper SAE/AE Report Form, and transmit the completed form to Alexion GPS via email (clinicalSAE@alexion.com) or fax (+1-203-439-9347) (fax number is provided as a back-up/contingency in case the site is unable to send the report via email).

8.3.5. Adverse Events of Special Interest

Meningococcal infections are considered to be adverse events of special interest (AESIs).

8.3.6. Medication Error, Drug Abuse, and Drug Misuse

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

8.3.6.1. 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.

8.3.6.2. 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 auxiliary medicinal product (AxMP) that either causes harm to the participant or has the potential to cause harm to the participant.

8.3.6.3. Drug Abuse

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

8.3.6.4. 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. Pharmacokinetics

- Blood samples will be collected for measurement of serum concentrations of eculizumab as specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples will be provided in a laboratory manual by Alexion. The actual date and time (24-hour clock time) of each sample collection will be recorded. In the event of breakthrough hemolysis, a serum sample for PK analysis will be collected at any time that day.
- Samples will be used to evaluate the PK properties of eculizumab. PK samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Full details of the analytical method used will be described in a separate bioanalytical report.

For storage, handling, reuse, and destruction of biological samples, refer to the laboratory manual, as applicable. PK samples collected in China will be stored and disposed of according to local laws and regulations. PK samples collected in China will be retained for a maximum 6 months of Bioanalytical Report publication.

8.5. Pharmacodynamics

- Serum samples for measurement of free and total C5 as specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample collection will be recorded. In the event of breakthrough hemolysis, a serum sample for PD analysis will be collected at any time that day.
- Samples will be used to evaluate the PD of eculizumab. PD samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Full details of the analytical method used will be described in a separate bioanalytical report.

For storage, handling, reuse, and destruction of biological samples, refer to the laboratory manual, as applicable. PD samples collected in China will be stored and disposed of according to local laws and regulations. PD samples collected in China will be retained for a maximum 6 months of Bioanalytical Report publication.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Serum samples for ADA and neutralizing antibody (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 deviation capture for immunogenicity samples follows that specified for PK sample collection (Section 8.4).

For storage, handling, reuse, and destruction of biological samples, refer to the laboratory manual, as applicable. Immunogenicity samples collected from participants in China will be retained for a maximum 1 year of the final CSR.

8.8.1. ADA Variables

ADA variables include ADA response category incidence and titer over the duration of the study as follows. ADA response category definitions and titer thresholds will be provided in the Statistical Analysis Plan (SAP).

ADA response categories

- ADA negative
- ADA positive

Participants that are ADA positive will be categorized as follows:

- Pre-existing immunoreactivity
- Treatment-emergent ADA responses
  - Persistent treatment-emergent responses
  - Indeterminant treatment-emergent responses
  - Transient treatment-emergent responses
- Treatment-boosted ADA responses
- NAb positive

8.9. Health Economics Data and/or Medical Resource Utilization

Medical resource utilization and/or health economics data will not be collected during this study.

8.10. Other Assessments and Procedures

8.10.1. Informed Consent

The Investigator or qualified designee must obtain a signed and dated ICF from each participant prior to conducting any study procedures. All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures.

8.10.2. Demographics

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

8.10.3. Inclusion and 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.

8.10.4. Medical History and PNH History

The participant's PNH medical history, including onset of first PNH symptom, and date of diagnosis, will be documented at the Screening Visit. The participant's medical history, including prior and concomitant conditions/disorders, will be recorded at the Screening Visit. Concomitant indications or disorders may include anemia, aplastic anemia, myelodysplastic syndrome, hematuria or hemoglobinuria, renal failure, and other, specify. 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 per Section 8.10.5.

8.10.5. Prior and Concomitant Medications

Prior Medications

Prior medications (including vitamins, herbal preparations, and those discussed in the exclusion criteria [Section 5.2]), vaccines, and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) that the participant takes or undergoes within 28 days before the start of Screening or during the Screening Period before the first dose of eculizumab, as well as any meningococcal vaccine administered, will be recorded in the participant's eCRF. Additionally, all medications or therapies ever used for relapse prevention or acute treatment of PNH before the first dose of eculizumab must be collected.

Concomitant Medications

Use of concomitant medications and nondrug therapies (Section 6.5) will be evaluated during the study. At each visit (specified in the SoA [Section 1.3]), participants should be questioned about any new medication or nondrug therapies or changes to concomitant medications and nondrug therapies since the last visit. Concomitant medications and nondrug therapies should be recorded in the source documents and the participant's eCRF.

8.10.6. Study Intervention Administration

This section describes the dosage regimen of study intervention. At the scheduled dosing visits (Section 1.3), study intervention administration should be performed after all other tests and procedures have been completed, excluding the postdose blood sampling for PK, free and total C5.

Refer to Section 6 for additional information about study intervention including preparation, handling, storage, and accountability. For detailed instructions, refer to the Pharmacy Manual.

Eculizumab is supplied for clinical studies as a sterile, preservative-free 10 mg/mL solution in single-use vials and designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via IV infusion. **Eculizumab must NOT be administered as an IV push or bolus injection.**

Eculizumab will be administered according to the following regimens:

- Eculizumab 600 mg or 900 mg will be administered by IV infusion over approximately 35 minutes (range of 25 to 45 minutes) according to the following regimen:
  - Induction dosing: 600 mg once a week (every 7 ± 1 days) × 4 doses (Day 1, Day 8, Day 15, and Day 22).
  - Maintenance dosing: 900 mg every 2 weeks (every 14 ± 2 days) starting at Day 29.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal statistical hypotheses will be tested.

9.2. Sample Size Determination

Approximately 25 participants will be enrolled.

The total sample size of 25 participants was chosen to provide approximately 90% power to detect a statistically significant treatment effect on the percentage change in LDH at Week 12, assuming a 20% dropout rate. The sample size calculations assume an average percent decrease in LDH at Week 12 of 30%, with an associated standard deviation of 40%. This is based on a 2-sided, paired t-test, with type I error set at 5%.

9.3. Populations for Analyses

Efficacy analyses will be performed on the Full Analysis Set (FAS). Safety analyses will be performed on the Safety Set. PK analyses will be performed on the PK Analysis Set. The populations are defined in Table 7.

Table 7: Populations for Analyses

Population	Description
Full Analysis Set	All participants who receive at least 1 dose of study intervention and have at least 1 efficacy assessment post first dose.
Safety Set	All participants who receive at least 1 dose of study intervention.
Pharmacokinetic Analysis Set	All participants who receive at least 1 dose of study intervention and who have evaluable pharmacokinetic data.
Pharmacodynamic Analysis Set	All participants who receive at least 1◦dose of study intervention and who have evaluable pharmacodynamic data.

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate SAP before database lock and analysis, including procedures for accounting for missing data. Any change to the data analysis methods described in the protocol will require an amendment only if it changes the primary or secondary objectives or the study conduct. Any other change to the data analysis methods described in the protocol or SAP, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data may be conducted as deemed appropriate.

All data collected will be presented using summary tables, figures, and data listings. All data, as well as any outcomes derived from the data, will be presented in detailed data listings. Graphical displays may also be provided, when appropriate. Continuous variables will be summarized using descriptive statistics, including the number of observations, and mean, standard deviation,

median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and the percentage of participants.

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

9.4.1. Efficacy Analyses

9.4.1.1. Analyses of Primary Efficacy Estimand and/or Endpoint

The primary endpoint is reduction in hemolysis as evaluated by percentage change from Baseline in LDH at Week 12. Mean percentage change from Baseline in LDH will be analyzed using restricted maximum likelihood (REML)-based repeated measures approach to test whether changes and percent changes differ from zero. Analyses will include the fixed, categorical effects of visit, and the continuous, fixed covariates of baseline value using mixed model for repeated measures (MMRM). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The estimation of mean percent change from Baseline at each defined visit alongside with 95% confidence intervals and p-values will be provided.

9.4.1.2. Analyses of Secondary Efficacy Estimand(s) and/or Endpoint(s)

Change in FACIT-Fatigue from Baseline to at Week 12 will be analyzed using a mixed model for repeated measures (MMRM) with the fixed effects of indicators of transfusion history, LDH Baseline, study visit and fixed covariates of Baseline FACIT-Fatigue. The observed proportions of participants who achieved LDH normalization and those who achieved LDH $\leq 1.5 \times$ ULN will be summarized at Week 12 along with 95% two-sided Clopper-Pearson exact CIs. The observed proportions of participants with breakthrough hemolysis and those who achieved Transfusion Avoidance during the Primary Treatment Period will be summarized along with 95% two-sided Clopper-Pearson exact CIs. Transfusion Avoidance is defined as remaining transfusion free (ie, have not received any transfusion) and not requiring transfusion as per protocol-specified guidelines (Section 8.1.5). Details of the analyses will be provided in the SAP.

9.4.1.3. Multiplicity Adjustment

There is no multiplicity adjustment in this study. All p-values for the secondary efficacy endpoints are nominal and descriptive.

9.4.1.4. Analyses of Exploratory Estimand(s) and/or Endpoint(s)

Not applicable.

9.4.2. Safety Analyses

All safety analyses will be made on the Safety Set.

The following definitions will be used for AEs:

- Pretreatment AEs: Any AE that starts after providing informed consent but before the first infusion of study intervention.
- TEAE: Any AE that starts during or after the first infusion of study intervention.

The incidence of TEAEs, TEAEs leading to withdrawal from the study, TEAEs leading to study intervention discontinuation, study intervention-related TEAEs, TEAEs during study intervention administration, severe TEAEs, treatment-emergent serious adverse events (TESAEs), and AESI will be summarized.

For the Primary Treatment Period, TEAEs through Day 99 (Week 12) will be tabulated and presented separately. For the Long-term Extension Period, TEAEs will be summarized starting from Week 12 through the end of study (EOS). TEAEs will also be summarized for the Overall Period.

All AEs will be coded using MedDRA version 24.0 or higher and will be summarized by System Organ Class and Preferred Term.

Vital signs, hematology, blood chemistry and urinalysis results will be summarized (actual values as well as change from Baseline) by visit using summary statistics (n, mean, median, standard deviation, minimum and maximum) for continuous variables and shift tables for categorical variables.

9.4.3. Other Analyses

Other analyses will be described in the SAP.

9.4.3.1. PK/PD

PK and PD analyses will be described in the SAP (or PK analysis plan, as applicable), and finalized before database lock. Individual serum eculizumab (PK), free and total C5 concentration-time data (PD) will be listed, plotted, and summarized with descriptive statistics, with mean concentration-time data plotted.

The PK data in this study might be pooled with other studies to conduct a population PK modelling analyses, which may be described in a separate SAP. The potential impact of participant characteristics (covariates) on PK may be evaluated. The relationship between PK exposure and response may be explored. The potential results of population PK and exposure-response analysis may be reported in a separate report.

9.4.3.2. Immunogenicity

ADA positive samples will be further characterized for antibody titer and presence of neutralizing antibodies. Samples may be stored for a maximum 1 year of the final CSR (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.

All ADA analyses will be performed on the Safety Set using the ADA variables included in Section 8.8.1. Additional details will be provided in the SAP.

9.5. Interim Analyses

An interim analysis, if deemed necessary, may be performed after all participants complete or withdraw early from the Primary Treatment Period.

9.6. Data Monitoring Committee

This study will not include a Data Monitoring Committee.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, substantial protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion and reviewed and approved by the IRB/IEC before the study is initiated.
  - If any of these documents require regulatory/health authority approval per local regulations, Alexion will also obtain such approval before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC and regulatory/health authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Directive 2001/20/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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 (written or electronic signature) informed consent from all study participants, or the participant's legally authorized representative, prior to performing any study-related procedures including screening assessments.
- The Investigator or designee will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent or a certified translation, if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must include a statement that signed (written or electronic) informed consent was obtained before any screening procedures were performed with a participant, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study, as applicable.
- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Original signed (written or electronic) consent forms must remain in each participant's study file and must be available for verification at any time.

Participants who are rescreened outside of the Screening window (Table 1) are required to sign a new ICF (Section 5.4).

10.1.4. Data Protection

- Participants will be assigned a unique identifier by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used in accordance with applicable data protection law, and participants must also be informed of any individuals rights they may have with regard to their personal data. Participants will be informed about how their personal study-related data will be disclosed and will be required to agree to the information contained in the informed

consent and provide consent to the processing of their personal data, if required by applicable data protection law.

- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, and inspectors from regulatory authorities.
- Alexion as a data controller has implemented privacy and security controls designed to help protect participant personal data; including information security controls, firewalls, incident detection, and secure transfer measures.
- In the event of any accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data ("breach"), the controller has implemented procedures and measures to promptly address and mitigate any risk to the data participant. In the event of a breach, the controller will notify the appropriate regulatory authorities and/or the data participant in accordance with applicable data protection law.

10.1.5. Dissemination of Clinical Study Data

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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on 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 electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
  - Remote source data verification may be employed where permitted by local regulations.

  - The scope of the source data verification will be described in detail in the Clinical Monitoring Plan.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator after study completion per local regulations or institutional policies. No records may be destroyed without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.7. Source Documents

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

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

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

10.1.8. Study and Site Start and Closure

The study start date is the date of the first signed ICF.

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

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

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

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

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

10.1.9. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12 to 18 months of the primary treatment date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.
- Primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.
  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.
- Alexion will comply with the requirements for publication of study results as defined by the Pharmaceutical Research and Manufacturers of America and the International Committee of Medical Journal Editors and per the Alexion Publication Policy. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual

site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.
- Alexion will publish Patient Lay Summaries and include participants and/or caregivers as reviewers for readability and understanding of lay person language.

10.1.10. Good Clinical Practice Compliance

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

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

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

10.2. Clinical Laboratory Tests

- The tests detailed in Table 8 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 entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Women of childbearing potential should only be enrolled after a negative serum pregnancy test. Additional pregnancy testing (urine or serum) should be performed per the timepoints specified in the SoA (Section 1.3).
- Investigators must document their review of each laboratory safety report.

Table 8: Protocol-Required Safety Laboratory Assessments

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

Abbreviations: ADA = antidrug antibody; C5 = complement component 5; HIV = human immunodeficiency virus; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; WBC = white blood cell

Investigators must document their review of each laboratory safety report.

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 participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A). • **Note**: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease [new or exacerbated] temporally associated with the use of the study intervention, whether or not considered related to the study intervention.

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

Events Not Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. (Section 10.4) • 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.

Events Not Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • "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.

10.3.2. Definition of SAE

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

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

An SAE is defined as any untoward medical occurrence that, at any dose:

threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

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

SUSARs will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable.

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

Recording of AE and/or SAE

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

Assessment of Intensity

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

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

Recording of AE and/or SAE

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

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

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Alexion via an Electronic Data Collection Tool

- All SAEs will be recorded and reported to Alexion immediately and within 24 hours of awareness.
- The primary mechanism for reporting an SAE to Alexion will be the EDC system.
- If the electronic system is unavailable or site staff is unable to process the SAE via the EDC system at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE Reporting via facsimile or email. Facsimile transmission or email may also be used in the event of electronic submission failure.
  - Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347
- The site will enter the SAE data into the EDC system as soon as it becomes available.
- When further information becomes available, the EDC should be updated immediately with the new information and an updated SAE report should be submitted to Alexion Global Drug Safety (GDS) within 24 hours of Investigator/site awareness.
- After the participant has completed the study, no new data or changes to existing data are expected to be entered in the EDC system.
  - If a site receives a report of a new SAE from a study participant which the Investigator considers to be related to the study intervention, or the site receives updated data on a previously reported SAE after the EDC system has been taken offline, then the site can report this information on a paper Contingency Form for SAE Reporting via facsimile or email.

10.3.5. 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 trial should be reported. Examples of such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as, carcinogenicity).

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

10.4. 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 (excluding Interactive Response Technology [IRT]/Randomization and Trial Supply Management [RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose [refer to Section 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 Guidance and Collection of Pregnancy Information

10.5.1. Definitions

Woman of Childbearing Potential (WOCBP)

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

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

Women in the Following Categories Are Not Considered WOCBP

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

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

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause prior to the Day 1 Visit.
        – A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement may be required. In the absence of 12 months of amenorrhea the reason for not obtaining FSH levels should be documented by the Investigator at the time of Screening.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
4. Permanent sterilization at least 6 weeks prior to the Day 1 Visit.

10.5.2. Contraception Guidance

Contraceptive use by male or female participants should be consistent with local regulations regarding the methods of contraception utilized for those participating in clinical studies. If teratogenic effects are suspected to be transferred to a fetus/embryo from a female spouse/partner of a male participant, pregnancy follow-up information will be obtained for the partner who becomes pregnant (refer to Section 10.5.3.1). In these cases, follow-up will be conducted on the pregnant partner in the same manner as a female participant who becomes pregnant during the study.

10.5.2.1. Guidance for Female Participants

Female participants of childbearing potential must have a negative serum pregnancy test as required by local regulations before the first dose of study intervention. Additional requirements for pregnancy testing during and after dosing with study intervention are indicated in the SoA (Section 1.3).

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

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

Female participants of childbearing potential must use a highly effective method of contraception, including at least 1 of the following until at least 5 months after the final dose of study intervention.

1. Intrauterine device in place for at least 6 weeks prior to first dose of study intervention.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of study intervention.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of study intervention.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of study intervention.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of study intervention.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose of study intervention). Male partner is still required to use condom during sexual intercourse.
7. Sexual abstinence for female participants:
    a. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent female participants must refrain from heterosexual intercourse for at least 5 months after the final dose of study intervention.

Other methods of contraception that are not considered as highly effective for female participants, but are acceptable birth control methods that result in a failure rate of more than 1% per year include:

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

The following methods are considered unacceptable in this study:

- Periodic abstinence (calendar, symptothermal, or post ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Female condom and male condom should not be used together

10.5.2.2. Guidance for Male Participants

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

Male participants who have had a vasectomy > 6 months prior to the first dose of study intervention must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to the first dose study intervention and those who have not had a vasectomy must use a condom and spermicide during heterosexual intercourse for at least 5 months after their final dose of study intervention.

10.5.2.2.1. Sexual Abstinence for Male Participants

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

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

Male participants must not donate sperm from the Day 1 Visit until 5 months (generally 5.5 terminal half-lives) after their final dose of study intervention.

10.5.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants from the first dose of study intervention until the Safety Follow-up Phone Call. Any female participant who becomes pregnant during the study should be

considered for discontinuation from the study intervention and withdrawn from the study. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study intervention via semen following paternal exposure. If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

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

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

10.5.3.1. Male Participants with Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate "Pregnancy/Breastfeeding Reporting and Outcome Form" and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be no longer than 3 months following the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5.3.2. Female Participants Who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The information will be recorded on the "Pregnancy/Breastfeeding Reporting and Outcome Form" and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- For all Alexion products, both in development or post approval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the

estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

10.6. 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 <u>past 7 days</u>.**

		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 <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> 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

SAMPLE - NOT FOR PATIENT USE

10.7. COVID-19 Risk Assessment

PNH can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining an investigational study with a therapeutic treatment is potentially significant. In this particular case, the fact that the study is open-label and every participant is treated with the study intervention also contributes to the potential benefit a participant may derive from partaking in the study. Given that treatment for PNH does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in participants not receiving immunosuppressants. However, there is no specific data to further inform this risk. The site Investigator will therefore balance the risk/benefit considerations in the study participant taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 9.

Table 9: Potential Risks and Mitigation Measures due to COVID-19

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

Table 9: Potential Risks and Mitigation Measures due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
	inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits or participant study discontinuations due to COVID-19).

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

10.8. Protocol Amendment History

The Protocol Amendment Summary of Changes table for the current amendment is located immediately preceding the Table of Contents.

DOCUMENT HISTORY	
Document/Type of Amendment (Global or Country specific)/Date	**Summary of Key Changes in the Amendment**
Original Protocol/30 Nov 2021	Not applicable

10.9. Abbreviations

The following abbreviations and terms are used in this study protocol.

Table 10: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AxMP	Alexion auxiliary medicinal product
C	complement component
C5b-9	terminal complement complex
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	Clinical Study Report
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation from the study
EDC	electronic data capture
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GCP	good clinical practice
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act
Hgb	hemoglobin
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	informed consent form
IEC	Independent Ethics Committee

Table 10: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
MAVE	major adverse vascular event
MMRM	mixed model for repeated measures
NAb	neutralizing antibody
NO	nitric oxide
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
QoL	quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
WOCBP	woman of childbearing potential

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