A Phase 3, Open-label Study Of ALXN1210 In Children And Adolescents With Paroxysmal Nocturnal Hemoglobinuria (PNH)

Unique Protocol ID:	ALXN1210-PNH-304
NCT Number:	NCT03406507
EudraCT Number:	2017-002820-26
Date of Protocol:	22 April 2020

PROTOCOL ALXN1210-PNH-304

A PHASE 3, OPEN-LABEL STUDY OF ALXN1210 IN CHILDREN AND ADOLESCENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Sponsor:	Alexion Pharmaceuticals, Inc. (Alexion) 121 Seaport Boulevard Boston, MA 02210 USA
Sponsor Contact:	PI Alexion Pharma GmbH Giesshübelstrasse 30 Zurich, 8045, Switzerland Telephone: PI
Medical Monitor:	PI Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard Boston, MA 02210 USA
IND Number:	128367
EudraCT Number:	2017-002820-26
Date of Initial Protocol:	05 Sep 2017
Amendment 1 (France)	19 Dec 2017
Amendment 2 (Global)	23 Aug 2018
Amendment 2.1 (France)	13 Sep 2018
Amendment 2.2 (Norway)	06 Jun 2019
Amendment 3 (Global)	22 Apr 2020

SPONSOR SIGNATURE PAGE

A PHASE 3, OPEN-LABEL STUDY OF ALXN1210 IN CHILDREN AND ADOLESCENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

PROTOCOL NUMBER: ALXN1210-PNH-304

PI

27-Apr-2020 | 09:50:49 EDT

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ALXN1210. I have read the ALXN1210-PNH-304 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

STUDY CONTACT INFORMATION

Emergency Contact Information

Study Role	Name	Address and Telephone Number
Clinical Project Leader	PI	Alexion Pharma GmbH Giesshübelstrasse 30 Zurich, 8045, Switzerland Telephone: PI
Medical Monitor	PI	Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard Boston, MA 02210, USA Telephone: PI
24-Hour Emergency Contact Phone Number		PI Local Contact Numbers can be found in the Study Contact list distributed to Study Sites.

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, Open-Label Study of ALXN1210 in Children and Adolescents with Paroxysmal Nocturnal Hemoglobinuria (PNH)	
Protocol No: ALXN1210-PNH-304	**EudraCT Number:** 2017-002820-26
Study Center(s): Approximately 10 investigative sites globally.	
Length of Study: Estimated date first patient treated: February 2018 Estimated date last patient completed: March 2024	**Phase of Development:** 3
Objective: The objectives of this study are to assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of ALXN1210 in pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH).	
Study Design and Methodology: This is a Phase 3, open-label, single-arm multicenter study to evaluate the PK/PD, safety, and efficacy of ALXN1210 administered by intravenous (IV) infusion to pediatric patients (< 18 years of age) with PNH. The study consists of a 4-week Screening Period, a 26-week Primary Evaluation Period, and an Extension Period. Consenting patients will be screened for study eligibility up to 4 weeks prior to Day 1. Patients who satisfy all of the inclusion criteria and all of the exclusion criteria will be enrolled into the Primary Evaluation Period and receive a weight-based loading dose of ALXN1210 on Day 1, followed by weight-based maintenance treatment with ALXN1210 on Day 15 and once every 8 weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg, for a total of 26 weeks of treatment. For patients entering the study on eculizumab therapy, Day 1 of study treatment will occur 2 weeks from the patient's last dose of eculizumab. An interim analysis of data, including ALXN1210 PK and free complement component 5 (C5) levels, will be conducted after 4 patients weighing ≥ 5 kg to < 40 kg have completed dosing through Day 71. Enrollment of patients will proceed without interruption while the analysis is ongoing. The accrued safety and PK/PD data will be assessed to ensure that ALXN1210 treatment is well tolerated and is providing adequate complement inhibition. Based on this review, the dose regimen may be adjusted. In addition, an independent Data Monitoring Committee (DMC) will review safety data from the study on a regular basis. To support regulatory filings, interim analyses may be conducted based on efficacy, safety, PK, PD, and immunogenicity data collected through the end of the 26-week Primary Evaluation Period (Day 183) after 12 patients are enrolled, and after enrollment is completed. After completion of all pre-dose assessments on Day 183, all patients will enter an Extension Period and continue to receive ALXN1210 according to the appropriate weight-based regimen. The Extension Period will continue until the product is registered or approved (in accordance with country-specific regulations) or for up to 4 years, whichever occurs first, except in Norway where the Extension Period will be 4 years. The end of study is defined as the last patient's last visit or follow-up (whether on site or via phone call) in the Extension Period.	
Number of Patients (planned): Approximately 13 patients, from birth to < 18 years, will be enrolled to ensure at least 10 evaluable patients complete the 26-week period.	
Diagnosis and Main Criteria for Inclusion and Exclusion: Patients must meet all inclusion and no exclusion criteria. Patients who fail any of the eligibility criteria may be rescreened once for participation. **Inclusion Criteria:** 1. Male and female patients < 18 years of age and weighing ≥ 5 kg at the time of consent. 2. Documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry evaluation of red blood cells (RBCs) and white blood cells (WBCs), with granulocyte or monocyte clone size of ≥ 5%. 3. For patients not currently treated with complement inhibitor, presence of 1 or more of the following PNH-related signs or symptoms within 3 months of Screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia, history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed RBC transfusion due to PNH.	

4. Lactate dehydrogenase (LDH) values at Screening as follows:
   a. For patients not currently treated with eculizumab, LDH level ≥ 1.5 × upper limit of normal (ULN).
   b. For patients who are currently taking eculizumab, LDH ≤ 1.5× ULN (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).
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. Patients who cannot be vaccinated must receive antibiotic prophylaxis for the entire treatment period and for 8 months following last dose.
6. Patients must have been vaccinated against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* according to national and local vaccination schedule guidelines, as appropriate.
7. Female patients of childbearing potential (ie, have achieved menarche) and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug.
8. Patient's legal guardian must be willing and able to give written informed consent and the patient must be willing to give written informed assent (if applicable as determined by the central or local Institutional Review Board [IRB]/Institutional (or Independent) Ethics Committee [IEC]) and comply with the study visit schedule.

Exclusion Criteria:

1. Platelet count < 30,000/mm^3 (30×10^9/L) at Screening.
2. Absolute neutrophil count < 500/μL (0.5×10^9/L) at Screening.
3. History of bone marrow transplantation.
4. History of *N meningitidis* infection.
5. History of unexplained, recurrent infection.
6. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
7. History of malignancy within 5 years of Screening with the exception of adequately treated nonmelanoma skin cancer or carcinoma in situ of the cervix.
8. 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.
9. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of Screening, coexisting chronic anemia unrelated to PNH) that would make them unlikely to tolerate the requirements of the protocol.
10. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.
11. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
12. Females who plan to become pregnant or are currently pregnant or breastfeeding.
13. Females of childbearing potential who have a positive pregnancy test result at Screening or on Day 1.
14. 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.
15. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
16. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator or Sponsor, 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 for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg will be administered by IV infusion. Dosages are based on the patient's body weight recorded on dosing day or the most recently recorded weight, as shown in the table below:

Body Weight Range (kg)[a]	Loading Dose (mg)	Maintenance Doses (mg)	Maintenance Dosing Frequency
≥ 5 to < 10	600[b]	300	q4w
≥ 10 to < 20	600	600	q4w
≥ 20 to < 30	900	2100	q8w
≥ 30 to < 40	1200	2700	q8w
≥ 40 to < 60	2400	3000	q8w
≥ 60 to < 100	2700	3300	q8w
≥ 100	3000	3600	q8w

Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks
[a] Dose regimen will be based on body weight obtained at the study visit. If the study drug needs to be prepared the night prior to the visit, the weight from the previous visit may be used.
[b] With the agreement of the Alexion Medical Monitor, the 600 mg loading may be given to patients weighing ≥ 5 to < 10 kg as 2 separate infusions administered no more than 24 hours apart

Reference Therapy, Dosage, and Mode of Administration:
Not applicable

Planned Duration of Treatment: 26-week Primary Evaluation Period followed by an Extension Period until the product is registered or approved (in accordance with country-specific regulations) or for up to 4 years, whichever occurs first, except in Norway where the Extension Period will be 4 years.

Endpoints:
Primary endpoint:
- PK/PD parameters (trough and peak) at Baseline and Weeks 2, 10, 18, and 26
  - PK: maximum serum concentration (C_{max}), trough serum concentration (measured at end of dosing interval at steady state; C_{trough}), accumulation ratio
  - PD: change in free C5 concentrations and in chicken red blood cell (cRBC) hemolytic activity over time

Secondary endpoint:
- Percentage change in LDH from baseline to Day 183 (Week 26)
- Transfusion avoidance (TA), defined as the proportion of patients who remain transfusion-free and do not require a transfusion through Day 183 (Week 26)
- Change in quality of life (QoL), as measured by Pediatric Functional Assessment of Chronic Therapy (FACIT) Fatigue questionnaire (patients ≥ 5 years of age), from baseline to Day 183 (Week 26)
- 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 through Day 183 (Week 26)
- Percentage change in free hemoglobin from baseline to Day 183 (Week 26)
- 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, major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH as follows:
  - For patients who enter the study naïve to complement inhibitor treatment, elevated LDH ≥ 2 × ULN after prior LDH reduction to < 1.5 × ULN on therapy
  - For patients who enter the study stabilized on eculizumab treatment, elevated LDH ≥ 2 × ULN

Safety
The safety and tolerability of ALXN1210 will be evaluated from baseline to Week 26 and throughout the extension period by physical examinations, vital signs, physical growth, 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.

Statistical methods:

Pharmacokinetics/Pharmacodynamics:

Sparse PK and PD (free C5) samples will be collected over the course of the study. Individual serum concentration data for all patients who receive at least 1 dose of ALXN1210 and who have evaluable PK data will be used to derive PK parameters for ALXN1210. 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.

Pharmacodynamic analyses will be performed for all patients who receive at least 1 dose of ALXN1210 and who have evaluable PD data. Descriptive statistics will be presented for all ALXN1210 PD endpoints at each sampling time. The PD effects of ALXN1210 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 change from baseline in 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. Analyses will be conducted separately for naïve and previously eculizumab-treated patients.

This study is descriptive in nature and not statistically powered for hypothesis testing due to the rarity of disease in pediatric patients. A sample size of 10 should be sufficient to adequately describe PK/PD in pediatric patients with PNH.

Efficacy:

The efficacy analyses will be performed on the Full Analysis Set (FAS). The FAS will include all patients who receive at least 1 dose of ALXN1210 and have at least 1 postbaseline assessment. All data collected will be presented using summary tables, figures, and data listings. 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, SD, median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of patients. Analyses will be conducted separately for naïve and previously eculizumab-treated patients.

Safety:

All safety analyses will be performed on the Safety Set, defined as all patients who receive at least 1 dose of ALXN1210. The incidence of treatment-emergent AEs will be summarized by system organ class and preferred term overall, by severity, and by relationship to treatment. Observed values and changes from baseline (last assessment prior to ALXN1210) in ECGs, vital signs, and laboratory assessments, as well as presence of ADA, will be summarized. Shifts from baseline in laboratory assessments will be summarized for all study visits.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

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
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum serum concentration
cRBC	chicken red blood cell
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough serum concentration (measured at end of dosing interval at steady state)
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMLA	eutectic mixture of local anesthetics
EOI	end of infusion
EOS	end of study
ET	early termination
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FAS	Full Analysis Set
GCP	good clinical practice
GDS	Global Drug Safety
Hib	Haemophilus influenzae type b
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
LLT	lowest level term
mAb	monoclonal antibody
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
PD	pharmacodynamic(s)
PEF	peak expiratory flow
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
pRBC	packed red blood cell
PT	preferred term

Abbreviation	Definition
q4w	once every 4 weeks
q8w	once every 8 weeks
QoL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
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 a progressive, debilitating, and life-threatening disease characterized by complement-mediated hemolysis, thrombosis, and bone marrow failure. PNH has an estimated worldwide incidence of 1.3 per million population (Hill, 2006). The onset of PNH is typically in adulthood, with pediatric cases accounting for < 5% of reported cases (Ware, 1991). Given the extremely small target population, studies of children with PNH have been limited to case reports, case series, and a small clinical trial (Reiss, 2014).

In adults, the clinical manifestations of PNH include hemoglobinuria, chronic renal insufficiency, erectile dysfunction, thrombosis, abdominal pain, dyspnea, and dysphagia (Parker, 2005). In contrast, children with PNH usually present with nonspecific symptoms related to the underlying bone marrow disorder, such as pallor, fatigue, or jaundice, with hemoglobinuria appearing less commonly (Ware, 1991). Clinical evaluation in pediatric patients also reveals bone marrow failure syndromes, such as aplastic anemia and refractory cytopenia (van den Heuvel-Eibrink, 2007). Once the bone marrow disorder is resolved in the child or the PNH clone expands (the cause of which is still unknown), the disease eventually evolves into one more typically seen in adults at presentation. Thus, pediatric patients can be expected to suffer substantial morbidity related to hemolysis, as seen in adult PNH patients (Parker, 2005).

The ALXN1210 clinical program in patients with PNH includes a Phase 3 study in adults with PNH who are naïve to eculizumab therapy, a Phase 3 study in adults with PNH who are stable on eculizumab therapy, a Phase 1b dose-ranging study, and a Phase 2 dose regimen optimization study. Each of these studies also includes a 2-year extension phase. In addition, a Phase 1 study to assess the pharmacokinetic (PK) profile of ALXN1210 in healthy Japanese subjects has been completed.

In this Phase 3, open-label study, the PK, pharmacodynamics (PD), efficacy, and safety of ALXN1210 will be assessed in pediatric patients with PNH. 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

As described above, 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, nitric oxide 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 (QoL). The current standard of care for the treatment of PNH is eculizumab (Soliris®), a recombinant humanized monoclonal antibody (mAb) that binds to human complement component 5 (C5) 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 lactate dehydrogenase (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. Meningococcal Infection

Increased susceptibility to infection caused by *Neisseria meningitidis* 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.

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 a spouse or partner, 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

The objectives of this study are to assess the PK, PD, safety, and efficacy of ALXN1210 in pediatric patients with PNH.

6.2. Endpoints

6.2.1. Primary Endpoints

- PK/PD parameters (trough and peak) at Baseline and Weeks 2, 10, 18, and 26
  - PK: maximum serum concentration (C_{max}), trough serum concentration (measured at end of dosing interval at steady state; C_{trough}), accumulation ratio
  - PD: change in free C5 concentrations and in chicken red blood cell (cRBC) hemolytic activity over time

6.2.2. Secondary Endpoints

- Percentage change in LDH from baseline to Day 183 (Week 26)
- Transfusion avoidance (TA), defined as the proportion of patients who remain transfusion-free and do not require a transfusion through Day 183 (Week 26)
- Change in quality of life (QoL), as measured by Pediatric Functional Assessment of Chronic Therapy (FACIT) Fatigue questionnaire (patients ≥ 5 years of age), from baseline to Day 183 (Week 26)
- 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 through Day 183 (Week 26)
- Percentage change in free hemoglobin from baseline to Day 183 (Week 26)
- 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, major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH as follows:
  - For patients who enter the study naïve to complement inhibitor treatment, elevated LDH ≥ 2 × the upper limit of normal (ULN) after prior LDH reduction to < 1.5 × ULN on therapy
  - For patients who enter the study stabilized on eculizumab treatment, elevated LDH ≥ 2 × ULN

6.2.3. Safety Endpoints

The safety and tolerability of ALXN1210 will be evaluated from baseline to Week 26 and throughout the extension period by physical examinations, vital signs, physical growth (height,

weight, and head circumference [the latter only in patients who are ≤ 3 years of age]), electrocardiograms (ECGs), laboratory assessments, and incidence of AEs and serious adverse events (SAEs). The proportion of patients who develop antidrug antibodies (ADAs) will also be assessed.

7. INVESTIGATIONAL PLAN

7.1. Summary of Study Design

This is a Phase 3, open-label, single-arm multicenter study to evaluate the PK/PD, safety, and efficacy of ALXN1210 administered by intravenous (IV) infusion to pediatric patients (< 18 years of age) with PNH. The study consists of a 4-week Screening Period, a 26-week Primary Evaluation Period, and an Extension Period.

Consenting patients will be screened for study eligibility up to 4 weeks prior to Day 1. Patients who satisfy all of the inclusion criteria and all of the exclusion criteria will be enrolled into the Primary Evaluation Period and receive a weight-based loading dose of ALXN1210 on Day 1, followed by weight-based maintenance treatment with ALXN1210 on Day 15 and once every 8 weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg, for a total of 26 weeks of treatment. For patients entering the study on eculizumab therapy, Day 1 of study treatment will occur 2 weeks from the patient's last dose of eculizumab.

An interim analysis of data, including ALXN1210 PK and free C5 levels, will be conducted after 4 patients weighing ≥ 5 kg to < 40 kg have completed dosing through Day 71. Enrollment of patients will proceed without interruption while the analysis is ongoing. The accrued safety and PK/PD data will be assessed to ensure that ALXN1210 treatment is well tolerated and is providing adequate complement inhibition. Based on this review, the dose regimen may be adjusted. In addition, an independent Data Monitoring Committee (DMC) will review safety data from the study on a regular basis.

After completion of all pre-dose assessments on Day 183, all patients will enter an Extension Period and continue to receive ALXN1210 according to the appropriate weight-based regimen. The Extension Period will continue until the product is registered or approved (in accordance with country-specific regulations) or for up to 4 years, whichever occurs first, except in Norway where the Extension Period will be 4 years. The end of study is defined as the last patient's last visit or follow-up (whether on site or via phone call) in the Extension Period.

7.2. Discussion of Design and Control

This is an uncontrolled, open-label study of ALXN1210 treatment in pediatric patients. Given the ongoing ALXN1210 clinical program in adults with PNH and the data already generated in an eculizumab clinical study in pediatric patients with PNH (M07-005), a single-arm design was deemed appropriate to investigate the PK/PD, efficacy, and safety of ALXN1210 in the pediatric population. The rarity of PNH in the pediatric population precludes feasibility of a trial with a larger sample size. Ten patients should be sufficient to adequately describe PK/PD in this population while enabling study conduct within a reasonable time frame for making this important treatment available to patients, given the challenges of finding these rare pediatric patients and enrolling them into a prospective, interventional study. The proposed sample size is consistent with the principles of extrapolating the PK/PD and safety/efficacy from adults to pediatric patients given that the disease pathogenesis and mechanism of action of the drug are similar between these two population subsets. This study is descriptive in nature and not

statistically powered for hypothesis testing. This approach was discussed in the context of the agreed pediatric investigation plan of ALXN1210 in PNH (EMEA-002077-PIP01-16).

The disease pathophysiology and clinical response to ALXN1210 treatment is expected to be similar between adult and pediatric PNH populations, as demonstrated in the eculizumab clinical development program. Thus, the efficacy parameters in this study of ALXN1210 are modelled on those selected for study in adult patients with PNH.

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

7.3. Schedule of Assessments

The Schedule of Assessments is provided in Table 1 for the Screening and Primary Evaluation Period and in Table 2 and Table 3 for the Extension Period.

Refer to Appendix A and 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. All 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 hemolysis 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.

If a supplemental dose of study drug is administered, PK/PD samples will be collected predose and at end of infusion (EOI) and a physical examination including vital signs (blood pressure, heart rate, respiratory rate, temperature) will be performed. If the loading dose for patients ≥ 5 to < 10 kg is administered as 2 separate infusions < 24 hours apart (as described in Section 9.2), blood samples for PK/PD analysis will be collected before the first infusion (ie, the predose sample) and after the second infusion (ie, the EOI sample).

Table 1: Schedule of Study Visits and Assessments: Screening Through End of Primary Evaluation Period

Period	**Screening**	**Initial Evaluation Period**							
Study Day	**–28 to –1**	**1**	**15**	**43**	**71**	**99**	**127**	**155**	**183[a]/ET**
Window (day)	**N/A**		**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±2**
Informed consent	X								
Confirmation or administration of meningococcal vaccination[b]	X	X							
Confirmation of *H influenza type B and S pneumoniae* vaccination (per local/national guidelines)	X								
Medical history and demographics	X								
PNH clone size[c]	X	X			X				X
Head circumference (patients ≤ 3 years of age only)	X	X	X	X	X	X	X	X	X
Height and weight[d]	X	X	X	X	X	X	X	X	X
Pregnancy test[e]	X	X	X		X		X		X
Record transfusions (during and between visits)	X	X	X	X	X	X	X	X	X
PNH symptomatology[f]	X	X	X	X	X	X	X	X	X
Pediatric FACIT-Fatigue questionnaire[g]		X	X		X		X		X
Physical examination	X								X
Abbreviated physical examination[h]		X	X	X	X	X	X	X	
Vital signs[i]	X	X	X	X	X	X	X	X	X
Safety 12-Lead ECG[j]	X				X				X
Chemistry including LDH[k]	X[l]	X	X	X	X	X	X	X	X
Hematology including free hemoglobin and coagulation[k]	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry[k]	X	X	X		X		X		X
PK/PD sampling[m]		X	X		X		X		X
Immunogenicity (ADA)[n]		X			X		X		X
Review safety card[o]		X	X	X	X	X	X	X	X
Breakthrough hemolysis[p]		←Monitor continuously→							
Concomitant medications	X	←Monitor continuously→							
Adverse events	X	←Monitor continuously→							
ALXN1210 administration (patients weighing < 20 kg)[q,r]		X[s]	X	X	X	X	X	X	
ALXN1210 administration (patients weighing ≥ 20 kg)[q]		X[s]	X		X		X		

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; eCRF = electronic case report form; EOI = end of infusion; ET = early termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; LDH = lactate dehydrogenase; N/A = not applicable; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; WBC = white blood cell

Note: If a patient discontinues from the study, an ET visit will be performed, and the Sponsor and site monitor should be notified as soon as possible. In addition, a Follow-up Phone Call will be performed 8 weeks (± 5 days) following the patient's last ALXN1210 dose to collect concomitant medications, procedures, and adverse events.

[a] The primary 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 postdose assessments in Table 2.

Table 1: Schedule of Study Visits and Assessments: Screening Through End of Primary Evaluation Period (Continued)

[b] 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. Patients who have not been vaccinated prior to initiating ALXN1210 treatment should receive prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination. Patients who cannot be vaccinated must receive antibiotic prophylaxis for the entire treatment period and for 8 months following last dose.

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

[d] Height at baseline and Day 183 only; weight is collected predose on dosing days.

[e] Pregnancy testing is required only for female patients of childbearing potential (ie, have achieved menarche). Serum pregnancy test is performed at Screening and Day 183, urine (or serum if required by site policy) pregnancy test at all other required time points. A negative pregnancy test result is required prior to administering study drug to female patients of childbearing potential at the indicated study visits.

[f] Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. On dosing days, assessments will be performed prior to dosing.

[g] On dosing days, assessments will be performed prior to dosing. Pediatric FACIT-Fatigue only in patients ≥ 5 years of age (self-reported by patients who were ≥ 8 years of age at the time of enrollment and reported by caregivers for patients who were ≥ 5 to < 8 years of age at the time of enrollment).

[h] Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or qualified designee) judgment and patient symptoms. At least 1 body system must be checked for an abbreviated exam.

[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 (BP) (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 predose.

[j] Single 12-lead ECG will be collected at Screening and predose on Day 71 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.

[l] For patients entering the study on eculizumab therapy, screening LDH should be obtained within 24 hours prior to a scheduled eculizumab dose.

[m] Serum samples for PK/PD analyses will be collected at the indicated visits. Samples will be collected predose (within 0.5 hours prior to the start of infusion) and at EOI (within 0.5 hours after the EOI from the patient's opposite, noninfused arm). In order to minimize needle sticks to the patient, the predose sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. As noted, the postdose sample must be drawn from the opposite, noninfused arm. If a supplemental dose is administered, PK/PD samples will be collected predose and at EOI. If a loading dose is administered as 2 separate infusions < 24 hours apart (as described in Section 9.2), PK/PD samples will be collected before the first infusion (ie, the predose sample) and after the second infusion (ie, the EOI sample). All collection times will be recorded in the eCRF.

[n] ADA serum samples will be collected predose on Days 1, 71, and 127 or at any time during an ET visit. Day 183 collection will occur prior to first dose in the Extension Period.

[o] Review the Clinical Trial Participant Safety Information Card with the patient/caregiver and discuss the importance of carrying the safety card at all times, and the risks associated with ALXN1210 treatment, including the risk of meningococcal infection.

[p] 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 hemolysis 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.

[q] Dose regimen is based on body weight obtained at the study visit. If the study drug needs to be prepared the night prior to the visit, the weight from the previous visit may be used.

[r] Should a patient's weight change from < 20 kg to ≥ 20 kg on a "q4w only" visit, the patient will receive the q4w dose that day; at the patient's next q8w visit, the new q8w dose will be given.

[s] For patients entering the study on eculizumab therapy, Day 1 should occur 2 weeks from the patient's last dose of eculizumab.

Table 2: Schedule of Study Visits and Assessments: Extension Period – Day 183 to Day 911

Period	**Extension Period**																										
Study Day	**183**[a]	***211 q4w only***	**239**	***267 q4w only***	**295**	***323 q4w only***	**351**	***379 q4w only***	**407**	***435 q4w only***	**463**	***491 q4w only***	**519**	***547 q4w only***	**575**	***603 q4w only***	**631**	***659 q4w only***	**687**	***715 q4w only***	**743**	***771 q4w only***	**799**	***827 q4w only***	**855**	***883 q4w only***	**911**
Window (day)	**±2**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**
PNH clone size[b]							X								X												X
Head circumference (patients ≤ 3 years of age)			X		X		X		X		X		X		X		X		X		X		X		X		X
Height and weight[c]		*X*	X	*X*	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[d]			X		X		X		X		X		X		X		X		X		X		X		X		X
PNH symptomatology[e]			X		X		X								X						X						X
Pediatric FACIT-Fatigue questionnaire[f]							X								X						X						X
Abbreviated physical examination[g]			X		X		X								X						X						X
Vital signs[h]			X		X		X								X						X						X
Chemistry including LDH[i]			X		X		X								X						X						X
Hematology including free hemoglobin and coagulation[i]			X		X		X								X						X						X
Urinalysis and urine chemistry[i]			X		X		X								X						X						X
PK/PD sampling[j]	X						X								X						X						X
Immunogenicity (ADA)[k]							X								X						X						X
Review safety card[l]	X	*X*	X	*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→																										
Record Transfusions	←Monitor continuously→																										
ALXN1210 administration (patients weighing < 20 kg)[n,o]	X[a]	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X
ALXN1210 administration (patients weighing ≥ 20 kg)[n]	X[a]		X		X		X		X		X		X		X		X		X		X		X		X		X

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; eCRF = electronic case report form; EOI = end of infusion; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; q4w = once every 4 weeks; RBC = red blood cell

Note: A follow-up phone call to collect concomitant medications, procedures, and adverse events is required 8 weeks (± 5 days) after the patient's last dose of ALXN1210 in the following circumstances:

Table 2: Schedule of Study Visits and Assessments: Extension Period – Day 183 to Day 911 (Continued)

1. Patient terminates from the study early.
2. Patient completes the study on the q4w regimen and does not initiate commercially available PNH treatment within 8 weeks of their last ALXN1210 dose.

[a] Extension Period begins at the start of Day 183 dosing.

[b] Granulocyte and RBC clone size measured by high-sensitivity flow cytometry.

[c] Height on Days 575 and 911 only; weight is collected predose.

[d] Pregnancy testing is required only for female patients of childbearing potential (ie, have achieved menarche). Serum pregnancy test is performed only if required by site policy. Urine pregnancy testing may be performed by local laboratory. A negative pregnancy test result is required prior to administering study drug to female patients of childbearing potential at the indicated study visits. Additional pregnancy tests (urine or serum) may also be performed at any visit at the Investigator's discretion.

[e] Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. On dosing days, assessments will be performed prior to dosing.

[f] On dosing days, assessments will be performed prior to dosing. Pediatric FACIT-Fatigue only in patients ≥ 5 years of age (self-reported by patients who were ≥ 8 years of age at the time of enrollment and reported by caregivers for patients who were ≥ 5 to < 8 years of age at the time of enrollment).

[g] Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or qualified designee) judgment and patient symptoms. At least 1 body system must be checked for an abbreviated exam.

[h] Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic BP (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 predose.

[i] Clinical laboratory measurements will be collected predose and not from a heparinized line.

[j] Serum samples for PK/PD analyses will be collected at end-of-infusion (EOI) on Day 183; predose (within 0.5 hours prior to the start of infusion) and at EOI (within 0.5 hours after the end of infusion) on Days 351, 575, 743, and 911. To minimize needle sticks to the patient, the predose sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion samples will be drawn from the patient's opposite, noninfused arm. All collection times will be recorded in the eCRF. In the event that a supplemental dose is administered, predose and EOI blood samples will be collected for PK/PD analysis. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.

[k] Samples for ADA will be collected predose or at any time during the visit when a dose of study drug is not administered.

[l] Review the Clinical Trial Participant Safety Information Card with the patient and discuss the importance of carrying the safety card at all times, and the risks associated with ALXN1210 treatment, including the risk of meningococcal infection.

[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 hemolysis 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] Dose regimen is based on body weight obtained at the study visit. If the study drug needs to be prepared the night prior to the visit, the weight from the previous visit may be used.

[o] Should a patient's weight change from < 20 kg to ≥ 20 kg on a "q4w only" visit, the patient will receive the q4w dose that day; at the patient's next q8w visit, the new q8w dose will be given.

Table 3: Schedule of Study Visits and Assessments: Extension Period – Day 939 to Day 1639

Period		**Extension Period**																							
Study Day	***939 q4w only***	**967**	***995 q4w only***	**1023**	***1051 q4w only***	**1079**	***1107 q4w only***	**1135**	***1163 q4w only***	**1191**	***1219 q4w only***	**1247**	***1275 q4w only***	**1303**	***1331 q4w only***	**1359**	***1387 q4w only***	**1415**	***1443 q4w only***	**1471**	***1499 q4w only***	**1527**	***1555 q4w only***	**1583**	***1611 q4w only***	**1639 ET/ EOS** [a]
Window (day)	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**	***±5***	**±5**
PNH clone size[b]						X								X												X
Head circumference (patients ≤ 3 years of age)		X		X		X		X		X		X		X		X		X		X		X		X		X
Height and weight[c]	*X*	X	*X*	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[d]		X		X		X		X		X		X		X		X		X		X		X		X		X
PNH symptomatology[e]						X								X						X						X
Pediatric FACIT-Fatigue questionnaire[f]						X								X						X						X
Physical examination																										X
Abbreviated physical examination[g]						X								X						X						
Vital signs[h]						X								X						X						X
Safety 12-Lead ECG[i]																										X
Chemistry including LDH[j]						X								X						X						X
Hematology including free hemoglobin and coagulation[j]						X								X						X						X
Urinalysis and urine chemistry[j]						X								X						X						X
PK/PD sampling[k]						X								X						X						X
Immunogenicity (ADA)[l]						X								X						X						X
Review safety card[m]	*X*	X	*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[n]	←Monitor continuously→																									
Concomitant medications	←Monitor continuously→																									
Adverse events	←Monitor continuously→																									
Record transfusions	←Monitor continuously→																									
ALXN1210 administration (patients weighing < 20 kg)[o,p]	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	X	*X*	
ALXN1210 administration (patients weighing ≥ 20 kg)[o]		X		X		X		X		X		X		X		X		X		X		X		X		

Table 3: Schedule of Study Visits and Assessments: Extension Period – Day 939 to Day 1639 (Continued)

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; eCRF = electronic case report form; EOI = end-of-infusion; 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; q4w = once every 4 weeks; RBC = red blood cell

Note: A follow-up phone call to collect concomitant medications, procedures, and adverse events is required 8 weeks (± 5 days) after the patient's last dose of ALXN1210 in the following circumstances:

1. Patient terminates from the study early.
2. Patient completes the study on the q4w regimen and does not initiate commercially available PNH treatment within 8 weeks of their last ALXN1210 dose.

[a] If a patient withdraws early form the study (eg, to begin treatment with marketed product), an ET visit will be performed.

[b] Granulocyte and RBC clone size measured by high-sensitivity flow cytometry.

[c] Height on Day 1247 and Day 1639/EOS or ET only; weight is collected predose

[d] Pregnancy testing is required only for female patients of childbearing potential (ie, have achieved menarche). Urine pregnancy testing may be performed by local laboratory. Serum pregnancy test is performed at ET or Day 1639/EOS only, unless required by site policy; urine pregnancy test at all other visits. A negative pregnancy test result is required prior to administering study drug to female patients of childbearing potential at the indicated study visits. Additional pregnancy tests (urine or serum) may also be performed at any visit at the Investigator's discretion.

[e] Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. On dosing days, assessments will be performed prior to dosing.

[f] On dosing days, assessments will be performed prior to dosing. Pediatric FACIT-Fatigue only in patients ≥ 5 years of age (self-reported by patients who were ≥ 8 years of age at the time of enrollment and reported by caregivers for patients who were ≥ 5 to < 8 years of age at the time of enrollment).

[g] Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or qualified designee) judgment and patient symptoms. At least 1 body system must be checked for an abbreviated exam.

[h] Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic BP (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 predose.

[i] Single 12-lead ECG will be collected on Day 1639/EOS 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 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 (EOI) (within 0.5 hours after the EOI) on Days 1079, 1303, and 1471; and at any time on Day 1639/EOS or ET. To minimize needle sticks to the patient, the predose sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion samples will be drawn from the patient's opposite, noninfused arm. All collection times will be recorded in the eCRF. In the event that a supplemental dose is administered, predose and EOI blood samples will be collected for PK/PD analysis. 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 during the visit when a dose of study drug is not administered.

[m] Review the Clinical Trial Participant Safety Information Card with the patient and discuss the importance of carrying the safety card at all times, and the risks associated with ALXN1210 treatment, including the risk of meningococcal infection.

[n] 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 hemolysis 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.

[o] Dose regimen is based on body weight obtained at the study visit. If the study drug needs to be prepared the night prior to the visit, the weight from the previous visit may be used.

[p] Should a patient's weight change from < 20 kg to ≥ 20 kg on a "q4w only" visit, the patient will receive the q4w dose that day; at the patient's next q8w visit, the new q8w dose will be given.

8. STUDY POPULATION

Pediatric patients (age < 18 years) with a documented diagnosis of PNH will be enrolled and treated with ALXN1210 at approximately 10 investigative sites globally. Approximately 13 patients will be enrolled to ensure at least 10 evaluable patients complete the 26-week period.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

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 and female patients < 18 years of age and weighing ≥ 5 kg at the time of consent.
2. Documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry evaluation (Borowitz, 2010) of red blood cells (RBCs) and white blood cells (WBCs), with granulocyte or monocyte clone size of ≥ 5%.
3. For patients not currently treated with eculizumab, presence of 1 or more of the following PNH-related signs or symptoms within 3 months of Screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia, history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed red blood cell (pRBC) transfusion due to PNH.
4. Lactate dehydrogenase (LDH) values at Screening as follows:
   a. For patients not currently treated with eculizumab, LDH level ≥ 1.5 × ULN.
   b. For patients who are currently taking eculizumab, LDH ≤ 1.5× ULN (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).
5. To reduce the risk of meningococcal infection (*N 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. Patients who cannot be vaccinated must receive antibiotic prophylaxis for the entire treatment period and for 8 months following last dose.
6. Patients must have been vaccinated against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* according to national and local vaccination schedule guidelines, as appropriate.
7. Female patients of childbearing potential (ie, have achieved menarche) and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug.

8. Patient's legal guardian must be willing and able to give written informed consent and the patient must be willing to give written informed assent (if applicable as determined by the central or local Institutional Review Board [IRB]/Institutional (or Independent) Ethics Committee [IEC]) and comply with the study visit schedule.

8.2. Exclusion Criteria

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

1. Platelet count < 30,000/mm^3 (30×10^9/L) at Screening.
2. Absolute neutrophil count < 500/µL (0.5×10^9/L) at Screening.
3. History of bone marrow transplantation.
4. History of *N meningitidis* infection.
5. History of unexplained, recurrent infection.
6. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
7. History of malignancy within 5 years of Screening with the exception of adequately treated nonmelanoma skin cancer or carcinoma in situ of the cervix.
8. 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.
9. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of Screening, coexisting chronic anemia unrelated to PNH) that would make them unlikely to tolerate the requirements of the protocol.
10. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.
11. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
12. Females who plan to become pregnant or are currently pregnant or breastfeeding.
13. Females of childbearing potential who have a positive pregnancy test result at Screening or on Day 1.
14. 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.
15. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
16. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator or Sponsor, 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 discontinues from the study, an Early Termination (ET) visit (as shown in the Schedule of Assessments, Section 7.3) will be performed, and the Sponsor and site monitor should be notified as soon as possible. In addition, a Follow-up Phone Call will be performed 8 weeks (± 5 days) following the patient's last dose of study drug to collect concomitant medications, procedures, and adverse events. 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 B) 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 to be 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 AE 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 AE 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 (see 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 IRB/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 or follow-up (whether on site or via phone call) in the Extension Period.

9. STUDY TREATMENT

9.1. Materials and Supplies

9.1.1. Description of Study Drugs

ALXN1210 is a humanized, anti-C5 mAb produced in Chinese hamster cells. It 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 drug product is supplied for clinical studies as a sterile, preservative-free 10-mg/mL solution in single-use vials and is designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via IV infusion (Table 4).

Refer to the current ALXN1210 IB for additional information.

Table 4: Study Drug

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

9.1.2. Study Drug Packaging and Labeling

ALXN1210 is 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 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.

9.1.4. Study Drug Preparation and Infusion

ALXN1210 must NOT be administered as an IV push or bolus injection. Infusions of study drug must be prepared using aseptic technique. The patient's required dose of ALXN1210 will be further diluted into commercially available saline (0.9% sodium chloride; country-specific pharmacopeia) at the volume specified in Table 5. ALXN1210 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.

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	≥ 5 to < 10	600	60	60	120	228 (3.8)	31.5
	≥ 10 to < 20	600	60	60	120	113 (1.9)	63.1
	≥ 20 to < 30	900	90	90	180	86 (1.5)	120.0
	≥ 30 to < 40	1200	120	120	240	77 (1.3)	184.6
	≥ 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	≥ 5 to < 10	300	30	30	60	113 (1.9)	31.5
	≥ 10 to < 20	600	60	60	120	113 (1.9)	63.1
	≥ 20 to < 30	2100	210	210	420	194 (3.3)	127.2
	≥ 30 to < 40	2700	270	270	540	167 (2.8)	192.8
	≥ 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] Body weight is obtained at the study visit. If the study drug needs to be prepared the night prior to the visit, the weight from the previous visit may be used.

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 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

Patients will receive a loading dose of ALXN1210 on Day 1, followed by maintenance dosing of ALXN1210 on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg, as shown in Table 6. With the agreement of the Alexion Medical Monitor, the 600 mg loading dose may be given to patients weighing ≥ 5 to < 10 kg as 2 separate infusions administered no more than 24 hours apart. Dosages are based on the patient's body weight recorded on the day of dosing or the most recently recorded weight. For patients entering the study on eculizumab therapy, Day 1 of study treatment will occur 2 weeks from the patient's last dose of eculizumab.

Table 6: Loading and Maintenance Treatment Regimens

Body Weight Range (kg)[a]	Loading Dose (mg)	Maintenance Doses (mg)	Maintenance Dosing Frequency
≥ 5 to < 10	600[b]	300	q4w
≥ 10 to < 20	600	600	q4w
≥ 20 to < 30	900	2100	q8w
≥ 30 to < 40	1200	2700	q8w
≥ 40 to < 60	2400	3000	q8w
≥ 60 to < 100	2700	3300	q8w
≥ 100	3000	3600	q8w

Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks

[a] Dose regimen will be based on body weight obtained at the study visit. If the study drug needs to be prepared the night prior to the visit, the weight from the previous visit may be used.

[b] With the agreement of the Alexion Medical Monitor, the 600 mg loading may be given to patients weighing ≥ 5 to < 10 kg as 2 separate infusions administered no more than 24 hours apart.

With the agreement of the Alexion Medical Monitor, administration of a supplemental dose of ALXN1210 is permitted.

After the Primary Evaluation Period, all patients will roll over into an Extension Period and continue their weight-based maintenance dose of ALXN1210 on Day 183 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg, until the product is registered or approved (in accordance with country specific regulation) or for up to 4 years, whichever occurs first, except in Norway where the Extension Period will be 4 years.

The actual time of all dose administrations, including any supplemental dose or dose administered as 2 separate infusions as noted above, will be recorded on the patient's eCRF.

9.3. Method of Assignment to Treatment

All enrolled patients will receive ALXN1210.

9.4. Rationale for Selection of Doses in the Study

The weight-based dosages of ALXN1210 in this study (Table 6) 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 the ALXN1210 dose regimen is based on targeting immediate, complete, and sustained inhibition of terminal complement in pediatric patients with PNH throughout the dosing interval. Body weight-based dosing in pediatric patients is proposed to limit body weight-based variability in ALXN1210 drug exposure. ALXN1210 pediatric dosing is predicted to not exceed maximum ALXN1210 exposures achieved in PNH patients in Phase 2.

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 B for guidance on identifying and managing potential drug infusion reactions.

9.6. Blinding

This is an open-label study, so blinding is not applicable.

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 and vaccination history for Hib and *S pneumoniae* must be collected from birth.

If patients had been treated with eculizumab, a documented regimen history will be collected. Transfusions of pRBCs received within 1 year prior to first study drug administration will be recorded on the patient's eCRF.

All medication used 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 and procedures 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.

Concomitant use of complement inhibitors other than the study treatment is prohibited.

9.8. Vaccination

Due to its mechanism of action, the use of ALXN1210 increases the patient's susceptibility to meningococcal infection (*N meningitidis*). To reduce the risk of meningococcal infection, 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. 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 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).

Patients must also be vaccinated against Hib and *S pneumoniae* according to national and local vaccination schedule guidelines.

Vaccinations for *N meningitidis*, Hib, and *S pneumoniae* 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

To ensure patient safety and treatment continuity during the COVID-19 pandemic, the following will apply where patients are not able to reach the study sites, and until patients are able to resume study visits at the site.

Patients may have an opportunity to receive ALXN1210 administration remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. Home infusions may be considered only for patients who have tolerated previous drug infusions well, without clinically significant infusion reactions, at the study site.

Remote visit options may be at the Investigator's discretion and oversight, in accordance with the local regulations, and conducted by a qualified medical professional. Information about AEs, concomitant medications, and signs and symptoms of breakthrough hemolysis must be sent to the Investigator's site for evaluation on the day of the remote visit. In case of any signs or symptoms indicating an SAE or breakthrough hemolysis, the patient will need to be evaluated at the study site.

Monitoring, treatment, and management of infusion reactions for patients receiving drug infusions at home are described in detail in the home health care manual and Appendix B.

9.11. Contraception Guidance

Female patients of childbearing potential (ie, who have achieved menarche) 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

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

10.2. Lactate Dehydrogenase 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)
- estimated glomerular filtration rate (calculated using the Schwartz formula)

10.3. Paroxysmal Nocturnal Hemoglobinuria 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

The Pediatric FACIT-Fatigue scale is a 13-item questionnaire that assesses fatigue and its impact upon daily activities and function over the preceding 7 days. Each item is scored on a 5-point scale, and total scores range from 0 to 52, with higher score indicating better QoL. The questionnaire will be self-reported by patients who were ≥ 8 years of age at the time of enrollment and reported by caregivers for patients who were ≥ 5 to < 8 years of age at the time of enrollment. Patients < 5 years of age will not be assessed. The Pediatric FACIT-Fatigue scale is shown in Appendix C.

10.5. Major Adverse Vascular Events

Major adverse vascular events 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 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. Head circumference will be recorded for patients who are ≤ 3 years of age.

11.1.2. Disease Characteristics

The patient's PNH medical history, including PNH symptoms, date of diagnosis, 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 will also be recorded. Details of prior treatment with eculizumab, including dose level and frequency, will be collected.

Meningococcal vaccination within 3 years prior to the first dose of study drug, and vaccination history for Hib and *S pneumoniae* from birth, 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 (or qualified designee) judgment and patient symptoms. Physical growth (height, weight, and head circumference [the latter only in patients ≤ 3 years of age]) will be assessed.

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. An alternative blood sampling schedule for infants, for whom less blood volume should be collected, must be used as detailed in the laboratory manual. 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 (ie, have achieved menarche), a serum or urine pregnancy test (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.

Chemistry assessments will be performed at the time points specified in the Schedule of Assessments (Section 7.3). The estimated glomerular filtration rate will be calculated using the Schwartz 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.

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 CRF. 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 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.

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 *N meningitidis*. The following event is an important identified risk in this study:

- Meningococcal infections

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 7).

Table 7: 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 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 8). This assessment must be recorded on the eCRF and any additional forms as appropriate.

Table 8: 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.

Abbreviation: AE = adverse event

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

Alexion procedures for the reporting of suspected unexpected serious adverse reactions (SUSARs) are in accordance with United States Title 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance documents or national regulatory requirements in participating countries, as well as IRBs/IECs where applicable.

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 Drug Safety (GDS) 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 GDS 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) or the Safety Gateway is unavailable at the site(s), the SAE must be reported on the paper SAE contingency form. Facsimile transmission or email may be used in the event of electronic submission failure.

Email: PI

Facsimile: PI (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 GDS via Safety Gateway.

If applicable, additional information such as relevant medical records should be submitted to Alexion GDS 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 GDS 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

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 a spouse or partner, will use a highly effective or acceptable method of contraception.

In the event of a pregnancy event, 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 post approval, exposure during pregnancy must be recorded and the pregnancy followed until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the 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 GDS 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 GDS. 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 GDS 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, GDS 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 GDS 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 concentration over time
- Free and total C5 concentrations over time
- cRBC hemolytic activity 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, and/or facsimile.
- Review and evaluate eCRF data and use standard computer edit checks 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 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. Analyses of efficacy and safety will be performed using SAS® release, version 9.4 or higher (SAS Institute Inc., Cary, North Carolina, 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. Analyses will be conducted separately for naïve and previously eculizumab-treated patients. Analyses of PK will be performed using Phoenix® WinNonlin®, version 7.0 or higher (Certara USA, Inc., Princeton, New Jersey, USA).

Details of the statistical analyses described below will be specified in a separate Statistical Analysis Plan (SAP) before first 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.

To support regulatory filings, interim CSRs may be prepared based on efficacy, safety, PK, PD, and immunogenicity data collected through the end of the 26-week Primary Evaluation Period (Day 183) after 12 patients are enrolled, and after enrollment is completed. A final CSR to summarize long-term efficacy, safety, PK, PD, and immunogenicity parameters will be produced at study completion.

14.2. Determination of Sample Size

This study is descriptive in nature and not statistically powered for hypothesis testing due to the rarity of disease in pediatric patients. Approximately 13 patients will be enrolled to ensure at least 10 evaluable patients complete the 26-week period, which is expected to be sufficient to adequately describe PK/PD in pediatric patients with PNH.

14.3. Analysis Sets

Efficacy analyses will be performed on the Full Analysis Set (FAS). The FAS will include all patients who received at least 1 dose of ALXN1210 and have at least 1 postbaseline assessment.

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

Pharmacokinetic and PD analyses will be performed on all patients who receive at least 1 dose of ALXN1210 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 for the FAS and Safety sets.

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.

The numbers of patients who are treated, discontinue treatment (along with reason for treatment discontinuation), complete or withdraw from the Primary Evaluation 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.

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 class and generic 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 for the FAS and Safety sets.

14.8. Efficacy Analyses

Efficacy analyses will be performed using the FAS. Continuous variables will be summarized using descriptive statistics, including number of observations and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of patients. Analyses will be conducted separately for naïve and previously eculizumab-treated patients.

14.9. Safety Analyses

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: Any AE that starts during or after the first infusion of study drug.
- Treatment-emergent SAE: A treatment-emergent AE (TEAE) that is serious (refer to Section 11.7.4 for definitions).

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 and PT. Detailed by-patient listings of TEAEs, SAEs, related TEAEs, TEAEs during study drug administration, TEAEs leading to withdrawal from the study, and TEAEs leading to study treatment discontinuation will be provided.

14.9.2. Physical Examination, Vital Signs, and Growth

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.

Height, weight, and head circumference (the latter only for patients ≤ 3 years of age) 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

Changes in clinical chemistry, hematology, and urinalysis results from baseline to postbaseline study time points will be summarized descriptively. Shift tables over time will be presented for all central laboratory values, where applicable, using normal, low, or high based on normal range values. Listings of patients with abnormal results will be provided.

14.9.4. Electrocardiograms

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

14.9.5. Immunogenicity

Incidence and titers for ADAs to ALXN1210 will be summarized in tabular format.

14.10. Pharmacokinetic/Pharmacodynamic Analyses

Individual serum concentration data for all patients who receive at least 1 dose of ALXN1210 and who have evaluable PK data will be used to derive PK parameters for ALXN1210.

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.

Pharmacodynamic analyses will be performed for all patients who receive at least 1 dose of ALXN1210 and who have evaluable PD data.

Descriptive statistics will be presented for all ALXN1210 PD endpoints at each sampling time (Section 7.3). The PD effects of ALXN1210 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 change from baseline in 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. Analyses will be conducted separately for naïve and previously eculizumab-treated patients.

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 instrument instructions.

15. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

15.1. Informed Consent

The Investigator or designee is responsible for ensuring that the patient/caregiver 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 informed consent given by patients or, as applicable, informed assent by their legal representatives.

15.2. Data Monitoring Committee

An independent DMC comprising expert personnel in relevant biomedical fields who have no direct relationship with the study will be appointed by the Sponsor. The DMC will review and evaluate the accumulated study data for patient safety and make recommendations on continuing study drug administration or termination of the study. The DMC will review study information on a regular basis as outlined in the DMC charter, which is maintained separately from the study protocol.

Final decisions regarding the conduct of the study will be made by the Sponsor after consultation with the DMC. All appropriate regulatory authorities and IRBs/IECs will be notified of any significant action.

Each member of the DMC will be required to sign a contract agreement, which includes a confidentiality and financial disclosure statement, assuring no conflicts of interest as a condition for membership on the committee.

The specific responsibilities of the DMC are described in the DMC Charter, which is maintained as a separate document.

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.

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]
- The ICH Clinical Trials of Medicinal Products in the Pediatric Population [E11]
- 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 third-party organization(s).

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.

16. LIST OF REFERENCES

Borowitz MJ, Craig FE, DiGiuseppe JA, et al. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. Cytometry Part B. 2010;78B:211-230.

Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804-2711.

Hill A, Platts PJ, Smith A, et al. The incidence and prevalence of paroxysmal nocturnal haemoglobinuria (PNH) and survival of patients in Yorkshire. Blood. 2006;108:985.

Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005;106(12):3699-3709.

Reiss UM, Schwartz J, Sakamoto KM, et al. Efficacy and safety of eculizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria. Pediatr Blood Cancer 2014;61:1544–1550

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med. 2006;47(4):373-380.

Socie G, Mary J-Y, de Gramont A, et al. Paroxysmal nocturnal hemoglobinuria: long term follow-up and prognostic factors. Lancet. 1996;348:573-577.

van den Heuvel-Eibrink MM. Paroxysmal nocturnal haemoglobinuria in children. Paediatr Drugs. 2007;9(1):11-16.

Ware RE, Hall SE, Rosse WF. Paroxysmal nocturnal haemoglobinuria with onset in childhood and adolescence. N Engl J Med. 1991;325(14):991-996.

17. APPENDICES

APPENDIX A. BLOOD SAMPLING VOLUMES

The following procedures for blood collection should be adhered to:

1. Number of attempts: The number of attempts for sampling blood is limited to 3 times per day. This means that, after 3 punctures for collection of blood have been performed and no or insufficient blood could be collected, no other puncture will be done on the same day.
2. Volume of blood samples: Per study patient, the study-related blood loss (including any losses in the collection procedure) should not exceed 3% of the total blood volume during a period of 4 weeks, and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight. Three percent (3%) is 2.4 mL blood per kg of body weight. If an investigator decides to deviate from these limits, the deviation must be fully documented, and the investigator should provide justification for the deviation. If the required blood volume cannot be obtained, due to the above mentioned safety limits, priority will be given to safety-relevant investigations.
3. EMLA (eutectic mixture of local anesthetics) cream/plaster: To minimize the possible pain and discomfort due to collection of blood, the Investigator should apply an EMLA cream/plaster at the puncture site.

Reference: European Commission. European Commission Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to the good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008.

APPENDIX B. 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 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), and at least 1 of the following: a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced 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 C. PEDIATRIC FACIT-FATIGUE

Pediatric (Paediatric) Functional Assessment of Chronic Illness Therapy – Fatigue

Header to be completed by study site

Study Number: ALXN1210-PNH-304 Subject ID: _____

Date Completed: _____ Time Completed: _____

Completed by: ☐ Patient ☐ Caregiver (Initials): _____

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

		None of the time	A little bit of the time	Some of the time	Most of the time	All of the time
pF1	I feel tired	0	1	2	3	4
pF2	I have energy (or strength)	0	1	2	3	4
pF3	I could do my usual things at home	0	1	2	3	4
pF4	I had trouble <u>starting</u> things because I was too tired	0	1	2	3	4
pF5	I had trouble <u>finishing</u> things because I was too tired	0	1	2	3	4
pF6	I needed to sleep during the day	0	1	2	3	4
pF7	I got upset by being too tired to do things I wanted to do	0	1	2	3	4
pF8	Being tired made it hard for me to play or go out with my friends as much as I'd like	0	1	2	3	4
pF9	I needed help doing my usual things at home	0	1	2	3	4
pF10	I feel weak	0	1	2	3	4
pF11	I was too tired to eat	0	1	2	3	4
pF12	Being tired made me sad	0	1	2	3	4
pF13	Being tired made me mad (angry)	0	1	2	3	4

APPENDIX D. PROTOCOL LABORATORY TESTS

Hematology

- Free hemoglobin
- Haptoglobin
- Hematocrit
- Hemoglobin
- Mean corpuscular hemoglobin
- Platelet count
- RBC count
- RBC distribution width
- RBC mean corpuscular volume
- Reticulocyte count
- WBC count
- WBC differential

Coagulation Panel

- International normalized ratio
- Partial thromboplastin time
- Prothrombin time

Urinalysis

- Appearance
- Bilirubin
- Blood
- Color
- Glucose
- Ketone
- Nitrite
- pH
- Specific gravity
- Urobilinogen

Urine Chemistry

- Microalbumin

Clinical Chemistry

- Alanine aminotransferase
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase
- Bicarbonate
- Blood urea nitrogen
- Calcium
- Chloride
- Creatinine
- Gamma-glutamyltransferase
- Glucose
- Lactate dehydrogenase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Total bilirubin (direct and indirect)
- Total protein
- Uric acid

Other

- Antidrug antibody
- Beta human chorionic gonadotropin (*females of childbearing potential only*)
- Chicken RBC assay
- Free and total C5
- Pharmacokinetic assay
- PNH clone size

Abbreviations: C5 = complement component 5; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; WBC = white blood cell