

**A Phase 3, Randomized, Open-Label, Active-Controlled
Study of ALXN1210 Versus Eculizumab in Adult Patients
With Paroxysmal Nocturnal Hemoglobinuria (PNH)
Currently Treated With Eculizumab**

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PROTOCOL ALXN1210-PNH-302

A PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY OF ALXN1210 VERSUS ECULIZUMAB IN ADULT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) CURRENTLY TREATED WITH ECULIZUMAB

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Amendment 2 (Global): 01 March 2019

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SPONSOR SIGNATURE PAGE

A PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY OF ALXN1210 VERSUS ECULIZUMAB IN ADULT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) CURRENTLY TREATED WITH ECULIZUMAB

PROTOCOL NUMBER: ALXN1210-PNH-302

PPD



Alexion Pharmaceuticals, Inc.

03-Mar-2019 | 13:30:13 EST

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ALXN1210. I have read the ALXN1210-PNH-302 study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

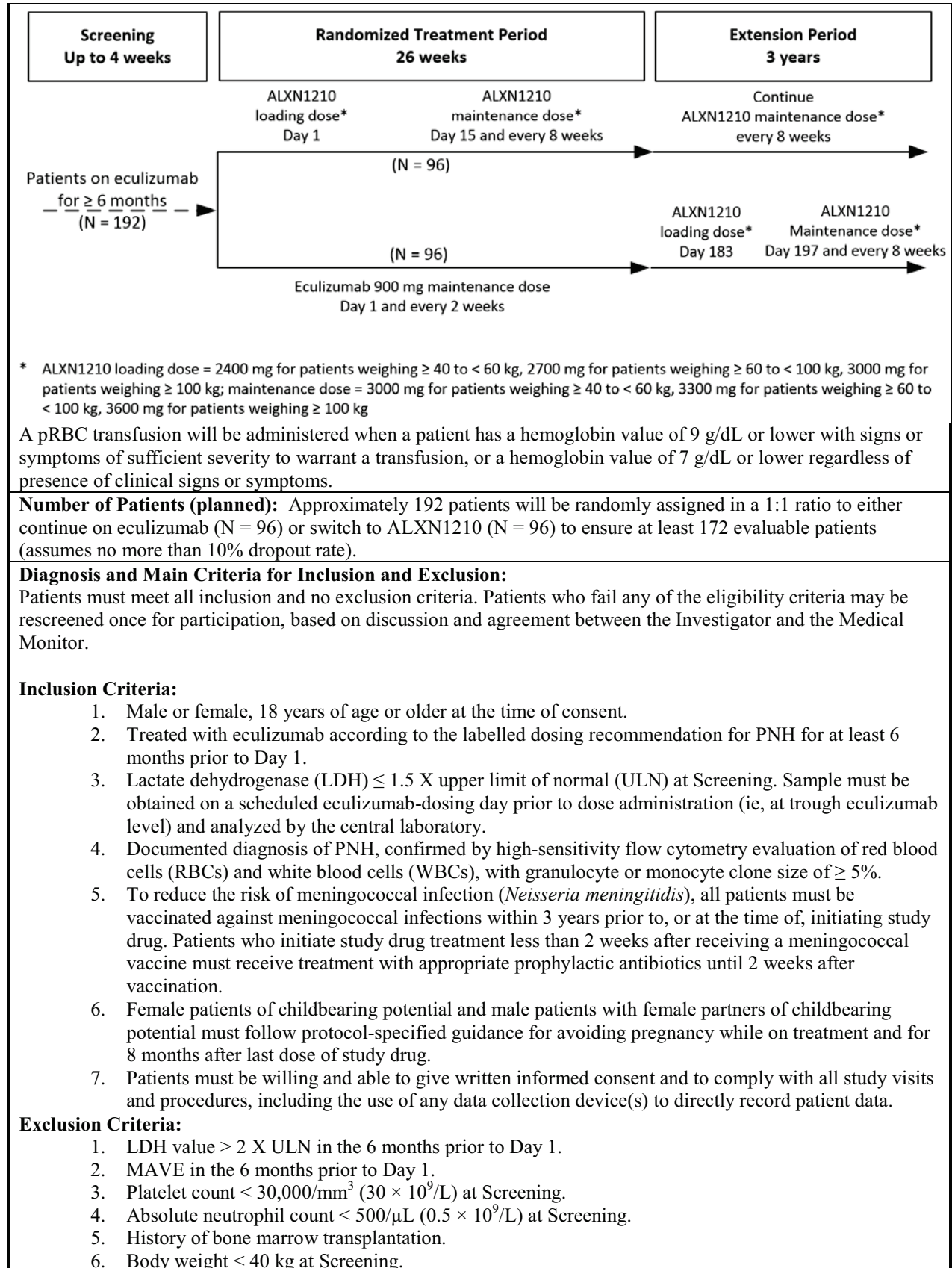
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2. SYNOPSIS

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc.	
Name of Investigational Product: ALXN1210	
Name of Active Ingredient: ALXN1210	
Title of Study: A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated With Eculizumab	
Protocol No: ALXN1210-PNH-302	EudraCT Number: 2016-002026-36
Study Center(s): Approximately 125 centers globally.	
Length of Study: Estimated date first patient randomized: Apr 2017 Estimated date last patient completed: Mar 2021	Phase of Development: 3
<p>Objectives: The primary objective is to assess the noninferiority of ALXN1210 compared to eculizumab in adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months.</p> <p>Noninferiority will be claimed if after 26 weeks of treatment the upper bound of the 95% confidence interval (CI) for the difference (ALXN1210-eculizumab) in percent change in lactate dehydrogenase level (LDH-PCHG) is less than 15%.</p>	
<p>Study Design and Methodology: This is a Phase 3, open-label, randomized, active-controlled, multicenter study to evaluate the safety and efficacy of ALXN1210 versus eculizumab administered by intravenous (IV) infusion to adult patients with PNH who have been treated with eculizumab for at least the past 6 months. The study consists of a 4-week screening period, a 26-week randomized treatment period, and an extension period of up to 3 years. Patients will be stratified into 1 of 2 groups based on their transfusion history (received a transfusion of packed red blood cells [pRBCs] within 12 months prior to Day 1, yes or no). Patients within each of the 2 groups will then be randomly assigned in a 1:1 ratio to either continue on eculizumab or switch to ALXN1210.</p> <p>Prior to randomization and within 5 days prior to study drug administration on Day 1, each patient's hemoglobin must be evaluated by either local or central laboratory. If at that time the patient's hemoglobin value meets protocol-specified transfusion guidelines, the patient must be transfused with pRBCs to a hemoglobin level above the protocol-specified transfusion threshold in order to be eligible for randomization. The patient's post-transfusion hemoglobin value should be confirmed by local or central laboratory to be above the protocol-specified transfusion threshold.</p> <p>Day 1 of study treatment will occur 2 weeks from the patient's last dose of eculizumab. Patients randomly assigned to the ALXN1210 group will receive a loading dose (see dosing table below) of ALXN1210 on Day 1, followed by maintenance doses of ALXN1210 on Day 15 and every 8 weeks (q8w) thereafter for a total of 26 weeks of treatment. Patients randomly assigned to the eculizumab group will continue to receive the approved dose of eculizumab for the treatment of PNH (900 mg every 2 weeks [q2w]) for a total of 26 weeks of study treatment.</p> <p>After completion of all assessments on Day 183, all patients will enter an extension period and receive ALXN1210 until the product is registered or approved (in accordance with country-specific regulations) or for up to 3 years, whichever occurs first. Beginning on Day 183, patients who had been randomized to the ALXN1210 treatment group will receive a maintenance dose of ALXN1210 q8w, and patients who had been randomized to the eculizumab group will receive a loading dose of ALXN1210 followed 2 weeks later and q8w thereafter by a weight-based maintenance dose of ALXN1210.</p>	



7. History of *N. meningitidis* infection.
8. History of unexplained, recurrent infection.
9. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
10. Presence of fever $\geq 38^{\circ}\text{C}$ (100.4°F) within 7 days prior to study drug administration on Day 1.
11. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer).
12. Immunized with a live-attenuated vaccine within 1 month prior to study drug administration on Day 1.
13. 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.
14. History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease (eg, active hepatitis) that, in the opinion of the Investigator or Sponsor, precludes the patient's participation in an investigational clinical trial.
15. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of randomization, coexisting chronic anemia unrelated to PNH) that would make them unlikely to tolerate the requirements of the protocol (eg, transfusion guidelines).
16. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.
17. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
18. Females who plan to become pregnant or are currently pregnant or breastfeeding.
19. Females who have a positive pregnancy test result at Screening or on Day 1.
20. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater.
21. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
22. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the patient's full participation in the study, pose any additional risk for the patient, or confound the assessment of the patient or outcome of the study.

Investigational Product, Dosage, and Mode of Administration:

ALXN1210 loading dose on Day 1 and maintenance doses on Day 15 and q8w thereafter, administered by IV infusion. Dosages are based on the patient's body weight, as shown in the table below:

Body Weight ^a	Loading Dose (Day 1)	Maintenance Dose (Days 15, 71, 127)
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

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

Reference Therapy, Dosage, and Mode of Administration:

Eculizumab 900 mg maintenance dose on Day 1 and q2w to Day 183, administered by IV infusion.

Planned Duration of Treatment: 26-week randomized treatment period followed by an extension period in which all patients will receive ALXN1210 until the product is registered or approved (in accordance with country-specific regulations) or for up to 3 years, whichever occurs first.

Endpoints:

Efficacy

Primary

Hemolysis as directly measured by LDH-PCHG from Baseline to Day 183.

Key Secondary (to be tested in a hierarchical manner)

1. Proportion of patients with breakthrough hemolysis, 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 $\geq 2 \times$ ULN
2. Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from Baseline to Day 183
 3. Transfusion avoidance (TA), defined as the proportion of patients who remain transfusion-free and do not require a transfusion as per protocol-specified guidelines from Baseline to Day 183
 4. Proportion of patients with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion from Baseline to Day 183

Other Secondary

- Total number of units of pRBCs transfused from Baseline to Day 183
- Proportion of patients with LDH in normal range at Day 183
- Change in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, from Baseline to Day 183
- Change in clinical manifestations of PNH (fatigue, hemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia, and erectile dysfunction) from Baseline to Day 183
- Proportion of patients experiencing MAVEs from Baseline to Day 183

Pharmacokinetic/Pharmacodynamic (PK/PD)

- Change in serum ALXN1210 and eculizumab concentrations over time
- Change in chicken red blood cell (cRBC) hemolytic activity over time (exploratory)
- Change in free complement component 5 (C5) concentrations over time

Safety

The safety and tolerability of ALXN1210 compared with eculizumab will be evaluated by physical examinations, vital signs, electrocardiograms (ECGs), laboratory assessments, and incidence of adverse events (AEs) and serious adverse events (SAEs). The proportion of patients who develop antidrug antibodies (ADAs) will also be assessed through the end of the study.

Statistical methods:

General: A clinical study report (CSR) will be produced based on efficacy, safety, PK, and PD data collected through the end of the 26-week randomized treatment period (Day 183). A final CSR to summarize long-term efficacy, safety, PK, and PD parameters will be produced at study completion.

Efficacy: Efficacy analyses will be performed on the Full Analysis Set (FAS). The primary efficacy endpoint analysis, as well as key secondary endpoint analyses, will also be performed on the Per Protocol (PP) set. The FAS is the primary population for all efficacy analyses. The FAS will include all patients who receive at least 1 dose of ALXN1210 or eculizumab.

The PP set will consist of FAS patients who meet all of the following criteria:

- Missed no doses of ALXN1210 or no more than 1 dose of eculizumab during the 26-week randomized treatment period.
- Met inclusion criteria #2, 3, and 4
- Did not meet exclusion criteria #1, 2, 3, 4, or 5
- Never received the wrong randomized treatment
- Followed the protocol-specified transfusion guidelines

Primary Efficacy Analyses

The primary efficacy endpoint is the difference between treatment arms in LDH-PCHG from Baseline to Day 183. Baseline is defined as the average of all assessments analyzed by the central laboratory prior to first study drug administration.

The percentage change in LDH will be analyzed using a mixed model for repeated measures (MMRM) with the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction as well as the continuous, fixed covariate of baseline LDH and the stratification randomization indicator of pRBC transfusion history (yes/no within 12 months prior to Day 1). The Kenward-Roger approximation will be used to estimate

denominator degrees of freedom. A difference in LDH-PCHG between the ALXN1210 and eculizumab treatment groups along with a two-sided 95% CI will be calculated.

If the upper bound of the 95% CI for the difference (ALXN1210-eculizumab) is less than the noninferiority margin (NIM) of 15%, then ALXN1210 treatment will be concluded to be noninferior to eculizumab.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints of proportion of patients with breakthrough hemolysis, change from baseline in FACIT-Fatigue, proportion of patients who do not require a transfusion, and proportion of patients with stabilized hemoglobin will be summarized by treatment group. The percentage of patients with breakthrough hemolysis will be computed for both the ALXN1210 and eculizumab treatment groups. A difference in the percentage of patients with breakthrough hemolysis in the 2 treatment groups will be calculated, along with a 95% CI for the difference. The 95% CI for the difference between ALXN1210 and eculizumab treatment groups will be calculated using the Newcombe confidence interval method. The same approach will be employed for transfusion avoidance and stabilized hemoglobin. Transfusion avoidance will be achieved only by those patients who did not receive a transfusion and did not meet the protocol-specified guidelines for transfusion. For change from baseline in FACIT-Fatigue, the same approach used for the primary endpoint will be employed.

These key secondary endpoints will be tested in a hierarchical manner provided that noninferiority was declared for the primary endpoint.

When performing the analyses for the key secondary efficacy endpoints, a closed-testing procedure will be used; lack of significance of a test precludes assessment of subsequent tests. Estimates and CIs will be computed for all key secondary efficacy endpoints regardless of whether a lack of significance of a test precludes assessment of subsequent tests.

1. If the upper bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with breakthrough hemolysis is less than the NIM of 20%, then ALXN1210 will be declared noninferior for this parameter and the next parameter will be tested.
2. If the lower-bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in change from baseline in FACIT-Fatigue is greater than the NIM of -3, then ALXN1210 will be declared noninferior for this parameter and the next parameter will be tested.
3. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups for TA is greater than the NIM of -20%, then ALXN1210 will be declared to be noninferior to eculizumab and the next parameter will be tested.
4. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with stabilized hemoglobin is greater than the NIM of -20%, then ALXN1210 will be declared noninferior for this parameter.

If noninferiority is established for all key secondary endpoints, and a larger effect for ALXN1210 is observed, then superiority will be assessed using a closed-testing procedure and using a 2 sided 0.05 test for each parameter as follows:

5. PCHG-LDH from baseline to Day 183 (Week 26)
6. Change from baseline to Day 183 (Week 26) in FACIT-Fatigue
7. Proportion of patient with breakthrough hemolysis through Day 183 (Week 26)
8. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)
9. Transfusion avoidance

Due to the hierarchical testing order being prespecified, no adjustment for type I error is required.

Other Secondary Endpoints

Total number of units of pRBCs transfused during treatment and the number (%) of patients with LDH within the normal range at each study visit will be computed for both ALXN1210 and eculizumab treatment groups. Changes from baseline in EORTC-QLQ-C30 will be summarized by treatment group at baseline and at the study visits where these assessments are collected. Shifts from baseline in clinical manifestations of PNH will be summarized by treatment group and at the study visits where these assessments are collected. The number of any treatment-emergent MAVEs (n) and number of patients with events (n, %) will be displayed by treatment group.

Safety: All safety analyses will be conducted for the Safety set, defined as all patients who receive at least 1 dose of ALXN1210 or eculizumab. Safety results will be reported by treatment group. The incidence of treatment-emergent adverse events (TEAEs) will be summarized by system organ class (SOC) and preferred term (PT) overall, by severity, and by relationship to treatment overall and by treatment group. The incidence of serious adverse events (SAEs) will also be summarized. Changes from baseline (last assessment prior to ALXN1210 or eculizumab) in ECGs, vital signs, and laboratory assessments will be summarized by treatment group. Shifts from baseline in laboratory assessments will be summarized for all study visits by treatment group. Abnormal immunogenicity findings, including the incidence and titers for ADAs to ALXN1210 or eculizumab, will be summarized by treatment group.

Pharmacokinetics/Pharmacodynamics: PK and PD samples will be collected over the course of the study. Individual serum concentration data for all patients who receive at least 1 dose of study drug (ie, ALXN1210 or eculizumab) and who have evaluable PK data will be used to derive PK parameters for ALXN1210 and eculizumab. Graphs of mean serum concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual patients may also be generated. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate. Assessment of population-PK may be considered using data from this study or in combination with data from other studies.

PK and PD analyses will be performed for all patients who receive at least 1 dose of ALXN1210 or eculizumab and who have evaluable PK and PD data. Descriptive statistics will be presented for all ALXN1210 and eculizumab PD endpoints at each sampling time. The PD effects of ALXN1210 and eculizumab will be evaluated by assessing the absolute values and changes and percentage changes from baseline in total and free C5 serum concentrations and cRBC hemolysis over time, as appropriate. Assessments of ALXN1210 PK/PD relationships may be explored using data from this study or in combination with data from other studies.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
BP	blood pressure
C5	complement component 5
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
cRBC	chicken red blood cell
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
ET	early termination
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GCP	good clinical practice
GPV	Global Pharmacovigilance
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
IxRS	interactive voice- or web-response system
LDH	lactate dehydrogenase
LDH-PCHG	lactate dehydrogenase percent change
LLT	lowest level term
mAb	monoclonal antibody
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NIM	noninferiority margin
NO	nitric oxide
PD	pharmacodynamic(s)
PEF	peak expiratory flow
PK	pharmacokinetic(s)

Abbreviation	Definition
PNH	paroxysmal nocturnal hemoglobinuria
PP	per protocol
pRBC	packed red blood cell
PT	preferred term
q2w	once every 2 weeks
q8w	once every 8 weeks
QLQ-C30	Quality of Life Questionnaire-Core 30 Scale
QoL	quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMT	Safety Management Team
SOC	system organ class
SRB	Safety Review Board
SUSAR	suspected unexpected serious adverse reactions
TA	transfusion avoidance
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

5. INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic disorder that occurs most frequently in adults (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 glycosphosphatidylinositol 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 component 5 (C5) into C5a and C5b. The pathology and clinical presentations in patients with PNH are driven by uncontrolled terminal complement activation on red blood cells (RBCs).

C5a is a potent anaphylatoxin, chemotactic factor, and cell-activating molecule that mediates multiple pro-inflammatory and pro-thrombotic activities (Matis 1995; Prodingler 1999). C5b recruits the terminal complement components C6, C7, C8, and C9 to form the pro-inflammatory, pro-thrombotic cytolytic pore molecule C5b-9, a process that under normal circumstances would be blocked on the RBC membrane by CD59. In patients with PNH, however, these final steps proceed unchecked, culminating in hemolysis and the release of free hemoglobin, as well as platelet activation (Hill 2013). The signs and symptoms of PNH can be attributed to chronic, uncontrolled complement C5 cleavage and release of C5a and C5b-9 leading to RBC hemolysis, which results in the release of intracellular free hemoglobin and lactate dehydrogenase (LDH) into circulation; irreversible binding to and inactivation of nitric oxide (NO) by hemoglobin, and inhibition of NO synthesis; vasoconstriction and tissue-bed ischemia due to absence of vasodilatory NO as well as possible microthrombi manifesting as abdominal pain, dysphagia, and erectile dysfunction; platelet activation; and a pro-inflammatory and prothrombotic state (Hill 2013; Brodsky 2014). A substantial proportion of patients with PNH experience renal dysfunction and pulmonary hypertension (Hillmen 2010; Hill 2012b; Hill 2013). Patients also experience venous or arterial thrombosis in diverse sites, including the abdomen or central nervous system (Brodsky 2014).

Eculizumab (Soliris[®]) is a humanized monoclonal antibody (mAb) approved for treating PNH. Eculizumab specifically binds to the complement protein C5 with high affinity. Eculizumab 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 the 3 pivotal Phase 3 clinical studies and supported by subsequent postmarketing experience.

ALXN1210 was engineered from eculizumab to preserve immediate and complete C5 inhibition while providing sustained complement inhibition throughout a prolonged dosing interval (1 month or longer). ALXN1210 and eculizumab share > 99% amino acid sequence homology. ALXN1210 is a recombinant humanized protein produced in Chinese hamster cells and was designed through minimal targeted engineering to substitute 4 amino acids in the eculizumab heavy chain. Two of these substitutions are in the complementarity determining regions, lowering the affinity of ALXN1210 for C5; the other two are in the Fc binding region which improves recycling of ALXN1210 into the vascular space instead of degrading. These changes

were specifically designed (and have subsequently been proven) to increase the half-life of ALXN1210 relative to eculizumab, increasing the duration of terminal complement inhibition, while preserving both the high degree of specificity for binding to C5 and the effectorless nature of the antibody.

The main objective of effective PNH treatment with targeted therapy is to provide immediate, complete, and sustained inhibition of terminal complement activity to block hemolysis and prevent thrombosis. More specifically, incomplete C5 blockade may increase risk of potentially life-threatening breakthrough hemolysis (Hill 2012a; Lee 2013). Any loss of efficacy at the end of a dosing interval or missed doses due to inconvenience of dosing intervals may put patients at substantial medical risk. Patients treated with eculizumab are required to receive maintenance infusions every 2 weeks. Given that PNH is a chronic disease, this regimen may have a significant impact on patients in terms of individual patient concerns associated with missed work and more importantly may impact treatment compliance.

ALXN1210 has been designed to have the same rapid onset of action and effective blockade of complement, with an increased serum half-life to yield an increased duration of pharmacologic activity relative to eculizumab. The substantially longer half-life of ALXN1210 is expected to produce sustained terminal complement inhibition during a longer dosing interval and thus reduce the potential risk of breakthrough complement-mediated hemolysis during the treatment period, thus improving the overall health of patients.

Three studies of ALXN1210 are ongoing in patients with PNH who are naïve to treatment with complement inhibitors. Study ALXN1210-PNH-103 is a Phase 1b, open-label, multiple-dose study, and Study ALXN1210-PNH-201 is a Phase 2, open-label, multiple-dose, proof-of-concept study. Study ALXN1210-PNH-301 is a Phase 3, randomized, open-label study designed to assess the noninferiority of ALXN1210 to eculizumab. ALXN1210-PNH-103 is designed to assess dose ranging over a 2-fold range of trough exposure levels, while Study ALXN1210-PNH-201 is designed to assess dose intervals of 4, 6, 8, and 12 weeks. Each study in patients with PNH also includes a 2-year extension phase. In addition, Study ALXN1210-HV-104 is being conducted to assess the pharmacokinetic (PK) profile of ALXN1210 in healthy Japanese subjects.

In this Phase 3, open-label, randomized study, the efficacy and safety of ALXN1210 will be assessed compared to eculizumab in patients with PNH who are clinically stable having been treated with eculizumab for at least the past 6 months prior to study entry. The study design rationale is further discussed in [Section 7.2](#).

More information about the PK, mechanism of action, known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of ALXN1210 may be found in the current edition of the Investigator's Brochure (IB).

5.1. Benefits and Risks Assessment

5.1.1. Potential Benefits

PNH is an ultra-rare, progressive, debilitating, and life-threatening disease, driven by chronic uncontrolled complement activation. The resulting inflammation and cellular damage lead to systemic complications, principally through intravascular hemolysis and thrombophilia

(Brodsky 2014, Socie 1996). Chronic intravascular hemolysis due to continuous activation of the complement pathway leads to the release of free hemoglobin, NO consumption and persistent smooth muscle cell contraction, chronic anemia, and an increased risk of severe thromboembolism. Patients with PNH are at risk of substantial morbidity and mortality and altered quality of life. The current standard of care for the treatment of PNH is eculizumab (Soliris[®]), a recombinant humanized mAb that binds to the human C5 complement protein and inhibits the activation of terminal complement. The efficacy and safety of eculizumab for the treatment of PNH are well established. The approved dosage regimen for eculizumab for PNH involves 4 weekly induction doses, followed by maintenance doses administered every 2 weeks starting at Week 5.

Given that PNH is a chronic disease, the current eculizumab regimen may significantly affect patients, many of whom have to miss days of work or school to accommodate treatment. In some cases, patients may refuse treatment or may be unable to comply with the treatment frequency of eculizumab. Practice survey research supports the assumption that the less frequent infusions associated with ALXN1210 will have a positive impact on daily life for patients and their caregivers.

ALXN1210 is a recombinant, humanized mAb derived through minimal targeted engineering of eculizumab by introducing 4 unique amino acid substitutions. ALXN1210 has been designed to have the same rapid onset of action and effective blockade of complement, with an increased serum half-life to yield an increased duration of pharmacologic activity relative to eculizumab. By providing patients and physicians with an option for less frequent dosing, ALXN1210 will allow greater access to care for those patients who may not initiate treatment or may discontinue eculizumab due to frequency of dosing, or patients who are currently on therapy receiving eculizumab every 2 weeks. Additionally, the substantially longer half-life of ALXN1210 is expected to produce sustained terminal complement inhibition during a longer dosing interval. In PNH this may reduce the potential risk of breakthrough, complement-mediated hemolysis, as suggested by preliminary clinical data from the ongoing PNH studies, which demonstrate rapid and sustained reduction in LDH levels, a direct measure of hemolytic activity that is of comparable magnitude to that seen in studies of eculizumab.

5.1.2. Identified and Potential Risks

5.1.2.1. Infections (N. Meningitidis and Other Encapsulated Organisms)

Increased susceptibility to infection, especially with encapsulated bacteria, is a known risk associated with complement inhibition. Similar to eculizumab, the main risk associated with ALXN1210 is the risk of meningococcal infections. Specific risk mitigation measures are in place to address this risk, as described in [Section 9.8](#).

5.1.2.2. Immunogenicity

As a humanized mAb, administration of ALXN1210 may be associated with immunogenicity reactions similarly to any therapeutic protein. Monitoring of immunogenicity is in place for this study, as described in [Section 7.3](#) and [Section 11.6](#). No immunogenicity reactions have been observed to date in clinical studies with ALXN1210.

5.1.2.3. Pregnancy Exposure

No studies of ALXN1210 have been conducted in pregnant women. Pregnant or nursing female patients are excluded from the clinical trial. Patients enrolled in the study, and their spouses/partners, will use a highly effective or acceptable method of contraception as required in [Section 9.11](#).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Study Objectives

6.1.1. Primary Objective

The primary objective is to assess the noninferiority of ALXN1210 compared to eculizumab in adult patients with PNH who have been treated with eculizumab for at least the past 6 months.

Noninferiority will be claimed if after 26 weeks of treatment the upper bound of the 95% confidence interval (CI) for the difference (ALXN1210-eculizumab) in percent change in LDH level (LDH-PCHG) is less than 15%.

6.1.2. Secondary Objectives

The secondary objectives of the study are to assess the following:

- To characterize the safety and tolerability of ALXN1210 in patients who switch from eculizumab to ALXN1210
- To evaluate the efficacy of ALXN1210 by additional efficacy measures
- To characterize the pharmacokinetics/pharmacodynamics (PK/PD) and immunogenicity of ALXN1210
- To evaluate the long-term safety and efficacy of ALXN1210

6.2. Endpoints

6.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of the study is hemolysis as directly measured LDH-PCHG from Baseline to Day 183.

6.2.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints of the study (to be tested in a hierarchical manner) are:

1. Proportion of patients with breakthrough hemolysis, 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 $\geq 2 \times$ upper limit of normal (ULN)
2. Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from Baseline to Day 183
3. Transfusion avoidance (TA), defined as the proportion of patients who remain transfusion-free and do not require a transfusion as per protocol-specified guidelines from Baseline to Day 183

4. Proportion of patients with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion from Baseline to Day 183

6.2.3. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints of the study are:

- Total number of units of packed red blood cells (pRBCs) transfused from Baseline to Day 183
- Proportion of patients with LDH in normal range at Day 183
- Change in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, from Baseline to Day 183
- Change in clinical manifestations of PNH (fatigue, hemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia, and erectile dysfunction) from Baseline to Day 183
- Proportion of patients experiencing MAVEs from Baseline to Day 183

6.2.4. Pharmacokinetic and Pharmacodynamic Endpoints

- Change in serum ALXN1210 and eculizumab concentration over time
- Change in chicken red blood cell (cRBC) hemolytic activity over time (exploratory)
- Change in free C5 concentrations over time

6.2.5. Safety Endpoints

The safety and tolerability of ALXN1210 compared with eculizumab will be evaluated by physical examinations, vital signs, electrocardiograms (ECGs), laboratory assessments, and incidence of adverse events (AEs) and serious adverse events (SAEs). The proportion of patients who develop antidrug antibodies (ADAs) will also be assessed through the end of the study.

7. INVESTIGATIONAL PLAN

7.1. Summary of Study Design

Study ALXN1210-PNH-302 is a Phase 3, open-label, randomized, active-controlled, multicenter study to evaluate the safety and efficacy of ALXN1210 versus eculizumab administered by intravenous (IV) infusion to adult patients with PNH who have been treated with eculizumab for at least the past 6 months. The study will enroll approximately 192 patients (96 patients per treatment group).

The study consists of a 4-week screening period, a 26-week randomized treatment period, and an extension period of up to 3 years. Patients will be stratified into 1 of 2 groups based on their transfusion history (received a transfusion of pRBCs within 12 months prior to Day 1, yes or no). Patients within each of the 2 groups will then be randomly assigned in a 1:1 ratio to either continue on eculizumab or switch to ALXN1210.

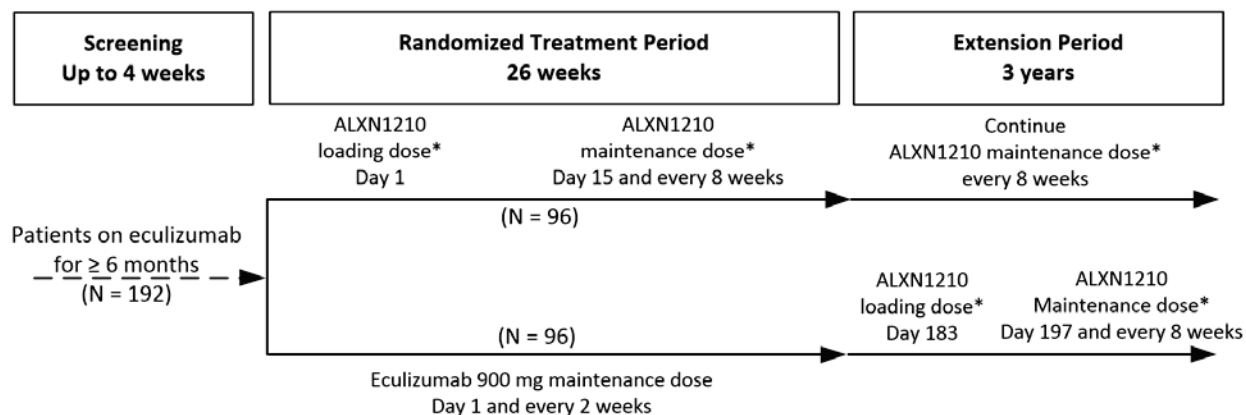
Prior to randomization and within 5 days prior to study drug administration on Day 1, each patient's hemoglobin must be evaluated by either local or central laboratory. If at that time the patient's hemoglobin value meets protocol-specified transfusion guidelines, the patient must be transfused with pRBCs to a hemoglobin level above the protocol-specified transfusion threshold in order to be eligible for randomization. The patient's post-transfusion hemoglobin value should be confirmed by local or central laboratory to be above the protocol-specified transfusion threshold.

Day 1 of study treatment will occur 2 weeks from the patient's last dose of eculizumab. Patients randomly assigned to the ALXN1210 group will receive a loading dose (see [Table 7](#)) of ALXN1210 on Day 1, followed by maintenance doses of ALXN1210 on Day 15 and every 8 weeks (q8w) thereafter for a total of 26 weeks of treatment. Patients randomly assigned to the eculizumab group will continue to receive the approved dose of eculizumab for the treatment of PNH (900 mg every 2 weeks [q2w]) for a total of 26 weeks of study treatment.

After completion of all assessments on Day 183, patients will enter an extension period and receive ALXN1210 until the product is registered or approved (in accordance with country-specific regulations) or for up to 3 years, whichever occurs first. Beginning on Day 183, patients who had been randomized to the ALXN1210 treatment group will receive a maintenance dose (as described above) of ALXN1210 q8w, and patients who had been randomized to the eculizumab group will receive a loading dose (as described above) of ALXN1210 followed 2 weeks later and q8w thereafter by a weight-based maintenance dose of ALXN1210.

[Figure 1](#) illustrates the study design.

Figure 1: Study Design Schematic for Clinical Protocol ALXN1210-PNH-302



* ALXN1210 loading dose = 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg; maintenance dose = 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg

A pRBC transfusion will be administered when a patient has a hemoglobin value of 9 g/dL or lower with signs or symptoms of sufficient severity to warrant a transfusion, or a hemoglobin value of 7 g/dL or lower regardless of presence of clinical signs or symptoms.

7.2. Discussion of Design and Control

Published data support LDH as a reliable, objective, and direct measure of intravascular hemolysis in patients with PNH and is considered by experts to be the best measure of complement-mediated hemolysis, the hallmark of PNH disease activity (Dale 1972; Parker 2005; Canalejo 2013). Results from the eculizumab clinical program showed that LDH concentrations remained markedly elevated and unchanged in untreated (placebo) patients, while eculizumab-treated patients had an immediate reduction (within 1 week following initiation of treatment) in serum LDH to normal or near normal levels (Brodsky 2008; Hillmen 2006). This reduction mirrored a rapid reduction in symptoms and improvement in fatigue (Hillmen 2006; Brodsky 2008).

The safety parameters being evaluated are commonly used in clinical trials per International Conference on Harmonisation (ICH) and good clinical practice (GCP) guidances.

Eculizumab was selected as the active control for ethical reasons. Eculizumab is currently the standard of care for patients with PNH.

7.3. Schedule of Assessments

The Schedule of Assessments is provided in Table 1 for the Screening and Randomized Treatment Period and in Table 2 (patients entering from ALXN1210 group) and Table 3 (patients entering from eculizumab group) for the Extension Period.

Refer to the Laboratory Manual for details on the number of samples and volumes for all sampling and tests during the study.

Additional (unscheduled) visits outside the specified visits are permitted at the discretion of the Investigator. Procedures, tests, and assessments will be performed at the discretion of the Investigator. Any tests, procedures, or assessments performed at the Unscheduled Visits must be recorded on the electronic case report forms (eCRFs).

Additionally, if a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD parameters must be analyzed at the central laboratory. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD parameters. For purposes of defining breakthrough hemolysis, assessment of LDH must be based on a central laboratory value.

Table 1: Schedule of Study Visits and Assessments: Screening Through End of Randomized Treatment Period

Period Study Day	Screening -28 to -1	Randomized Treatment Period															
		1	8	15	22	29	43	57	71	85	99	113	127	141	155	169	183/ ET
Window (day)	N/A	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Informed consent	X																
Confirmation or administration of meningococcal vaccination ^a	X	X															
Medical history and demographics	X																
HIV testing	X																
PNH clone size ^b	X	X							X								X
Height	X																
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^c	X	X	X	X					X				X				X
Record transfusions and transfusion parameters ^d	X ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PNH symptomatology ^{f,g}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FACIT-Fatigue ^g	X	X	X			X			X				X				X
EORTC QLQ-C30 ^g	X	X	X			X			X				X				X
Physical examination	X																
Abbreviated physical examination ^h		X							X								X
Vital signs ⁱ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety 12-Lead ECG ^j	X							X									X
Chemistry including LDH ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology including free hemoglobin and coagulation ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry ^k	X	X		X		X			X				X				X
PK/PD sampling		X ^l	X ^m	X ^l	X ^m	X ^m	X ^m	X ^m	X ^l	X ^m	X ^m	X ^m	X ^l	X ^m	X ^m	X ^m	X ^l
Immunogenicity (ADA) ⁿ		X							X				X				X
Review safety card		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breakthrough hemolysis ^o		←Monitor continuously→															
Concomitant medications	X	←Monitor continuously→															
Adverse events	X	←Monitor continuously→															
Randomization ^p		X															
ALXN1210 administration ^q		X		X					X				X				-- ^r
Eculizumab administration		X		X		X	X	X	X	X	X	X	X	X	X	X	

**Table 1: Schedule of Study Visits and Assessments: Screening Through End of Randomized Treatment Period
(Continued)**

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale; ET = early termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; N/A = not applicable; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria

- ^a All patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
- ^b White blood cell (WBC; granulocyte and monocyte) and red blood cell (RBC) clone size measured by high-sensitivity flow cytometry at Screening and Day 1; RBC clone size only on Day 71 and Day 183.
- ^c Female patients of childbearing potential only. Serum pregnancy test at Screening and Day 183; urine pregnancy test at all other required time points. A negative urine test result is required prior to administering ALXN1210 or eculizumab to female patients of childbearing potential at the indicated visits.
- ^d Transfusions given during and between visits will be recorded.
- ^e Prior to randomization and within 5 days prior to study drug administration on Day 1, each patient's hemoglobin must be evaluated by either local or central laboratory. If at that time the patient's hemoglobin value meets protocol-specified transfusion guidelines ([Section 10.1](#)), the patient must be transfused with pRBCs to a hemoglobin level above the protocol-specified transfusion threshold in order to be eligible for randomization. The patient's post-transfusion hemoglobin value should be confirmed by local or central laboratory to be above the protocol-specified transfusion threshold.
- ^f Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.
- ^g Physician- and patient-reported assessments will be performed prior to study drug administration.
- ^h Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or designee) judgment and patient symptoms. At least 1 body system must be checked for an abbreviated physical examination.
- ⁱ Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic blood pressure (millimeters of mercury [mmHg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). On dosing days, vital signs will be taken before study drug administration.
- ^j Single 12-lead ECG will be collected at Screening and predose on Day 57 and Day 183. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- ^k Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line. Follicle stimulating hormone levels will be measured during Screening only in order to confirm postmenopausal status.
- ^l Serum samples for PK/PD analyses will be collected predose (within 0.5 hours prior to the start of infusion) and at end-of-infusion (within 0.5 hours after the end of infusion). The predose PK/PD sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion PK/PD samples will be drawn from the patient's opposite, noninfused arm. Note that the Day 183 end-of-infusion sample is considered an Extension Period assessment (see [Table 2](#) and [Table 3](#)). All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.
- ^m Serum samples for PK/PD analyses will be collected predose (within 0.5 hours prior to the start of infusion) for eculizumab-treated patients and at any time for ALXN1210-treated patients or for eculizumab-treated patients when no eculizumab dose is given. All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.
- ⁿ Samples for ADA will be collected predose.

**Table 1: Schedule of Study Visits and Assessments: Screening Through End of Randomized Treatment Period
(Continued)**

- ^o If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD parameters will be analyzed at the central laboratory. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD parameters.
- ^p Patients will be randomly assigned to treatment through an interactive voice or web response system (IxRS).
- ^q The dose of ALXN1210 is based on the patient's last recorded study visit body weight.
- ^r The primary efficacy endpoint assessment is before dosing on Day 183. Dosing on Day 183 is the start of the Extension Period. Please refer to additional Day 183 post dose procedures in [Table 2](#) and [Table 3](#).

Table 2: Schedule of Study Visits and Assessments: Extension Period – Patients Entering from ALXN1210 Group

Period	Extension Period																				1303 EOS/ ET
	183 ^a	239	295	351	407	463	519	575	631	687	743	799	855	911	967	1023	1079	1135	1191	1247	
Study Day	± 2	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Window (day)	± 2	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
PNH clone size ^b		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^c		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record transfusions and transfusion parameters ^d		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PNH symptomatology ^e		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FACIT-Fatigue ^f				X			X			X			X			X					X
EORTC QLQ-C30 ^f				X			X			X			X			X					X
Abbreviated physical examination ^g		X		X		X		X		X		X		X		X		X		X	X
Vital signs ^h		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety 12-Lead ECG ⁱ																					X
Chemistry including LDH ^j		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology including free hemoglobin and coagulation ^j		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry ^j		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK/PD sampling ^k	X			X			X					X			X			X			X
Immunogenicity (ADA) ^l		X		X		X		X		X		X		X		X		X			X
Review safety card		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breakthrough hemolysis ^m	←Monitor continuously→																				
Concomitant medications	←Monitor continuously→																				
Adverse events	←Monitor continuously→																				
ALXN1210 administration ⁿ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale; EOS = end of study; ET = early termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria

^a All patients who roll over into the Extension Period will receive ALXN1210 on Day 183 after all assessments have been performed.

^b Granulocyte and red blood cell (RBC) clone size measured by high-sensitivity flow cytometry on Days 351, 743, and 1135; RBC clone size only at other visits.

^c Female patients of childbearing potential only. Serum pregnancy test at ET only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ALXN1210 to female patients of childbearing potential on dosing days.

^d Transfusions given during and between visits will be recorded.

**Table 2: Schedule of Study Visits and Assessments: Extension Period – Patients Entering from ALXN1210 Group
(Continued)**

- ^e Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.
- ^f Physician- and patient-reported assessments will be performed prior to study drug administration.
- ^g Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or qualified designee) judgment and patient symptoms. At least one body system must be checked for an abbreviated physical examination.
- ^h Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic blood pressure (millimeters of mercury [mmHg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). Vital signs will be taken before each study drug administration.
- ⁱ Single 12-lead ECG will be collected at Day 1303 or ET. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- ^j Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line.
- ^k Serum samples for PK/PD analyses will be collected at end-of-infusion on Day 183; predose (within 0.5 hours prior to the start of infusion) and at end-of-infusion (within 0.5 hours after the end of infusion) on Days 351, 575, 799, 967, and 1135; and at any time on Day 1303 or ET. The predose PK/PD sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion PK/PD samples will be drawn from the patient's opposite, noninfused arm. All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.
- ^l Samples for ADA will be collected predose or at any time when a dose of study drug is not administered.
- ^m If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD parameters will be analyzed at the central laboratory. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD parameters.
- ⁿ The dose of ALXN1210 is based on the patient's last recorded study visit body weight.

Table 3: Schedule of Study Visits and Assessments: Extension Period – Patients Entering from Eculizumab Group

Period	Extension Period																					1317 EOS/ ET			
	183 ^b	197	225	253	309	365	421	477	533	589	645	701	757	813	869	925	981	1037	1093	1149	1205		1261		
Study Day	± 2	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7		
Window (day)	± 2	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7		
PNH clone size ^b		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test ^c		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record transfusions and transfusion parameters ^d		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PNH symptomatology ^c		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
FACIT-Fatigue ^f						X				X			X			X			X					X	
EORTC QLQ-C30 ^f						X				X			X			X			X					X	
Abbreviated physical examination ^g		X	X	X		X		X		X		X		X		X		X		X		X		X	
Vital signs ^h		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety 12-Lead ECG ⁱ																								X	
Chemistry including LDH ^j		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology including free hemoglobin and coagulation ^j		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry ^j		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK/PD sampling ^k	X	X	X			X				X				X			X			X				X	
Immunogenicity (ADA) ^l				X		X		X		X		X		X		X		X		X		X		X	
Review safety card		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breakthrough hemolysis ^m		← Monitor continuously →																							
Concomitant medications		← Monitor continuously →																							
Adverse events		← Monitor continuously →																							
ALXN1210 administration ⁿ	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale; EOS = end of study; ET = early termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria

^a All patients who roll over into the Extension Period will receive ALXN1210 on Day 183 after all assessments have been performed.

^b Granulocyte and red blood cell (RBC) clone size measured by high-sensitivity flow cytometry on Days 365, 757, and 1149; RBC clone size only at other visits.

^c Female patients of childbearing potential only. Serum pregnancy test at ET only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ALXN1210 to female patients of childbearing potential on dosing days.

^d Transfusions given during and between visits will be recorded.

**Table 3: Schedule of Study Visits and Assessments: Extension Period – Patients Entering from Eculizumab Group
(Continued)**

- ^e Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.
- ^f Physician- and patient-reported assessments will be performed prior to study drug administration.
- ^g Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or qualified designee) judgment and patient symptoms. At least one body system must be checked for an abbreviated physical examination.
- ^h Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic blood pressure (millimeters of mercury [mmHg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). Vital signs will be taken before each study drug administration.
- ⁱ Single 12-lead ECG will be collected at Day 1317 or ET. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- ^j Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line.
- ^k Serum samples for PK/PD analyses will be collected predose (within 0.5 hours prior to the start of infusion) and at end-of-infusion (within 0.5 hours after the end of infusion) on Days 197, 365, 589, 813, 981, and 1149; at end-of-infusion on Day 183; and at any time on Days 225 and 1317 or ET. The predose PK/PD sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion PK/PD samples will be drawn from the patient's opposite, noninfused arm. All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.
- ^l Samples for ADA will be collected predose or at any time when a dose of study drug is not administered.
- ^m If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD parameters will be analyzed at the central laboratory. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD parameters.
- ⁿ The dose of ALXN1210 is based on the patient's last recorded study visit body weight.

8. STUDY POPULATION

Approximately 192 patients with documented PNH will be enrolled and randomly assigned to treatment with either ALXN1210 or eculizumab at approximately 50 investigative sites globally.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once based on discussion and agreement between the Investigator and the Medical Monitor.

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

8.1. Inclusion Criteria

Patients are eligible for enrollment in the study only if they meet all of the following criteria and none of the exclusion criteria:

1. Male or female, 18 years of age or older at the time of consent.
2. Treated with eculizumab according to the labelled dosing recommendation for PNH for at least 6 months prior to Day 1.
3. Lactate dehydrogenase (LDH) $\leq 1.5 \times \text{ULN}$ at Screening. Sample must be obtained on a scheduled eculizumab-dosing day prior to dose administration (ie, at trough eculizumab level) and analyzed by the central laboratory.
4. Documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry evaluation (Borowitz 2010) of RBCs and white blood cells (WBCs), with granulocyte or monocyte clone size of $\geq 5\%$.
5. To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
6. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance (Section 9.11) for avoiding pregnancy while on treatment and for 8 months after last dose of study drug.
7. Patients must be willing and able to give written informed consent and to comply with all study visits and procedures, including the use of any data collection device(s) to directly record patient data.

8.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria:

1. LDH value $> 2 \times \text{ULN}$ in the 6 months prior to Day 1.
2. MAVE in the 6 months prior to Day 1.
3. Platelet count $< 30,000/\text{mm}^3$ ($30 \times 10^9/\text{L}$) at Screening.

4. Absolute neutrophil count $< 500/\mu\text{L}$ ($0.5 \times 10^9/\text{L}$) at Screening.
5. History of bone marrow transplantation.
6. Body weight < 40 kg at Screening.
7. History of *N. meningitidis* infection.
8. History of unexplained, recurrent infection.
9. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
10. Presence of fever $\geq 38^\circ\text{C}$ (100.4°F) within 7 days prior to study drug administration on Day 1.
11. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer).
12. Immunized with a live-attenuated vaccine 1 month prior to study drug administration on Day 1.
13. 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.
14. History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease (eg, active hepatitis) that, in the opinion of the Investigator or Sponsor, precludes the patient's participation in an investigational clinical trial.
15. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of randomization, coexisting chronic anemia unrelated to PNH) that would make them unlikely to tolerate the requirements of the protocol (eg, transfusion guidelines).
16. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.
17. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
18. Females who plan to become pregnant or are currently pregnant or breastfeeding.
19. Females who have a positive pregnancy test result at Screening or on Day 1.
20. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater.
21. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
22. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the patient's full participation in the study, pose any additional risk for the patient, or confound the assessment of the patient or outcome of the study.

8.3. Discontinuation

8.3.1. Withdrawal of Patients

A patient has the right to withdraw from the study at any time. If a patient withdraws consent, the assessments specified for the Early Termination (ET) visit (as shown in the Schedule of Assessments, [Section 7.3](#)) will be performed and the Sponsor and site monitor notified as soon as possible. Patients who withdraw from the study will not be replaced.

Patients should be permanently discontinued from ALXN1210 treatment if any of the following occur during the study:

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

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

The reason for the treatment or study discontinuation will be recorded on the eCRF.

If a patient is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that, in the opinion of the Investigator, is significantly outside of the reference range and clinically significant ([Section 11.4](#)), the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

If a female patient is permanently discontinued from ALXN1210 treatment due to pregnancy, the Investigator will attempt to follow-up until the outcome of the pregnancy ([Section 11.8](#)).

8.3.2. Discontinuation of Study/Site Termination by Sponsor or Health Authority

The Sponsor 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 to patients enrolled in the study
- Sponsor decision to suspend or discontinue testing, evaluation, or development of the study drug
- Failure of the Investigator to comply with the approved protocol, pertinent guidelines, and/or regulations
- Submission of knowingly false information from the Investigator to the Sponsor and/or health authorities

Should the study be terminated early, the Sponsor will notify the health authority and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to local requirements.

8.4. End of Study Definition

The end of the study is defined as the date of the last patient's last visit in the Extension Period.

9. STUDY TREATMENT

9.1. Materials and Supplies

9.1.1. Description of Study Drugs

The study drugs in this study are ALXN1210 and eculizumab (active control). Both ALXN1210 and eculizumab are humanized, anti-C5 monoclonal antibodies.

Eculizumab is an IgG2/4 kappa immunoglobulin consisting of human constant regions, and murine complementarity-determining regions grafted onto human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains.

ALXN1210 is produced in Chinese hamster cells and was designed through minimal targeted engineering of eculizumab by introducing 4 unique amino acid substitutions to its heavy chain to extend antibody half-life. ALXN1210 and eculizumab share over 99% primary amino acid sequence identity and have very similar pharmacology.

ALXN1210 and eculizumab drug products are supplied for clinical studies as sterile, preservative-free 10-mg/mL solutions 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.

Refer to [Table 4](#), the current ALXN1210 IB, and the approved eculizumab local labeling or current eculizumab IB for additional information.

Table 4: Study Drug

	Study Drug	
Product Name	ALXN1210	Eculizumab
Dosage Form	Concentrated solution (10 mg/mL) for infusion	Concentrated solution (10 mg/mL) for infusion
Route of Administration	Intravenous infusion	Intravenous infusion
Physical Description	Clear to translucent, slight whitish color, practically free from particles	Clear, colorless solution practically free from particles
Manufacturer	Alexion or Contracted Manufacturing Organization	Alexion or Contracted Manufacturing Organization

9.1.2. Study Drug Packaging and Labeling

ALXN1210 and eculizumab are packaged in US Pharmacopeia/European Pharmacopeia Type 1 borosilicate glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits. Please refer to the Pharmacy Manual for details.

Study drug orders will be released to each site upon receipt of all required documents based upon applicable regulations.

9.1.3. Study Drug Storage

Upon arrival of the study drug kits at the study site, the pharmacist or designee should promptly remove the study drug kits from the shipping cooler and store them in their original cartons under refrigerated conditions at 2°C to 8°C (35°F to 47°F) and protected from light. ALXN1210 and eculizumab should not be frozen. Study drug must be stored in a secure, limited-access storage area, and the temperature must be monitored daily.

The admixed drug product should be at room temperature prior to administration. The material must **not** be heated (eg, by using a microwave or other heat source) other than by ambient air temperature.

Please consult the Pharmacy Manual for further information regarding the storage conditions of reconstituted ALXN1210 or eculizumab.

9.1.4. Study Drug Preparation and Infusion

Eculizumab or ALXN1210 must NOT be administered as an IV push or bolus injection.

Infusions of study drug should be prepared using aseptic technique. The patient's required dose of ALXN1210 or eculizumab will be further diluted into commercially available saline (0.9% sodium chloride; country-specific pharmacopeia) at the volume specified in [Table 5](#) for ALXN1210 or [Table 6](#) for eculizumab (see also approved local labeling or current IB for eculizumab). ALXN1210 or eculizumab admixture will be administered to the patient using an IV tubing administration set via an infusion pump. Use of a 0.2 micron filter is required during infusion of ALXN1210. The permitted duration of an eculizumab infusion (excluding IV flush) ranges from a minimum of 25 minutes to a maximum of 45 minutes for both the 600 mg and 900 mg doses, except in the management of an AE, when the duration may be extended to a maximum of 120 minutes. If an IV flush is included (expected to last no more than 15 minutes), the total infusion duration for eculizumab plus IV flush must not exceed 60 minutes (no more than 135 minutes if slowed or stopped due to AE). The total infusion duration, including an IV flush, will be recorded on the eCRF.

Table 5: Dosing Reference Chart for ALXN1210 Dose Preparation

Dose Type	Body Weight (kg) ^a	Dose (mg)	ALXN1210 Volume (mL)	Saline Volume (mL)	Total Volume (mL)	Minimum Infusion Duration minutes (hours)	Maximum Infusion Rate (mL/hour)
Loading	≥ 40 to < 60	2400	240	240	480	114 (1.9)	253
	≥ 60 to < 100	2700	270	270	540	102 (1.7)	318
	≥ 100	3000	300	300	600	108 (1.8)	333
Maintenance	≥ 40 to < 60	3000	300	300	600	140 (2.4)	250
	≥ 60 to < 100	3300	330	330	660	120 (2.0)	330
	≥ 100	3600	360	360	720	132 (2.2)	328

Note: Please refer to the Pharmacy Manual for additional dose preparation instructions.

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

Table 6: Dosing Reference Chart for Eculizumab Dose Preparation

Dose Type	Dose (mg)	Eculizumab Volume (mL)	Saline Volume (mL)	Total Volume (mL)	Approximate Infusion Duration ^a (minutes)	Approximate Infusion Rate (mL/hour)
Maintenance	900	90	90	180	35	300

^a Acceptable range is 25-60 minutes, which includes a flush of up to 15 minutes. If an adverse event occurs during the administration of eculizumab, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time may not exceed 135 minutes.

Doses of study drug must only be prepared and dispensed by qualified study personnel. Study drug is to be dispensed only to enrolled patients who are confirmed eligible for participation in this study. Once study drug is prepared for a patient, it can only be administered to that patient. Vials of study drug are for one-time use only and any drug product remaining in the vial should not be used for another patient. Any drug remaining in the infusion tubing or infusion bag should not be used for another patient.

Further details on preparation and dose administration of study drug, as well as disposal of study drug, can be found in the Pharmacy Manual.

9.1.5. Study Drug Handling and Disposal

All clinical study material provided to the Investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. Detailed records of the amounts of the investigational product received, dispensed, and destroyed will be maintained.

Unless otherwise notified, empty vials and vials with residual materials should be kept for inspection and accountability by the study monitor prior to their destruction or handled per local pharmacy standard operating procedures for clinical study drugs.

To satisfy regulatory requirements regarding drug accountability, at the end of the study all remaining ALXN1210 and eculizumab inventory will be reconciled and destroyed or returned to Alexion or designee according to applicable regulations.

Please refer to the Pharmacy Manual for further information.

9.2. Treatments Administered

This study involves a direct comparison of ALXN1210 versus the active control, eculizumab.

Patients will be randomly assigned in a 1:1 ratio to either continue on eculizumab or switch to ALXN1210 for 26 weeks. Study drug will be administered as a slow IV infusion (see [Table 5](#) and [Table 6](#)). Day 1 of study treatment will occur 2 weeks from the patient's last dose of eculizumab.

The dose regimen for ALXN1210 is a loading dose on Day 1 followed by maintenance doses on Day 15 and q8w thereafter. The dosage of ALXN1210 is based on the patient's last recorded study visit body weight, as indicated in [Table 7](#).

Table 7: ALXN1210 Weight-Based Dosages

Body Weight ^a	Loading Dose	Maintenance Dose
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

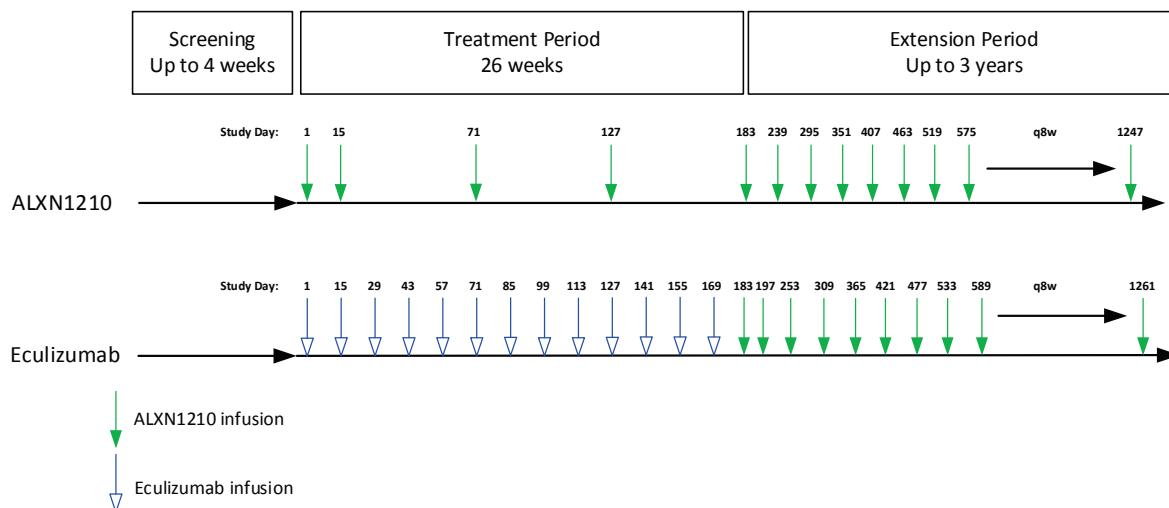
^a Dose regimen will be based on the last recorded study visit body weight. If the study drug is prepared the night before a visit, the weight from the most recent study visit should be used.

Patients randomly assigned to the eculizumab group will continue to receive eculizumab maintenance dosing according to the approved dosing regimen for the PNH indication, which is 900 mg q2w.

After the randomized treatment period all patients will enter the Extension Period and receive ALXN1210 until the product is registered or approved (in accordance with country-specific regulations) or for up to 3 years, whichever occurs first. Beginning on Day 183, patients who had been randomized to the ALXN1210 treatment group will receive their weight-based maintenance dose of ALXN1210 q8w, and patients who had been randomized to the eculizumab group will receive a weight-based loading dose of ALXN1210 followed 2 weeks later and q8w thereafter by a weight-based maintenance dose of ALXN1210 (Table 7; Figure 2).

The actual time of all dose administrations will be recorded on the patient’s eCRF.

Figure 2: Dosing Schematic



9.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomly assigned to study treatment with ALXN1210 or eculizumab at the Baseline Visit (Day 1). Treatment group assignment will be determined by a computer-generated random sequence using an interactive voice- or web-response system (IxRS). The randomization will be a stratified randomization. Patients will be stratified into 1 of 2 groups based on their transfusion history (received a transfusion of pRBCs within 12 months prior to Day 1, yes or no). Patients within both groups will then be randomly assigned in a 1:1 ratio to either continue on eculizumab or switch to ALXN1210 during the 26-week randomized treatment period.

9.4. Rationale for Selection of Doses in the Study

The weight-based dosages of ALXN1210 in this study (Table 7) are premised on PK/PD data from early development studies in healthy adult volunteers as well as the available data from patients with PNH in an ongoing Phase 1b dose-finding study (ALXN1210-PNH-103) and an ongoing Phase 2 proof-of-concept study (ALXN1210-PNH-201). The selection of ALXN1210 dose regimen is based on targeting immediate, complete and sustained inhibition of terminal complement in patients with PNH.

The eculizumab dosage is the approved dose for the treatment of patients with PNH (Soliris[®] United States Prescribing Information [USPI] and Summary of Product Characteristics [SmPC]).

9.5. Special Treatment Considerations

Infusion of other monoclonal antibodies has been associated with infusion reactions, with onset typically during or shortly after completion of the infusion. Please refer to Appendix A for guidance on identifying and managing potential drug infusion reactions.

9.6. Blinding

This is an open-label study.

9.7. Prior and Concomitant Medications and Nonpharmacologic Procedures

Prior medications (including vitamins and herbal preparations)—including those discussed in the exclusion criteria (Section 8.2) and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the patient takes or undergoes within 28 days prior to the start of Screening until the first dose of study drug—will be recorded on the patient's eCRF. In addition history of meningococcal vaccination must be collected for the 3 years prior to first dose of study drug.

Transfusions of pRBCs received within 1 year prior to first study drug administration will be recorded on the patient's eCRF.

All medication use and procedures undertaken during the study will be recorded in the patient's source document/medical chart and eCRF. This record will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and current medications for PNH. Concomitant medications will be recorded from the first infusion of study drug through 56 days after the patient's last dose of study drug. Any changes in concomitant medications also will be recorded in the patient's source document/medical chart and eCRF. Any concomitant medication deemed necessary for the patient'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 patient's source document/medical chart and eCRF.

Concomitant use of anticoagulants is prohibited if not on a stable dose regimen for at least 2 weeks prior to Day 1.

Use of complement inhibitors other than the patient's assigned study treatment is prohibited.

9.8. Vaccination

Due to their mechanism of action, the use of eculizumab or ALXN1210 increases the patient's susceptibility to meningococcal infection (*N. meningitidis*). To reduce the risk of meningococcal infection, all patients must have been vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating eculizumab. Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes. Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, eculizumab).

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 and vaccination. All patients 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 patients during the course of the study, patients 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 each visit as part of the review of the patient safety card as described in the Schedule of Assessments (Section 7.3). Vaccination status for *N. meningitidis* will be recorded on the patient's eCRF.

9.9. Treatment Compliance

Patients will be administered study drug in a controlled setting under the supervision of the Investigator or designee, thereby ensuring compliance with study drug administration. The Investigator or designee will ensure that all patients are adequately informed on the specific dosing regimen required for compliance with the study protocol, ensure that the patient receives the appropriate dose at the designated time points during the study and that adequate safety monitoring occurs during the infusion (Section 9.5).

9.10. Home Visits During the Extension Period

During the Extension Period (after Day 183), and only for visits not requiring an abbreviated physical exam, patients may have the opportunity to have ALXN1210 administered at a medical facility that is located near the patient's home if allowed by national legislation. Alternatively, ALXN1210 may be administered at the patient's home under the orders of the Investigator and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. These visits will be conducted by a trained qualified staff member from the medical facility near the patient's home or by qualified home health care professionals. The study drug will be prepared at the Investigator's pharmacy and transported under controlled conditions to the patient's home or the medical facility for administration by a dedicated courier. The use of a courier, specialized in medicinal product shipments, is needed to ensure traceability and temperature controlled delivery for the transfer of drug from Investigator's pharmacy to patient's home or the medical facility for administration, as specified in the home health care manual. During a remote dosing visit, all assessments will be performed according to the schedule of assessments, including recording of AEs and concomitant medications, collection of blood and

urine samples, assessment of PNH symptomatology, vital signs, QoL assessments, and review of safety card. Patients must return to the study site for any visit at which an abbreviated physical examination is required, as specified in the Schedule of Assessments (Table 2 and Table 3). In countries where local legislation does not allow infusions outside authorized study sites, the Investigators will be notified in writing that this provision is prohibited.

9.11. Contraception Guidance

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

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

Highly effective contraceptive methods include:

1. Hormonal contraception associated with inhibition of ovulation
2. Intrauterine device
3. Intrauterine hormone-releasing system
4. Bilateral tubal occlusion
5. Vasectomized partner, provided that the partner is the patient's sole sexual partner
6. Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug treatment; reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient

Acceptable contraceptive methods include:

1. A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods)

The above-listed method(s) of contraception chosen for an individual patient can be determined by the Investigator with consideration for the patient's medical history and concomitant medications.

Male patients with a female spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use double barrier contraception (male condom plus appropriate barrier method for the female partner) while on treatment and for at least 8 months after the last dose of study drug. Double barrier contraception is required even with documented medical assessment of surgical success of a vasectomy.

Male patients must not donate sperm while on treatment and for at least 8 months after the last dose of study drug.

10. EFFICACY ASSESSMENTS

10.1. Transfusions

A pRBC transfusion will be administered when a patient has a

- hemoglobin value of 9 g/dL or lower with signs or symptoms of sufficient severity to warrant a transfusion
- hemoglobin value of 7 g/dL or lower regardless of presence of clinical signs or symptoms

Signs or symptoms typically associated with or that precipitate the patient's need for transfusion will also be documented on the eCRF for each individual patient. Typical anemia-related symptoms warranting transfusions include angina, change in mental status (eg, syncope, light headedness, confusion, stroke, transient ischemic attack), severe or worsening shortness of breath, and severe or worsening fatigue. Other symptoms precipitating a potential need for transfusion should be discussed with the Medical Monitor before the transfusion is given.

If a patient meets either transfusion criterion during the study, the Investigator will determine the appropriate number of units of pRBCs to be transfused. It is recommended that the transfusion be performed within 48 hours of the hemoglobin determination responsible for the transfusion.

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

If there is a compelling medical need to deviate from these transfusion guidelines, the Alexion Medical Monitor must be consulted.

Prior to randomization and within 5 days prior to study drug administration on Day 1, each patient's hemoglobin must be evaluated by either local or central laboratory. If at that time the patient's hemoglobin value meets these transfusion guidelines, the patient must be transfused with pRBCs to a hemoglobin level above the transfusion threshold in order to be eligible for randomization. The patient's post-transfusion hemoglobin value should be confirmed by local or central laboratory to be above the transfusion threshold.

10.2. LDH and Other Disease-Related Laboratory Parameters

Blood and urine samples will be collected at the times indicated in the Schedule of Assessments ([Section 7.3](#)) and as indicated in [Section 11.4](#).

The following disease-related laboratory parameters will be measured during the study (refer to [Section 12](#) for PK/PD assessments):

- LDH
- free hemoglobin
- occult blood, urine
- total C5
- haptoglobin

- reticulocyte count
- PNH RBC clone size evaluated by high-sensitivity flow cytometry ([Borowitz 2010](#))
- D-dimer concentration
- estimated glomerular filtration rate (calculated using the Modification of Diet in Renal Disease formula)
- spot urine albumin:creatinine ratio
- C-reactive protein

10.3. PNH Symptomatology

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

10.4. Quality of Life, Additional Signs and Symptoms of PNH, and Resource Utilization Questionnaires

Two validated QoL scales will be administered to patients before study drug administration at the time points specified in the Schedule of Assessments ([Section 7.3](#)).

- The FACIT-Fatigue scale, Version 4.0, is a collection of 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. Patients will score each item on a 5-point scale: 0 (Not at all) to 4 (Very much). Total scores range from 0 to 52, with higher score indicating better QoL.
- The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, is a questionnaire developed to assess the QoL of cancer patients. The questionnaire includes the following subscales: global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social activity), symptom scales (fatigue, nausea and vomiting, and pain), and single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Thirty questions related to QoL, with the first 28 questions scored on a 4-point scale (1 = not at all to 4 = very much) and the final 2 questions that probe the patient's overall health and QoL scored on a scale of 1 (very poor) to 7 (excellent). Each subscale has a range of 0 to 100%, with a high score representing a higher response level. Thus, a high score for a functional scale represents a high level of functioning but a high score for a symptom scale represents a high level of symptomatology/problem.

The FACIT-Fatigue and EORTC QLQ-C30 scales are provided in [Appendix B](#) and [Appendix C](#), respectively.

10.5. Major Adverse Vascular Events

Major adverse vascular events (MAVEs) will be assessed as part of the planned evaluation for AEs as described in [Section 11.7](#).

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

A MAVE is defined as follows:

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

11. SAFETY ASSESSMENTS

The Investigator or his/her designee will meet with patients to discuss the potential safety risks of ALXN1210 and eculizumab and to give the Investigator the opportunity to address any of the patient's safety concerns regarding the study.

Investigators are instructed to follow any AEs through to their conclusion (resolution or stabilization), as described in [Section 11.7.6](#).

The timing of the clinical and laboratory assessments to be performed is specified in the Schedule of Assessments ([Section 7.3](#)). Any clinically significant abnormal results should be followed until resolution or stabilization.

11.1. Demographic/Medical History

11.1.1. Demographics and Baseline Characteristics

A review of demographic parameters, including age, gender, race, and ethnicity will be performed. A complete medical history will be taken and documented. Weight and height will be recorded. Height will be measured at Screening only.

11.1.2. Disease Characteristics

The patient's PNH medical history, including PNH symptoms, date of diagnosis, date of eculizumab initiation, PNH clone size, pRBC transfusions, and history of any MAVEs, will be documented at the Screening visit.

11.1.3. Medical History

The patient's medical history, including prior and concomitant conditions/disorders and transfusion history, will be recorded at the Screening Visit. Medication (prescription or over-the-counter, including vitamins and/or herbal supplements) use within 28 days prior to the start of Screening and meningococcal vaccination within 3 years prior to the first dose of study drug will also be recorded, as described in [Section 9.7](#).

11.2. Physical Examinations

A physical examination will include the following assessments: general appearance; skin; head, ear, eye, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limb; central nervous system; and musculoskeletal system. An abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms.

11.3. Vital Signs

Vital sign measurements will be taken after the patient has been resting for at least 5 minutes, and will include systolic and diastolic blood pressure (BP; millimeters of mercury [mmHg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]).

11.4. Laboratory Assessments

Samples for serum pregnancy, hematology, chemistry, coagulation, and urinalysis will be performed at the times specified in the Schedule of Assessments ([Section 7.3](#)). Specific laboratory assessments are provided in [Appendix D](#). Samples for laboratory assessments will be collected before each study drug administration. If a suspected event of breakthrough hemolysis occurs, an unscheduled visit must take place at which a sample is collected for analysis of LDH and PK/PD by the central laboratory.

Laboratory assessments will be tested at a central laboratory facility. Please refer to the Laboratory Manual for time windows for collection and detailed instructions for collecting, processing, storing, and shipping blood samples for safety assessments. Laboratory reports will be made available to the Investigators in a timely manner for clinical management of patients.

It is anticipated that some laboratory values may be outside the normal value range due to the underlying disease. The Investigators should use their medical judgment when assessing the clinical significance of these values. Clinical significance is defined as any variation in laboratory measurements that has medical relevance and which results in a change in medical care. If clinically significant laboratory changes from baseline value are noted, the changes will be documented as AEs on the AE eCRF. The Investigator will also assess the relationship to study treatment for all clinically significant out-of-range values ([Section 14.9.3](#)). The Investigator will continue to monitor the patient through additional laboratory assessments until (1) values have returned to the normal range or baseline level, or (2) in the judgment of the Investigator, values that are outside the normal range are not related to the administration of study drug or other protocol-specific procedures.

11.4.1. Pregnancy Testing

For females of childbearing potential, a serum or urine pregnancy test (ie, beta-human chorionic gonadotropin [β -hCG]) will be performed according to the Schedule of Assessments ([Section 7.3](#)).

11.4.2. Hematology

Blood samples will be analyzed for the hematology parameters listed in [Appendix D](#).

11.4.3. Serum Chemistry

Blood samples will be analyzed for the serum chemistry parameters listed in [Appendix D](#). Indirect bilirubin is calculated from total and direct bilirubin values; therefore, indirect bilirubin results will not be available if direct bilirubin is below the limit of quantification.

Serum FSH levels will be measured during Screening for postmenopausal female patients to confirm their postmenopausal status.

Chemistry assessments will be performed at the time points specified in the Schedule of Assessments ([Section 7.3](#)). Estimated glomerular filtration rate will be calculated using the Modification of Diet in Renal Disease formula for all visits at which serum chemistries are collected.

11.4.4. Coagulation

Blood samples will be analyzed for the coagulation parameters listed in [Appendix D](#).

11.4.5. Urinalysis and Urine Chemistry

Urine samples will be analyzed for the parameters listed in [Appendix D](#). A microscopic examination of urine samples will be performed if the results of the macroscopic analysis are abnormal.

Urine samples will also be analyzed to measure proteins and creatinine in order to calculate the urine protein:creatinine ratio.

11.4.6. Virus Serology

HIV testing for human immunodeficiency virus type 1 (HIV-1) and human immunodeficiency virus type 2 (HIV-2) is required for all patients prior to enrollment. Known HIV positive patients will not be enrolled.

11.5. Electrocardiograms

For each patient, single 12-lead digital ECGs will be collected according to the Schedule of Assessments ([Section 7.3](#)). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and to determine the clinical significance of the results. These assessments will be indicated on the eCRF. For any clinically significant abnormal ECG results, the Investigator must contact the Medical Monitor to discuss the patient's continued eligibility to participate in this protocol.

11.6. Immunogenicity

Blood samples will be collected to test for presence and titer of ADAs to ALXN1210 or eculizumab in serum prior to study drug administration as indicated in the Schedule of Assessments ([Section 7.3](#)). Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, PK/PD, safety, and activity of ALXN1210 or eculizumab.

11.7. Adverse Event Management

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the start of the study, admissions for social reasons or for convenience), and 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 are not AEs.

Transfusions are treated as efficacy endpoints (see [Section 6.2](#)). Transfusions administered in the inpatient or outpatient setting should not be captured as AEs or SAEs unless identified as such by the Investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect.

A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error.

Cases of pregnancy that occur during maternal or paternal exposure to investigational product 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.

Adverse events should be recorded from the time of signed consent. An AE reported after informed consent but before study drug administration will be considered a pretreatment AE.

Alexion has reporting standards for AEs that are to be followed as described in [Section 11.7.6](#), regardless of applicable regulatory requirements that may be less stringent.

11.7.1. Targeted Adverse Events

As noted in [Section 9.8](#), C5 inhibition is known to increase susceptibility to infections caused by encapsulated bacteria, particularly *N. meningitidis*. The following events are important identified risks in this study:

- Meningococcal infections
- Sepsis
- Serious infections
- Aspergillus infection
- Infusion reactions

Additional events of interest in this study include the following:

- Serious cutaneous adverse reactions
- Cardiac disorders (including ventricular fibrillation)
- Angioedema

11.7.2. Severity Assessment

The severity of AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher. A grading (severity) scale is provided for each AE term. Each CTCAE term is a Lowest Level Term (LLT) per the Medical Dictionary for Regulatory Activities (MedDRA[®]). Each LLT will be coded to a MedDRA preferred term (PT).

Grade refers to the severity of the AE. The CTCAE assigns a grade of 1 through 5, with unique clinical descriptions of severity for each AE ([Table 8](#)).

Table 8: Adverse Event Severity Grading Scale

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) ^a
Grade 3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL ^b
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Abbreviations: ADL = activities of daily living; AE = adverse event

^a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^b Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Any change in the severity of an AE should be documented based on specific guidelines in the eCRF Completion Guidelines.

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met specific criteria for an SAE as described in [Section 11.7.4](#).

11.7.3. Causality Assessment

An Investigator must provide a causality assessment (Unrelated, Unlikely, Possible, Probable, or Definite) for all AEs (both serious and nonserious) based upon the Investigator's medical judgment and the observed symptoms associated with the event ([Table 9](#)). This assessment must be recorded on the eCRF and any additional forms as appropriate.

Table 9: Causality Assessment Descriptions

Assessment	Description
Not Related/Unrelated	Suggests that there is no causal association between the investigational product and the reported event.
Unlikely Related	Suggests that the clinical picture is highly consistent with a cause other than the investigational product but attribution cannot be made with absolute certainty and a relationship between the investigational product and AE cannot be excluded with complete confidence.
Possibly Related	Suggests that treatment with the investigational product may have caused or contributed to the AE (ie, the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the investigational product but could also have been produced by other factors).
Probably Related	Suggests that a reasonable temporal sequence of the event with the investigational product administration exists and the likely causal association of the event with the investigational product. This will be based upon the known pharmacological action of the investigational product, known or previously reported adverse reactions to the investigational product or class of drugs, or judgment based on the Investigator's clinical experience.
Definitely Related	Temporal relationship to the investigational product, other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain event, corresponds with the known pharmaceutical profile, improvement on discontinuation, reappearance on rechallenge.

11.7.4. Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening (ie, patient was at risk of death at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

The expectedness of an SAE will be determined by Alexion, based on the current version of the IB.

Information pertaining to the collection and reporting of SAEs is provided in [Section 11.7.6](#).

11.7.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to investigational product or procedure. United States Title 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Alexion has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent

with global regulations and the associated detailed guidances. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs/IECs.

11.7.6. Collection and Reporting of Adverse Events

11.7.6.1. All Adverse Events

All AEs (serious and nonserious) will be collected from the signing of the informed consent form (ICF) until 56 days after the last dose of study drug for patients with ET or until 56 days after the last dose of study drug for patients who complete the study. All AEs must be recorded on the eCRF upon the Investigator or his/her staff becoming aware of their occurrence.

Investigators will be instructed to report the SAE including their assessment (eg, severity, seriousness, and potential relatedness to study drug) to Alexion Global Pharmacovigilance (GPV) within 24 hours of first awareness of the event via the Safety Gateway.

If a patient's treatment is discontinued as a result of an AE, study site personnel must clearly capture the circumstances and data leading to any such dose interruption or discontinuation of treatment in the AE and Exposure pages of the eCRF.

11.7.6.2. Serious Adverse Events

All SAEs will be recorded regardless of the Investigator's assessment of causality. No time limit exists on reporting SAEs that are thought to be causally related to the study drug. Investigators are at liberty to report SAEs irrespective of causality.

For all SAEs, the Investigator must provide the following:

- Appropriate and requested follow-up information in the time frame detailed below
- Causality of the SAE(s)
- Treatment of/intervention for the SAE(s)
- Outcome of the SAE(s)
- Supporting medical records and laboratory/diagnostic information

All SAEs must be reported to Alexion GPV within 24 hours of the Investigator or site staff awareness. These timelines for reporting SAE information to the Sponsor need to be followed for the initial SAE report and for all follow-up SAE information.

The Investigator or designee must record the SAE data in the eCRF and verify the accuracy of the information with corresponding source documents. The SAE report should be submitted electronically via the Safety Gateway.

In the event that either the electronic data capture (EDC) system or the Safety Gateway is unavailable at the site(s), the SAE must be reported on paper. Facsimile transmission or email may be used in the event of electronic submission failure.

Email: PPD [REDACTED]

Facsimile: PPD [REDACTED] (NOTE: A local facsimile number will be provided for non-US sites)

When further information becomes available, the eCRF should be updated with the new information and an updated SAE report should be submitted to Alexion GPV via Safety Gateway.

If applicable, additional information such as relevant medical records should be submitted to Alexion GPV via the email address or fax number noted above.

All paper forms and follow-up information submitted to the Sponsor outside of the Safety Gateway (eg, discharge summary) should be kept in the appropriate section of the study file.

11.7.7. Sponsor Reporting Requirements

Alexion GPV or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria. This protocol will use the current IB as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor from the Reference Safety Document.

11.7.8. Investigator Reporting Requirements

The Investigator must fulfill all local regulatory obligations required for the study Investigators. It is the Investigator's responsibility to notify the IRB/IEC of all SAEs that occur at his or her site, as required per IRB/IEC standard operating procedures (SOPs). Investigators will also be notified of all SUSAR events that occur during the clinical study. Each site is responsible for notifying its IRB/IEC of these additional SAEs as per IRB/IEC SOPs.

11.8. Exposure During Pregnancy and Lactation

Pregnancy data will be collected during this study for all patients and a female spouse/partner of male patients. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.

For all Alexion products, both in development or postapproval, exposure during pregnancy must be recorded and the pregnancy followed until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the patient discontinues study drug or withdraws from the study.

If a female patient or a patient's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion GPV via fax or email ([Section 11.7.6.2](#)). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GPV. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding") and any AEs experienced by the infant must be reported to Alexion GPV or designee via email or facsimile ([Section 11.7.6.2](#)).

Pregnancy in itself is not regarded as an AE unless there is a suspicion that the investigational product 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.

11.9. Safety Monitoring

The Alexion Medical Monitor, GPV physician, or both will monitor safety data throughout the course of the study.

Alexion will review all information pertaining to the SAEs within the time frames mandated by company procedures. The Alexion Medical Monitor will, as appropriate, consult with the GPV physician, to review trends in safety data.

12. PHARMACOKINETICS AND PHARMACODYNAMICS

Blood samples for determination of serum drug concentrations and PD assessments will be collected before and after administration of study drug at the time points indicated in the Schedule of Assessments ([Section 7.3](#)). The actual date and time (24-hour clock time) of each sampling will be recorded. The number of PK sampling time points for any given patient will not exceed the currently planned number of time points; in the event of breakthrough hemolysis, an additional PK/PD sample will be required.

End of infusion blood samples for PK and PD assessment should be collected from the arm opposite to the arm used for infusing drug. Please refer to the Laboratory Manual for details on sample collection, including blood volume requirements.

Assessments for PK/PD are as follows:

- Serum ALXN1210 and eculizumab concentration over time
- cRBC hemolytic activity over time (exploratory)
- Free and total C5 concentrations over time

13. DATA QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Perform start-up training to instruct the Investigators and site personnel. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by email, telephone, or facsimile.
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

Authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of an Alexion audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable IRBs/IECs with direct access to original source documents.

13.1. Data Collection and Storage

All clinical data will be recorded promptly and accurately in the EDC system. When recorded electronically, CRFs will be electronically generated. All raw data will be preserved in order to maintain data integrity. The Investigator or designee will assume the responsibility of ensuring the completeness, accuracy, and timeliness of the clinical data.

The EDC system is fully validated and compliant with CFR Title 21 Part 11. The EDC system will maintain a complete audit trail of all data changes. At each scheduled monitoring visit, the Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the EDC system.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate source documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each patient receiving study drug.

The Investigator will allow the Sponsor's representatives, contract designees, authorized regulatory authority inspectors, and the IRB/IEC to have direct access to all documents pertaining to the study.

13.2. Records Retention

The Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation or longer if required per local regulations. If it becomes necessary for the Sponsor or the Sponsor's designee or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

14. STATISTICAL METHODS AND PLANNED ANALYSES

14.1. General Considerations

All data collected will be presented in summary tabulations. All data, as well as any outcomes derived from the data, will be presented in detailed data listings. Graphical displays may also be provided, when appropriate. All analyses will be performed using SAS[®] release, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software. Continuous variables will be summarized using descriptive statistics, including number of observations and mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of patients. All statistical tests performed will be based on a 2-sided 5% level of significance unless otherwise specified. Any and all exclusions will be documented in patient listings.

Details of the statistical analyses described below will be specified in a separate Statistical Analysis Plan (SAP) before database lock and analysis. Any change to the data analysis methods described in the protocol will require an amendment only if it changes the primary or key 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.

A CSR will be produced based on efficacy, safety, PK, PD, and immunogenicity data when all patients who remain on study have completed the 26-week randomized treatment period. A final CSR to summarize long-term efficacy, safety, PK, PD, and immunogenicity data will be produced at study completion.

14.2. Determination of Sample Size

Approximately 192 patients will be randomly assigned in a 1:1 ratio to continue on eculizumab (N = 96) or switch to ALXN1210 (N = 96) to ensure at least 172 evaluable patients (assumes no more than a 10% dropout rate). The sample size estimation is based on a noninferiority design comparing patients treated with ALXN1210 to those treated with eculizumab. The primary endpoint of hemolysis as directly measured by LDH-PCHG from Baseline through Day 183 will be used to assess noninferiority.

For the primary endpoint of LDH-PCHG from baseline to Day 183, using a noninferiority margin (NIM) of 15% and a type I error of 1-sided 2.5%, a standard deviation of 30%, a minimum of 172 patients will provide 90% power to demonstrate noninferiority of ALXN1210 to eculizumab. This margin is based on data from Alexion's PNH registry. For patients who discontinued eculizumab, the mean percent change in LDH was +134% and represents the loss of benefit relative to patients who remained on eculizumab whose change in LDH is expected to remain stable. Preserving 50% of the benefit would give a margin of 67%; however, the more conservative and clinically appropriate margin of 15% was selected to preserve a more substantial amount of treatment effect (89%).

Adjusting for a possible 10% dropout rate, approximately 192 patients will be enrolled in this study.

Table 10: Summary of Parameters Used in Estimating Sample Size

Parameters	Percent Change in LDH
Power	90%
Type I error	1-sided 0.025
Noninferiority margin	0.15
Allocation ratio	1:1
Standard deviation of eculizumab/ALXN1210 response	0.30/0.30
Assumed treatment difference	0
Estimated sample size (SS)	172
Adjusted SS for 10% dropouts	192

Note: Software package: Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, US. www.ncss.com.

14.3. Analysis Sets

Efficacy analyses will be performed on the Full Analysis Set (FAS). The primary efficacy endpoint analysis, as well as key secondary endpoint analyses, will also be performed on the Per Protocol (PP) set. The FAS is the primary population for all efficacy analyses. The FAS will include all patients who received at least 1 dose of ALXN1210 or eculizumab.

The PP set, which will be finalized prior to database lock, will consist of FAS patients who meet all of the following criteria:

- Missed no doses of ALXN1210 or no more than 1 dose of eculizumab during the 26-week randomized treatment period
- Met inclusion criteria #2, 3, and 4
- Did not meet exclusion criteria #1, 2, 3, 4, or 5
- Never received the wrong randomized treatment
- Followed the protocol-specified transfusion guidelines

Safety analyses will be performed on the Safety Set, defined as all patients who receive at least 1 dose of ALXN1210 or eculizumab.

Pharmacokinetic and PD analyses will be performed on all patients who receive at least 1 dose of study drug and who have evaluable PK and PD data.

14.4. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history and transfusion history, will be summarized by treatment group and overall for the FAS, and Safety sets. No formal statistical comparisons will be made.

14.5. Patient Disposition

All patients will be included in the summaries of patient disposition, which will describe the frequency and percentage of patients screened and treated and who completed or withdrew from the study, along with reason for withdrawal from the study, by treatment group.

The numbers of patients who are treated, discontinue treatment (along with reason for treatment discontinuation), complete or withdraw from the Randomized Treatment Period (along with

reason for withdrawal), enter the Extension Period, and complete or withdraw from the Extension Period (along with reason for withdrawal) will be tabulated by treatment group and overall.

14.6. Prior and Concomitant Medications and Nonpharmacologic Procedures

Each patient's prior and concomitant medication use will be coded using the World Health Organization Drug Dictionary, and the frequency and percentage of concomitant medications will be summarized. Medications will be summarized by Anatomic-Therapeutic-Chemical (ATC) class and preferred drug name using frequency counts and percentages of patients in the Safety set.

14.7. Treatment Compliance

The number of infusions received per patient will be tabulated by treatment group for the FAS and Safety sets.

14.8. Efficacy Analyses

14.8.1. Primary Efficacy Analysis

The primary efficacy endpoint is the difference between treatment arms in LDH-PCHG from Baseline to Day 183. Baseline is defined as the average of all assessments analyzed by the central laboratory prior to first study drug administration.

The percentage change in LDH will be analyzed using a mixed model for repeated measures (MMRM; [Mallinckrodt 2001, 2004](#)) with the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction as well as the continuous, fixed covariate of baseline LDH and the stratification randomization indicator of pRBC transfusion history (yes/no within 12 months prior to Day 1). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. A difference in LDH-PCHG between the ALXN1210 and eculizumab treatment groups along with a two-sided 95% CI will be calculated.

If the upper bound of the 95% CI for the difference (ALXN1210-eculizumab) is less than the NIM of 15%, then ALXN1210 treatment will be concluded to be noninferior to eculizumab.

14.8.2. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints of proportion of patients with breakthrough hemolysis, change from baseline in FACIT-Fatigue, proportion of patients who do not require a transfusion, and proportion of patients with stabilized hemoglobin will be summarized by treatment group. The percentage of patients with breakthrough hemolysis will be computed for both the ALXN1210 and eculizumab treatment groups. A difference in the percentage of patients with breakthrough hemolysis in the 2 treatment groups will be calculated, along with a 95% CI for the difference. The 95% CI for the difference between ALXN1210 and eculizumab treatment groups will be calculated using the Newcombe confidence interval method. The same approach will be employed for transfusion avoidance and stabilized hemoglobin. Transfusion avoidance will be achieved only by those patients who did not receive a transfusion and did not meet the protocol-

specified guidelines for transfusion. For change from baseline in FACIT-Fatigue, the same approach used for the primary endpoint will be employed.

These key secondary endpoints will be tested in a hierarchical manner provided that noninferiority was declared for the primary endpoint.

When performing the analyses for the key secondary efficacy endpoints, a closed-testing procedure will be used; lack of significance of a test precludes assessment of subsequent tests. Estimates and CIs will be computed for all key secondary efficacy endpoints regardless of whether a lack of significance of a test precludes assessment of subsequent tests.

1. If the upper bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with breakthrough hemolysis is less than the NIM of 20%, then ALXN1210 will be declared noninferior for this parameter and the next parameter will be tested.
2. If the lower-bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in change from baseline in FACIT-Fatigue is greater than the NIM of -3, then ALXN1210 will be declared noninferior for this parameter and the next parameter will be tested.
3. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups for TA is greater than the NIM of -20%, then ALXN1210 will be declared to be noninferior to eculizumab and the next parameter will be tested.
4. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with stabilized hemoglobin is greater than the NIM of -20%, then ALXN1210 will be declared noninferior for this parameter.

If noninferiority is established for all key secondary endpoints, and a larger effect for ALXN1210 is observed, then superiority will be assessed using a closed-testing procedure and using a 2 sided 0.05 test for each parameter as follows:

5. PCHG-LDH from baseline to Day 183 (Week 26)
6. Change from baseline to Day 183 (Week 26) in FACIT-Fatigue
7. Proportion of patient with breakthrough hemolysis through Day 183 (Week 26)
8. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)
9. Transfusion avoidance

Due to the hierarchical testing order being prespecified, no adjustment of the type I error is required.

14.8.3. Other Secondary Efficacy Analyses

Total number of units of pRBCs transfused during treatment and the number (%) of patients with LDH within the normal range at each study visit will be computed for both ALXN1210 and eculizumab treatment groups. Changes from baseline in EORTC-QLQ-C30 will be summarized by treatment group at baseline and at the study visits where these assessments are collected

(Section 7.3). Shifts from baseline in clinical manifestations of PNH will be summarized by treatment group and at the study visits where these assessments are collected. The number of any treatment-emergent MAVEs (n) and number of patients with events (n, %) will be displayed by treatment group.

No statistical inference of these parameters is planned.

14.9. Safety Analyses

All safety analyses will be performed for the Safety set, defined as all patients who receive at least 1 dose of ALXN1210 or eculizumab. Safety results will be reported by treatment group.

14.9.1. Adverse Events

The following definitions will be used for AEs:

- Pretreatment adverse events: Any AE that starts after providing informed consent, but before the first infusion of study drug
- Treatment-emergent adverse event (TEAE): Any AE that starts during or after the first infusion of study drug.

The incidence of TEAEs, TEAEs leading to withdrawal from the study, TEAEs leading to study treatment discontinuation, drug-related TEAEs, TEAEs during study drug administration, severe TEAEs, and SAEs will be summarized. All AEs will be coded using MedDRA version 18 or higher, and will be summarized by system organ class (SOC) and PT.

14.9.2. Physical Examination and Vital Signs

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

Vital signs will be summarized descriptively at Baseline and postbaseline time points and for changes from Baseline by treatment group.

By-patient data listings will be provided.

14.9.3. Clinical Laboratory Tests

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

14.9.4. Electrocardiograms

By-patient data listings of ECG parameters will be provided. Changes from baseline in electrocardiogram intervals (PR, RR, QT, and QTcF) will be provided by treatment group. QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

14.9.5. Immunogenicity

Abnormal immunogenicity findings, including the incidence and titers for ADAs to ALXN1210 or eculizumab, will be summarized in tabular format by treatment group. The proportion of patients ever positive and the proportion of patients always negative may be explored.

14.10. Pharmacokinetic/Pharmacodynamic Analyses

Individual serum concentration data for all patients who receive at least 1 dose of study drug (ie, ALXN1210 or eculizumab) and who have evaluable PK data will be used to derive PK parameters for ALXN1210 and eculizumab.

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

Descriptive statistics will be presented for all ALXN1210 and eculizumab PD endpoints at each sampling time (Section 7.3). The PD effects of ALXN1210 and eculizumab administered IV will be evaluated by assessing the absolute values and changes and percentage changes from baseline in total and free C5 serum concentrations and cRBC hemolysis over time, as appropriate.

Assessments of ALXN1210 PK/PD relationships may be explored using data from this study or in combination with data from other studies.

14.11. Other Statistical Issues

14.11.1. Missing or Invalid Data

If a Day 1 assessment is missing, the Screening assessment will be used as the Baseline assessment.

Missing data for QoL instruments will be handled as specified in the instructions for each instrument.

15. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

15.1. Informed Consent

The Investigator or designee is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The Investigator or designee is responsible for ensuring that informed consent is given by each patient or the patient's legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product. The Investigator or designee must retain the original version of the signed ICF. If the ICF is amended, the original signed, amended version must also be retained. A copy of the signed ICF(s) must be given to the patient.

As used in this protocol, the term "informed consent" includes all consent given by patients or their legal representatives.

15.2. Safety Review

This study will be monitored by an Alexion Safety Management Team (SMT). The SMT is a multidisciplinary team responsible for safety that meets monthly and, if needed, on an ad-hoc basis. The team is composed of Alexion subject matter experts involved in the studies (eg, Medical Monitors/Global Medical Leads, Global Safety Leads). The objective of SMT review meetings is to ensure that emergent potential important safety concerns across all ALXN1210 clinical studies are reviewed and evaluated and to make recommendations on continuing study drug administration or termination of the studies.

In addition, a Safety Review Board (SRB) will meet periodically to review and evaluate the accumulated safety data for the study and make recommendations on continuing study drug administration or termination of the study. This SRB will be constituted of Alexion physicians who have no direct relationship to the study and will be chaired by the head of GPV. Formal recommendations and minutes will be recorded. All appropriate regulatory authorities and ethics committees will be notified of any significant action.

In order to closely monitor the known risk of meningococcal infection associated with the mechanism of action of eculizumab and ALXN1210, an independent Data Monitoring Committee (DMC) will evaluate all suspected or confirmed meningococcal cases (including meningococcal sepsis) across all ALXN1210 Phase 3 studies.

15.3. Ethical Review

All ICFs must be compliant with the ICH guideline on GCPs. Documentation of IRB/IEC approval of the protocol and the ICF must be provided to the Sponsor before the study may begin at the investigational sites. The IRB/IEC(s) will review the protocol as required.

15.4. Regulatory Considerations

This study will be conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- The ICH GCP Guideline [E6]
- Applicable national and local laws and regulations

The Investigator or designee will promptly submit the protocol to applicable IRB/IEC(s).

Some of the obligations of the Sponsor will be assigned to a third-party organization.

An identification code assigned to each patient by the EDC system will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and other study-related data.

15.4.1. Changes/Deviations to Protocol

The Investigator may need to deviate from the protocol to eliminate an immediate hazard to a trial subject without prior notification of the IRB/IEC. Any deviations from the protocol must be fully documented. The deviation and the reasons for it should be submitted to the IRB/IEC, Sponsor, and appropriate regulatory authority if required (ICH GCP E6 [R1] 4.5.4).

After the commencement of the clinical trial, the Sponsor may make changes to the protocol. If those changes are significant, the regulatory authority and applicable IRB/IEC will be notified.

15.5. Publication Policy

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

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17. APPENDICES

APPENDIX A. MANAGEMENT OF POTENTIAL DRUG INFUSION REACTIONS

Infusion of other monoclonal antibodies has been associated with infusion reactions, with onset typically during or shortly after completion of the infusion. For this reason, patients will be carefully observed during each infusion.

Patients who develop AEs of rash, hives, itching, or dysphagia of mild to moderate intensity during their infusion of ALXN1210 or eculizumab may continue to receive the infusion if deemed to be medically appropriate by the Investigator. Medical intervention may include, but is not limited to, slowing of the infusion rate (with or without treatment) or interrupting or stopping the infusion.

Any acute reaction should be treated according to standard medical practice depending upon clinical signs and symptoms. If a patient requires medical intervention, the patient should remain at the investigational site until his or her condition stabilizes. The AE and any associated concomitant medications must be captured on the patient's source document and electronic case report form (eCRF).

Some patients treated with IV infusions of monoclonal antibodies have experienced concurrent reactions with signs or symptoms that can be classified as acute allergic reactions/hypersensitivity reactions or cytokine release syndrome. Signs and symptoms include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Anaphylaxis might occur at any time during an infusion; therefore, patients will be monitored closely during the infusion. In addition, the re-administration of some monoclonal antibodies has been associated with serum sickness-like reactions manifesting 1 to 14 days after drug administration. All AEs that may indicate an infusion-related response will be graded according to the CTCAE v4.03 or higher.

Before any infusion is started, the treating physician and other appropriate personnel must make certain that medication (ie, adrenaline, inhaled beta agonists, antihistamines, corticosteroids) and other equipment to treat anaphylaxis are readily available. The infusion must be stopped immediately if Grade ≥ 2 allergic/hypersensitivity reactions (including drug fever) or Grade ≥ 3 cytokine release syndrome/acute infusion reaction occurs. The Sponsor must be notified within 24 hours of any infusion reaction requiring interruption or discontinuation of study drug.

Patients who experience a reaction during the administration of study drug should be treated according to institutional guidelines. For a Grade 1 or Grade 2 infusion reaction, the infusion should be temporarily stopped and treatment with an antihistamine (eg, diphenhydramine 25 to 50 mg orally or equivalent) and acetaminophen (650 mg orally or equivalent) may be considered. If the patient's signs and symptoms have resolved (with or without administration of the above medication), the infusion may be restarted. However, the patients should be infused at a slower rate and be monitored closely for any signs and symptoms of infusion reactions during the remainder of the infusion. Patients experiencing an infusion reaction should be observed in the clinic until resolution of the reaction, or until the Investigator determines the patient is no longer

at risk. Patients who experience a severe reaction during administration of study drug resulting in discontinuation of study drug should undergo all scheduled safety, PK, and PD evaluations required by the protocol.

If anaphylaxis occurs according to the criteria listed below, then administration of subcutaneous epinephrine (1/1000, 0.3 mL to 0.5 mL, or equivalent) should be considered. In the case of bronchospasm, treatment with an inhaled beta agonist also should be considered. Patients administered an antihistamine for the treatment or prevention of an infusion reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

Clinical Criteria for Diagnosing Anaphylaxis:

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

Source: [Sampson 2006](#)

Abbreviations: BP = blood pressure; PEF = peak expiratory flow

APPENDIX B. FACIT-FATIGUE SUBSCALE VERSION 4

FACIT Fatigue Scale (Version 4)

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

		Not at all	A little bit	Some- what	Quite a bit	Very much
H17	I feel fatigued.....	0	1	2	3	4
H12	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

APPENDIX C. EORTC QUALITY OF LIFE QUESTIONNAIRE (EORTC QLQ-C30)



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your first initial:

Your birth date (Day, Month, Year):

Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you:

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX D. PROTOCOL LABORATORY TESTS

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