# PROTOCOL ALXN1210-PNH-301

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

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| Amendment 5 (Global): | 01 March 2019 |
| Amendment 6 (Global): | 12 April 2021 |

# SPONSOR SIGNATURE PAGE

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

**PROTOCOL NUMBER: ALXN1210-PNH-301**

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[redacted]
Alexion Pharmaceuticals, Inc.

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Date

# INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ALXN1210. I have read the ALXN1210-PNH-301 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 |
|---|---|---|
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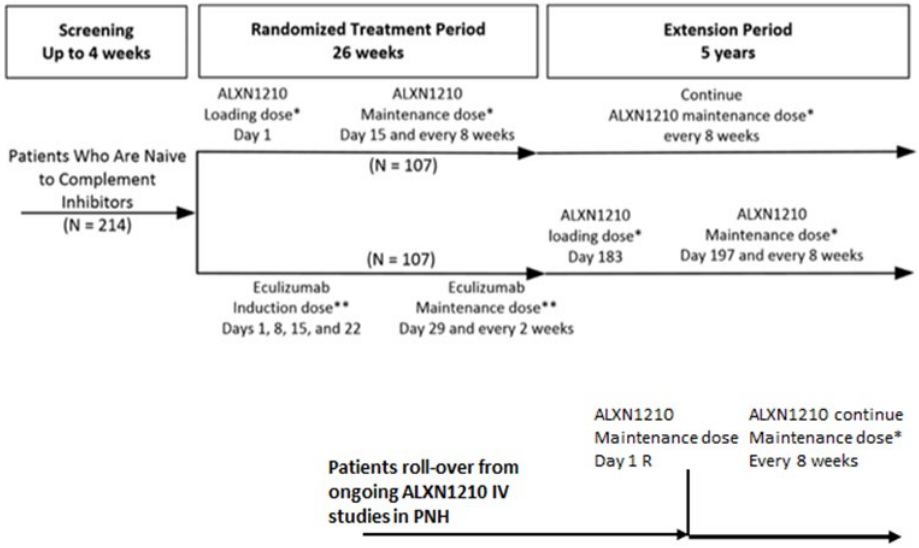
# 2. SYNOPSIS

| | |
|---|---|
| **Name of Sponsor/Company:** Alexion Pharmaceuticals, Inc. | |
| **Name of Investigational Product:** ALXN1210 | |
| **Name of Active Ingredient:** ALXN1210 | |
| **Title of Study:** A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) | |
| **Protocol No:** ALXN1210-PNH-301 | **EudraCT Number:** 2016-002025-11 |
| **Study Center(s):** Approximately 300 investigative sites globally. | |
| **Length of Study:**<br>Estimated date first patient treated: Dec 2016<br>Estimated date last patient completed: Jan 2023 | **Phase of Development:** 3 |
| **Objective:**<br>The primary objective of this study is to assess the noninferiority of ALXN1210 compared to eculizumab in adult patients with PNH who have never been treated with a complement inhibitor.<br><br>Noninferiority will be claimed if after 26 weeks of treatment: 1) the lower bound of the 95% confidence interval (CI) for the difference (ALXN1210-eculizumab) in transfusion avoidance (TA) rate is greater than -20%, and 2) the lower bound of the 95% CI for the odds ratio of ALXN1210 compared to eculizumab for lactate dehydrogenase normalization (LDH-N) is greater than 0.39. | |
| **Study Design and Methodology:** This is a Phase 3, open-label, randomized, active-controlled, multicenter study to evaluate the safety and efficacy of ALXN1210 versus eculizumab administered by intravenous (IV) infusion to adult patients with PNH who are naïve to complement inhibitor treatment. In addition, patients may be rolled over from other ongoing studies of ALXN1210 IV in patients with PNH into the Extension Period of Study ALXN1210-PNH-301 to receive ALXN1210 (hereafter referred to as Roll-over Cohort). Patients are allowed to roll over into Study ALXN1210-PNH-301 to receive continued ALXN1210 IV q8w maintenance treatment.<br><br>For patients enrolled directly into Study ALXN1210-PNH-301, the study consists of a 4-week screening period, a 26-week randomized treatment period, and an extension period of up to 5 years. Patients will be stratified into 1 of 6 groups based on their transfusion history (0, 1 to 14, or > 14 units of packed red blood cells [pRBCs] in the 1 year prior to first dose of study drug) and screening lactate dehydrogenase (LDH) levels (1.5 to < 3 × upper limit of normal [ULN] or ≥ 3 × ULN). The patients within each of the 6 groups will then be randomly assigned in a 1:1 ratio to receive ALXN1210 or eculizumab. Enrollment of patients without a history of transfusion in the past year will be capped at 20%.<br><br>Prior to randomization and within 5 days prior to study drug administration on Day 1, each patient's hemoglobin must be evaluated by either local or central laboratory. If at that time the patient's hemoglobin value meets protocol-specified transfusion guidelines, the patient must be transfused with pRBCs to a hemoglobin level above the protocol-specified transfusion threshold in order to be eligible for randomization. The patient's post-transfusion hemoglobin value should be confirmed by local or central laboratory to be above the protocol-specified transfusion threshold.<br><br>Patients randomly assigned to the ALXN1210 group will receive a loading dose of ALXN1210 (2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg) on Day 1, followed by maintenance doses of ALXN1210 (3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg) on Day 15 and every 8 weeks (q8w) thereafter for a total of 26 weeks of treatment. Patients randomly assigned to the eculizumab group will receive induction treatment with 600 mg of eculizumab IV on Days 1, 8, 15, and 22, followed by maintenance treatment with eculizumab 900 mg on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment. After completion of all assessments on Day 183, all patients will enter an extension period and receive ALXN1210 until the product is registered or approved (in accordance with country-specific regulations) or for up to 5 years, whichever occurs first. (In Norway and Denmark, patients will participate for a total of 2.5 years.) Beginning on Day 183, patients who had been randomized to the | |

ALXN1210 treatment group will receive a maintenance dose (as described above) of ALXN1210 q8w, and patients who had been randomized to the eculizumab group will receive a loading dose (as described above) of ALXN1210 followed 2 weeks later and q8w thereafter by a weight-based maintenance dose of ALXN1210.

For the Roll-over Cohort, patients will receive ALXN1210 weight-based q8w maintenance dosing.




* ALXN1210 dosage: loading dose = 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 for patients weighing ≥ 100 kg; maintenance dose = 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg
** Eculizumab dosage: induction dose = 600 mg; maintenance dose = 900 mg

Abbreviations: IV = intravenous;PNH = paroxysmal nocturnal hemoglobinuria; R = roll-over

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

**Number of Patients (planned) in the original Study ALXN1210-PNH-301 Cohort:** Based on the coprimary endpoint of TA, approximately 214 patients will be randomly assigned in a 1:1 ratio to receive ALXN1210 (N = 107) or eculizumab (N = 107) to ensure at least 193 evaluable patients (assumes no more than 10% drop-out rate).
A maximum number of approximately 56 patients may roll over from other ongoing studies of ALXN1210 IV in patients with PNH into the Extension Period of Study ALXN1210-PNH-301.

**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, based on discussion and agreement between the Investigator and the Medical Monitor.

**Eligibility Criteria for Patient Cohort Originally Enrolled in Study ALXN1210-PNH-301**
**Inclusion Criteria:**

1. Male or female, 18 years of age or older 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. Presence of 1 or more of the following PNH-related signs or symptoms within 3 months of Screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin < 10

g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion due to PNH.
4. LDH level ≥ 1.5 × ULN at screening.
5. To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
6. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug.
7. Patients must be willing and able to give written informed consent and to comply with all study visits and procedures, including the use of any data collection device(s) to directly record patient data.

**Exclusion Criteria:**

1. Current or previous treatment with a complement inhibitor.
2. Platelet count < 30,000/$mm^3$ ($30 \times 10^9$/L) at Screening.
3. Absolute neutrophil count < 500/μL ($0.5 \times 10^9$/L) at Screening.
4. History of bone marrow transplantation.
5. Body weight < 40 kg at Screening.
6. History of *N. meningitidis* infection.
7. History of unexplained, recurrent infection.
8. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
9. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study drug administration on Day 1.
10. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer).
11. Immunized with a live-attenuated vaccine 1 month prior to study drug administration on Day 1.
12. History of malignancy within 5 years of Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
13. 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.
14. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of randomization, coexisting chronic anemia unrelated to PNH) that would make them unlikely to tolerate the requirements of the protocol (eg, transfusion guidelines).
15. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.
16. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
17. Females who plan to become pregnant or are currently pregnant or breastfeeding.
18. Females who have a positive pregnancy test result at Screening or on Day 1.
19. 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.
20. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
21. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the 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.

**Eligibility Criteria for Roll-over Cohort**

1. All patients regardless of age, who are currently receiving ALXN1210 IV in an ongoing ALXN1210 study in patients with PNH
2. Patients must be willing and able to give written informed consent and to comply with all Extension study visits and procedures, including the use of any data collection device(s) to directly record patient data

3. Female patients of childbearing potential 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

**Investigational Product, Dosage, and Mode of Administration:**
ALXN1210 loading dose on Day 1 and maintenance doses on Day 15 and q8w thereafter, administered by IV infusion. For Roll-over Cohort, Day 1 will be the start of q8w weight-based maintenance dose. Dosages are based on the patient's body weight, as shown in the table below:

| Body Weight[a] | Loading Dose | Maintenance Dose |
|---|---|---|
| ≥ 30 to < 40 kg[b] | 1200 mg | 2700 mg |
| ≥ 40 to < 60 kg | 2400 mg | 3000 mg |
| ≥ 60 to < 100 kg | 2700 mg | 3300 mg |
| ≥ 100 kg | 3000 mg | 3600 mg |

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

[b] In the event that a patient drops below 30 kg during the course of the study, the approved ravulizumab atypical hemolytic uremic syndrome (aHUS) dosing for patients weighing ≥20 and < 30 kg will be used: a loading dose of 900 mg and maintenance dose of 2100 mg.

**Reference Therapy, Dosage, and Mode of Administration:**
Original Study ALXN1210-PNH-301 Cohort: Eculizumab 600 mg induction doses on Days 1, 8, 15, and 22; 900 mg maintenance dose on Day 29 and q2w to Day 183, administered by IV infusion.
For the Roll-over Cohort, there is no reference therapy.

**Planned Duration of Treatment:**
**Original Study ALXN1210-PNH-301 Cohort:** 26-week randomized treatment period followed by an extension period in which all patients will receive ALXN1210 until the product is registered or approved (in accordance with country-specific regulations) or for up to 5 years, whichever occurs first.
**Roll-over Cohort:** patients will receive ALXN1210 until the product is registered or approved (in accordance with country-specific regulations) or for the duration of the current study (end of study [EOS] estimated January 2023), whichever occurs first.

**Endpoints:**

**Original Study ALXN1210-PNH-301 Cohort**

Efficacy

*Coprimary*

- Transfusion avoidance (TA), defined as the proportion of patients who remain transfusion-free and do not require a transfusion as per protocol-specified guidelines through Day 183 (Week 26)
- Hemolysis as directly measured by the normalization of LDH levels (LDH-N) from Day 29 (first scheduled evaluation status post initiation of maintenance dosing) through Day 183 (Week 26)

*Key Secondary (to be tested in a hierarchical manner)*

1. Percentage change in LDH from Baseline to Day 183 (Week 26)
2. Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from Baseline to Day 183 (Week 26)
3. Proportion of patients with breakthrough hemolysis, defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy
4. Proportion of patients with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)

*Other Secondary*

- Change in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, from Baseline to Day 183 (Week 26)
- Time to first occurrence of LDH-N
- Total number of units of pRBCs transfused through Day 183 (Week 26)
- Change in clinical manifestations of PNH (fatigue, hemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia, and erectile dysfunction) from Baseline to Day 183 (Week 26)
- Proportion of patients experiencing MAVEs through Day 183 (Week 26)

Pharmacokinetic/Pharmacodynamic (PK/PD)

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

Safety

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

**Roll-over Cohort**

The long-term safety of Roll-over patients on ALXN1210 after their roll over into the Extension Period of Study ALXN1210-PNH-301 will be evaluated by the incidence of AEs and SAEs, laboratory assessments, and the proportion of patients who develop ADA.

**Statistical methods:**

**Original Study ALXN1210-PNH-301 Cohort:**

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

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

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

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

*Primary Efficacy Analyses*
The coprimary efficacy endpoints are 1) the difference between treatment groups in the proportion of patients who achieve TA through Day 183, and 2) the relative effect of treatment in LDH-N from Day 29 through Day 183 expressed as an odds ratio.

The percentage of patients who achieve TA with 95% CIs will be computed at Day 183 for both the ALXN1210 and eculizumab treatment groups and the randomization strata. A difference in the percentage of patients achieving TA in the 2 treatment groups will be calculated between ALXN1210 and eculizumab treatment groups, along with a 95% CI for the difference. The difference between ALXN1210 and eculizumab treatment groups will be computed as a weighted combination of the differences between the ALXN1210 and eculizumab treatment groups within stratification groups (using Mantel-Haenszel). The 95% CI for the difference between ALXN1210 and eculizumab treatment groups will be calculated using the stratified Newcombe confidence interval method.

LDH-N will be analyzed using a generalized estimating equation (GEE) approach which accounts for the repeated measures of LDH-N at each visit. The GEE approach provides odds ratios and CIs of treatment effect while controlling for the correlation between visits for a given patient and other baseline factors. LDH-N from Day 29 through Day 183 will be used as the dependent variable and an indicator variable for treatment, history of transfusion (as a categorical variable based on the stratification factor levels), and baseline LDH level (as a continuous variable) will be included in the model as explanatory variables. The within-patient correlation will assume a first-order autoregressive structure which assumes the highest correlation is between visits that are closest in time. Day 29 is the first scheduled assessment after initiation of maintenance dosing, and experience with eculizumab and Phase 1b/2 ALXN1210 data demonstrate near maximal suppression of LDH by 4 weeks of treatment. Results from the model will be presented as odds ratios with 95% CIs.

In order to conclude ALXN1210 is noninferior to eculizumab, both coprimary endpoints individually need to demonstrate noninferiority. If the lower-bound of the 95% CI for the difference (ALXN1210-eculizumab) is greater than the noninferiority margin (NIM) of -20% for TA and the lower bound of the 95% CI for the odds ratio of ALXN1210 compared to eculizumab is greater than the NIM of 0.39 for LDH-N, then ALXN1210 treatment will be concluded to be noninferior to eculizumab.

*Key Secondary Efficacy Analyses*
The 4 key secondary efficacy endpoints will be summarized by randomization strata and by treatment group at baseline and at the study visits where these assessments are collected during the 26-week randomized treatment period. Change in FACIT-Fatigue (and percent change in LDH) from baseline to Week 26 will be analyzed using a mixed model for repeated measures (MMRM) with the fixed, categorical effects of treatment, the stratification randomization indicators of transfusion history (0, 1 to 14, or > 14 units of pRBCs in the 1 year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 × ULN or ≥ 3 × ULN), study visit and study visit by treatment group interaction as well as the continuous, fixed covariates of baseline FACIT-Fatigue (or LDH) and baseline FACIT-Fatigue (or LDH)-by-visit interaction as covariates. For percent change in LDH, the baseline LDH level as a continuous variable will be included. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. A difference between the ALXN1210 and eculizumab treatment groups along with a 2-sided 95% CI will be calculated.

For breakthrough hemolysis and stabilized hemoglobin, the same approach used for TA will be employed. These key secondary efficacy endpoints will be tested in a hierarchical manner provided that noninferiority was declared for the coprimary endpoints.

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

1. If the upper bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the percentage change from Baseline to Week 26 in LDH is less than the NIM of 20%, then ALXN1210 will be declared noninferior for this parameter and the next parameter will be tested.
2. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in change from baseline in FACIT-Fatigue is greater than the NIM of -5, then ALXN1210 will be declared noninferior for this parameter and the next parameter will be tested.
3. If the upper bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with breakthrough hemolysis is less than the NIM of 20%, then ALXN1210 will be declared noninferior for this parameter and the next parameter will be tested.
4. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with stabilized hemoglobin is greater than the NIM of -20%, then ALXN1210 will be declared noninferior for this parameter.

If noninferiority is established for all key secondary endpoints then superiority will be assessed using a closed-testing procedure with the following order and using a 2-sided 0.05 test for each parameter:

5. Proportion of patients with breakthrough hemolysis through Day 183 (Week 26)
6. Percentage change from baseline to Day 183 (Week 26) in LDH
7. Hemolysis as directly measured by LDH-N from Day 29 through Day183 (Week 26)
8. Change from baseline to Day 183 (Week 26) in FACIT-Fatigue
9. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)
10. Transfusion avoidance

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

*Other Secondary Endpoints*
Changes from baseline in EORTC-QLQ-C30 will be summarized by treatment group at baseline and at the study visits where these assessments are collected. Shifts from baseline in clinical manifestations of PNH will be summarized by treatment group and at the study visits where these assessments are collected. The number of any treatment-emergent MAVEs (n) and number of patients with events (n, %) will be displayed by treatment group. Total number of units of pRBCs transfused during treatment will be summarized by treatment group. Kaplan-Meier curves for both treatment groups and estimates of time to first occurrence of LDH-N since first study drug will be produced. No statistical inference of these parameters is planned.

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

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

data at each sampling time, as appropriate. Assessment of population-PK may be considered using data from this study or in combination with data from other studies.

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

Analysis of Roll-over Cohort:
Analysis of data from patients who are rolled over from other ongoing ALXN1210 PNH studies will be performed as a separate cohort. The analysis will focus on the long-term safety after their roll over. The long-term safety will be evaluated by incidence of treatment-emergent adverse events and SAEs, laboratory assessments, and proportion of patients who develop ADAs.
The analyses will be performed on the Roll-over Safety Set defined as all patients who receive at least 1 ALXN1210 dose after roll over. A summary of long-term safety in the Roll-over Cohort will be included in the final CSR.

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# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ADA | antidrug antibody |
| ADL | activities of daily living |
| AE | adverse event |
| BP | blood pressure |
| C5 | complement component 5 |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| COVID-19 | coronavirus disease 2019 |
| cRBC | chicken red blood cell |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EOS | end of study |
| ET | early termination |
| FACIT-Fatigue | Functional Assessment of Chronic Illness Therapy-Fatigue Scale |
| FAS | Full Analysis Set |
| FSH | follicle-stimulating hormone |
| GCP | good clinical practice |
| GDS | Global Drug Safety |
| HIV | human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IV | intravenous |
| IxRS | interactive voice- or web-response system |
| LDH | lactate dehydrogenase |
| LDH-N | lactate dehydrogenase normalization |
| LLT | lowest level term |
| MAVE | major adverse vascular event |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NIM | noninferiority margin |
| NO | nitric oxide |
| PD | pharmacodynamic(s) |
| PEF | peak expiratory flow |
| PK | pharmacokinetic(s) |

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

# 5. INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic disorder that occurs most frequently in adults (Brodsky, 2015). The disease begins with the clonal expansion of a hematopoietic stem cell that has acquired a somatic mutation in the PIGA gene (Brodsky, 2014). Consequently, PNH blood cells lack the glycophosphatidylinositol anchor protein and are deficient in the membrane-bound complement inhibitory proteins CD55 and CD59. In the absence of CD55, there is increased deposition of complement protein C3 cleavage products on blood cell membrane surfaces, in turn leading to cleavage of component 5 (C5) into C5a and C5b. The pathology and clinical presentations in patients with PNH are driven by uncontrolled terminal complement activation on red blood cells (RBCs).

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

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

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

ALXN1210 relative to eculizumab, increasing the duration of terminal complement inhibition, while preserving both the high degree of specificity for binding to C5 and the effectorless nature of the antibody.

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

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

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

In this Phase 3, open-label, randomized study, the efficacy and safety of ALXN1210 will be assessed compared to eculizumab in patients with PNH who are naïve to treatment with complement inhibitor, including eculizumab. In addition, long-term safety of patients who rolled over from other ongoing studies of ALXN1210 intravenous (IV) in patients with PNH into the Extension Period of Study ALXN1210-PNH-301 will be evaluated. The study design rationale is further discussed in Section 7.2.

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

## 5.1. Benefits and Risks Assessment

### 5.1.1. Potential Benefits

PNH is an ultra-rare, progressive, debilitating, and life-threatening disease, driven by chronic uncontrolled complement activation. The resulting inflammation and cellular damage lead to systemic complications, principally through intravascular hemolysis and thrombophilia (Brodsky, 2014; Socie, 1996). Chronic intravascular hemolysis due to continuous activation of

the complement pathway leads to the release of free hemoglobin, 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. The current standard of care for the treatment of PNH is eculizumab (Soliris®), a recombinant humanized mAb that binds to the human C5 complement protein and inhibits the activation of terminal complement. The efficacy and safety of eculizumab for the treatment of PNH are well established. The approved dosage regimen for eculizumab for PNH involves 4 weekly induction doses, followed by maintenance doses administered every 2 weeks starting at Week 5.

Given that PNH is a chronic disease, the current eculizumab regimen may significantly affect patients, many of whom have to miss days of work or school to accommodate treatment. In some cases, patients may refuse treatment or be 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. Infections (N. Meningitidis and Other Encapsulated Organisms)

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

#### 5.1.2.2. Immunogenicity

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

#### 5.1.2.3. Pregnancy Exposure

No studies of ALXN1210 have been conducted in pregnant women. Pregnant or nursing female patients are excluded from the clinical trial. Patients enrolled in the study, and their spouses/partners, will use a highly effective or acceptable method of contraception as required in Section 9.13.

# 6. STUDY OBJECTIVES AND ENDPOINTS

## 6.1. Study Objectives

### 6.1.1. Original Study ALXN1210-PNH-301 Cohort

#### 6.1.1.1. Primary Objective

The primary objective of this study is to assess the noninferiority of ALXN1210 compared to eculizumab in adult patients with PNH who have never been treated with a complement inhibitor.

Noninferiority will be claimed if after 26 weeks of treatment: 1) the lower bound of the 95% confidence interval (CI) for the difference (ALXN1210-eculizumab) in transfusion avoidance (TA) rate is greater than -20%, and 2) the lower bound of the 95% CI for the odds ratio of ALXN1210 compared to eculizumab for lactate dehydrogenase normalization (LDH-N) is greater than 0.39.

#### 6.1.1.2. Secondary Objectives

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

- To characterize the safety and tolerability of ALXN1210 in this patient population
- To evaluate the efficacy of ALXN1210 by additional efficacy measures
- To characterize the pharmacokinetics/pharmacodynamics (PK/PD) and immunogenicity of ALXN1210
- To evaluate the long-term safety and efficacy of ALXN1210
- To evaluate the safety and efficacy in patients who switch from eculizumab to ALXN1210 in the Extension Period
- To quantify identified specific safety concerns during treatment with ALXN1210, including meningococcal infections, serious hemolysis after drug discontinuation in PNH, immunogenicity, serious infections, malignancies and hematologic abnormalities, and during pregnancy and breastfeeding

### 6.1.2. Rolled-over PNH Patients From Other Ongoing Studies of ALXN1210 IV

- Long-term safety of patients receiving ALXN1210 after roll over into Study ALXN1210-PNH-301

## 6.2. Endpoints

Section 6.2.1 through Section 6.2.4 describe the endpoints for the Original Study ALXN1210-PNH-301 Cohort. Section 6.2.5 describes the safety endpoints for both Original Study ALXN1210-PNH-301 Cohort and the Roll-over Cohort.

### 6.2.1. Coprimary Efficacy Endpoints

The coprimary efficacy endpoints of the study are:

- Transfusion avoidance, defined as the proportion of patients who remain transfusion-free and do not require a transfusion per protocol-specified guidelines through Day 183 (Week 26)
- Hemolysis as directly measured by LDH-N levels from Day 29 (first scheduled evaluation status post initiation of maintenance dosing) through Day 183 (Week 26)

### 6.2.2. Key Secondary Efficacy Endpoints

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

1. Percentage change in LDH from Baseline to Day 183 (Week 26)
2. Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from Baseline to Day 183 (Week 26)
3. Proportion of patients with breakthrough hemolysis, defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × upper limit of normal [ULN], after prior LDH reduction to < 1.5 × ULN on therapy
4. Proportion of patients with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)

### 6.2.3. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints of the study are:

- Change in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, from Baseline to Day 183 (Week 26)
- Time to first occurrence of LDH-N
- Total number of units of packed red blood cells (pRBCs) transfused through Day 183 (Week 26)
- Change in clinical manifestations of PNH (fatigue, hemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia, and erectile dysfunction) from Baseline to Day 183 (Week 26)
- Proportion of patients experiencing MAVEs through Day 183 (Week 26)

### 6.2.4. Pharmacokinetic and Pharmacodynamic Endpoints

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

- Change in free complement component 5 (C5) concentrations over time

### 6.2.5. Safety Endpoints

For the original Study ALXN1210-PNH-301 Cohort, the safety and tolerability of ALXN1210 compared with eculizumab will be evaluated by physical examinations, vital signs, electrocardiograms (ECGs), laboratory assessments, and incidence of adverse events (AEs) and serious adverse events (SAEs). The proportion of patients who develop antidrug antibodies (ADAs) will also be assessed.

The long-term safety of patients on ALXN1210 after their roll over into the Extension Period of Study ALXN1210-PNH-301 will be evaluated by the incidence of AEs and SAEs, laboratory assessments, and the proportion of patients who develop ADA.

# 7. INVESTIGATIONAL PLAN

## 7.1. Summary of Study Design

Study ALXN1210-PNH-301 is a Phase 3, open-label, randomized, active-controlled, multicenter study to evaluate the safety and efficacy of ALXN1210 versus eculizumab administered by intravenous (IV) infusion to adult patients with PNH who are naïve to complement inhibitor treatment. The study will enroll approximately 214 patients (107 patients per treatment group).

In addition, patients may be rolled over from other ongoing studies of ALXN1210 IV in patients with PNH into the Extension Period of Study ALXN1210-PNH-301 to receive ALXN1210 (hereafter referred to as Roll-over Cohort).

For patients enrolled directly into Study ALXN1210-PNH-301, the study consists of a 4-week screening period, a 26-week randomized treatment period, and an extension period of up to 5 years. Patients will be stratified into 1 of 6 groups based on their transfusion history (0, 1 to 14, or > 14 units of pRBCs in the 1 year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 × ULN or ≥ 3 × ULN). The patients within each of the 6 groups will then be randomly assigned in a 1:1 ratio to receive ALXN1210 or eculizumab. Enrollment of patients without a history of transfusion in the past year will be capped at 20%.

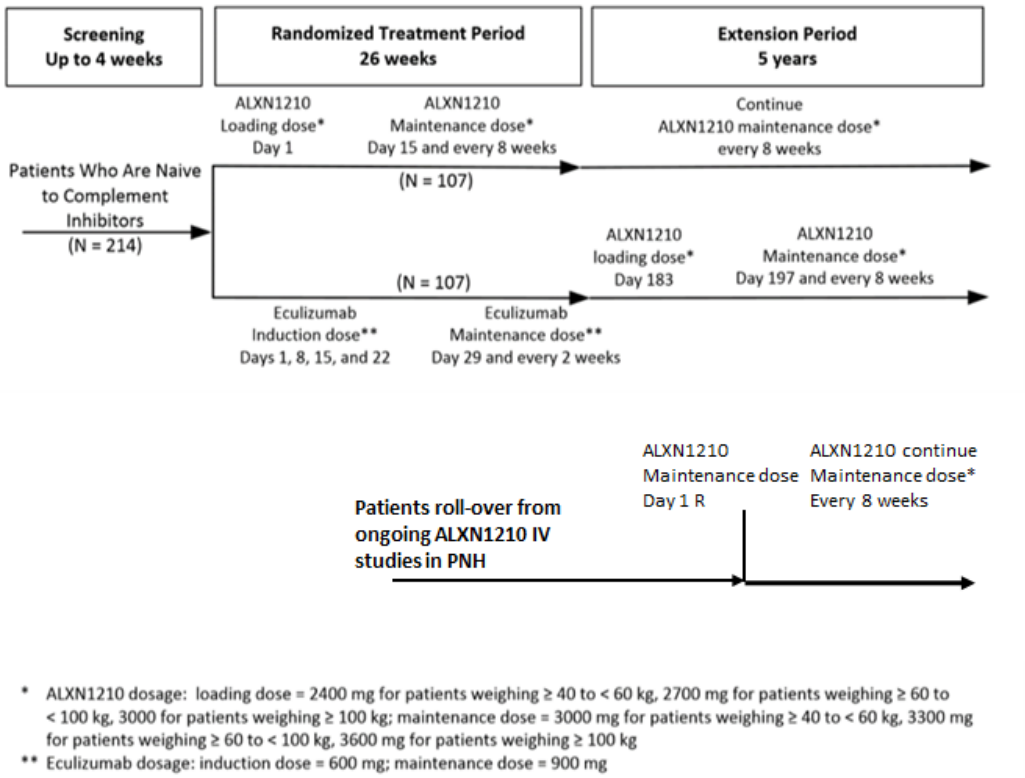
Prior to randomization and within 5 days prior to study drug administration on Day 1, each patient's hemoglobin must be evaluated by either local or central laboratory. If at that time the patient's hemoglobin value meets protocol-specified transfusion guidelines, the patient must be transfused with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

Patients randomly assigned to the ALXN1210 group will receive a loading dose of ALXN1210 (2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg) on Day 1, followed by maintenance doses of ALXN1210 (3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg) on Day 15 and every 8 weeks (q8w) thereafter for a total of 26 weeks of treatment. Patients randomly assigned to the eculizumab group will receive induction treatment with 600 mg of eculizumab IV on Days 1, 8, 15, and 22, followed by maintenance treatment with eculizumab 900 mg on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment. After completion of all assessments on Day 183, all patients will enter an extension period and receive ALXN1210 until the product is registered or approved (in accordance with country-specific regulations) or for up to 5 years, whichever occurs first. (In Norway and Denmark, patients will participate for a total of 2.5 years.) Beginning on Day 183, patients who had been randomized to the ALXN1210 treatment group will receive a maintenance dose (as described above) of ALXN1210 q8w, and patients who had been randomized to the eculizumab group will receive a loading dose (as described above) of ALXN1210 followed 2 weeks later and q8w thereafter by a weight-based maintenance dose of ALXN1210. For the Roll-over Cohort, patients will receive ALXN1210 weight-based q8w maintenance dosing until the product is registered or approved (in accordance

with country-specific regulations) or until the end of the current study (estimated end of study [EOS] January 2023), whichever occurs first.

Figure 1 illustrates the study design.

**Figure 1: Study Design Schematic for Clinical Protocol ALXN1210-PNH-301**




* ALXN1210 dosage: loading dose = 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 for patients weighing ≥ 100 kg; maintenance dose = 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg
** Eculizumab dosage: induction dose = 600 mg; maintenance dose = 900 mg

Abbreviations: IV = intravenous; PNH = paroxysmal nocturnal hemoglobinuria; R = roll-over

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

## 7.2. Discussion of Design and Control

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

Transfusion avoidance is chosen as the coprimary endpoint because it is informative regardless of the patient's transfusion history. The incidence of transfusions was a coprimary endpoint in the pivotal TRIUMPH study (C04-001) for eculizumab, and TA was a key secondary endpoint.

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

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

Patients with PNH receiving ALXN1210 IV in other ongoing ALXN1210 studies are allowed to roll over into Study ALXN1210-PNH-301 and receive continued ALXN1210 IV q8w maintenance treatment.

## 7.3. Schedule of Assessments

The Schedule of Assessments is provided in Table 1 for the Screening and Randomized Treatment Period and in Table 2 and Table 3 (patients entering from ALXN1210 group) and Table 4 and Table 5 (patients entering from eculizumab group) for the Extension Period. The Schedule of Assessments for patients who rolled over from ongoing ALXN1210 IV studies in patients with PNH is provided in Table 6.

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

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

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

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

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

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale; 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

[a] All patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

[b] 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.

[c] Female patients of childbearing potential only. Serum pregnancy test at Screening and Day 183; urine pregnancy test at all other required time points. A negative urine test result is required prior to administering ALXN1210 or eculizumab to female patients of childbearing potential at the indicated visits.

[d] Transfusions given during and between visits will be recorded.

[e] Prior to randomization and within 5 days prior to study drug administration on Day 1, each patient's hemoglobin must be evaluated by either local or central laboratory. If at that time the patient's hemoglobin value meets protocol-specified transfusion guidelines (Section 10.1), the patient must be transfused with pRBCs to a hemoglobin level above the protocol-specified transfusion threshold in order to be eligible for randomization. The patient's post-transfusion hemoglobin value should be confirmed by local or central laboratory to be above the protocol-specified transfusion threshold.

[f] Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.

[g] Physician- and patient-reported assessments will be performed prior to study drug administration.

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

[i] Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic 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 before study drug administration.

[j] Single 12-lead ECG will be collected at Screening and predose on Day 57 and Day 183. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[k] Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line. Follicle stimulating hormone levels will be measured during Screening only in order to confirm postmenopausal status.

[l] Serum samples for PK/PD analyses will be collected predose (within 0.5 hours prior to the start of infusion) and at end-of-infusion (within 0.5 hours after the end of infusion). The predose PK/PD sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion PK/PD samples will be drawn from the patient's opposite, noninfused arm. Note that the Day 183 end-of-infusion sample is considered an Extension Period assessment (see Table 2 and Table 4). All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.

[m] Serum samples for PK/PD analyses will be collected predose (within 0.5 hours prior to the start of infusion) for eculizumab-treated patients and at any time for ALXN1210-treated patients. All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.

[n] Samples for ADA will be collected predose.

[o] If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD samples for analysis will be collected. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD samples.

[p] Patients will be randomly assigned to treatment based on screening LDH result and history of blood transfusions through an interactive voice or web response system (IxRS).

[q] The dose of ALXN1210 is based on the patient's last recorded study visit body weight.

[r] The primary efficacy endpoint assessment is before dosing on Day 183. Dosing on Day 183 is the start of the Extension Period. Please refer to additional Day 183 post dose procedures in Table 2 and Table 4.

## Table 2: Schedule of Study Visits and Assessments: Extension Period Day 183 to Day 1023 – Patients Entering from ALXN1210 Group

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

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

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

[b] Granulocyte and RBC clone size measured by high-sensitivity flow cytometry on Days 351 and 743; RBC clone size only at other visits

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

[d] Transfusions given during and between visits will be recorded.

[e] Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.

[f] Physician- and patient-reported assessments will be performed prior to study drug administration.

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

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

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

[j] Serum samples for PK/PD analyses will be collected at end-of-infusion on Day 183; predose (within 0.5 hours prior to the start of infusion) and at end-of-infusion (within 0.5 hours after the end of infusion) on Days 351, 575, 799 and 1023; and at any time at ET. The predose PK/PD sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion PK/PD samples will be drawn from the patient's opposite, noninfused arm. All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.

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

[l] If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD samples for analysis will be collected. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD samples.

[m] The dose of ALXN1210 is based on the patient's last recorded study visit body weight.

## Table 3: Schedule of Study Visits and Assessments: Extension Period Day 1079 to Day 2031 – Patients Entering from ALXN1210 Group

| Period | Extension Period | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **1079** | **1135** | **1191** | **1247** | **1303** | **1359** | **1415** | **1471** | **1527** | **1583** | **1639** | **1695** | **1751** | **1807** | **1863** | **1919** | **1975** | **2031 EOS/ ET[n]** |
| **Window (day)** | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 |
| PNH clone size[a] | X | X | X | X | X | X | X | X | X | | | X | | | X | | | X |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test[b] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Record transfusions and transfusion parameters[c] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PNH symptomatology[d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| FACIT-Fatigue[e] | | | X | | | | X | | | | | X | | | X | | | X |
| EORTC QLQ-C30[e] | | | X | | | | X | | | | | X | | | X | | | X |
| Abbreviated physical examination[f] | | X | | X | | X | | X | | | | X | | | X | | | X |
| Vital signs[g] | X | X | X | X | X | X | X | X | X | | | X | | | X | | | X |
| Safety 12-Lead ECG[h] | | | | | | | | | | | | | | | | | | X |
| Chemistry including LDH[i] | X | X | X | X | X | X | X | X | X | | | X | | | X | | | X |
| Hematology including free hemoglobin and coagulation[i] | X | X | X | X | X | X | X | X | X | | | X | | | X | | | X |
| Urinalysis and urine chemistry[i] | X | X | X | X | X | X | X | X | X | | | X | | | X | | | X |
| PK/PD sampling[j] | | | | X | | | | X | | | | X | | | X | | | X |
| Immunogenicity (ADA)[k] | | X | | X | | X | | X | | | | X | | | X | | | X |
| Review safety card | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Breakthrough hemolysis[l] | ←Monitor continuously→ | | | | | | | | | | | | | | | | | |
| Concomitant medications | ←Monitor continuously→ | | | | | | | | | | | | | | | | | |
| Adverse events | ←Monitor continuously→ | | | | | | | | | | | | | | | | | |
| ALXN1210 administration[m] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

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

[a] Granulocyte and RBC clone size measured by high-sensitivity flow cytometry on Days 1135, 1471, and 1863; RBC clone size only at other visits.

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

[c] Transfusions given during and between visits will be recorded.
[d] Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.
[e] Physician- and patient-reported assessments will be performed prior to study drug administration.
[f] Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or qualified designee) judgment and patient symptoms. At least one body system must be checked for an abbreviated physical examination.
[g] 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]). Vital signs will be taken before each study drug administration.
[h] Single 12-lead ECG will be collected at Day 2031 or ET. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
[i] Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line.
[j] Serum samples for PK/PD analyses will be collected predose (within 0.5 hours prior to the start of infusion) and at end-of-infusion (within 0.5 hours after the end of infusion) on Days 1247, 1471, 1695, and 1863; and at any time on Day 2031 or ET. The predose PK/PD sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion PK/PD samples will be drawn from the patient's opposite, noninfused arm. All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.
[k] Samples for ADA will be collected predose or at any time when a dose of study drug is not administered.
[l] If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD samples for analysis will be collected. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD samples.
[m] The dose of ALXN1210 is based on the patient's last recorded study visit body weight.
[n] If a patient withdraws early from the study (eg, to begin treatment with marketed product), an ET visit will be performed.

## Table 4: Schedule of Study Visits and Assessments: Extension Period Day 183 to Day 1037– Patients Entering from Eculizumab Group

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

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

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

[b] Granulocyte and RBC clone size measured by high-sensitivity flow cytometry on Days 365 and 757; RBC clone size only at other visits.

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

[d] Transfusions given during and between visits will be recorded.

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

[f] Physician- and patient-reported assessments will be performed prior to study drug administration.

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

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

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

[j] Serum samples for PK/PD analyses will be collected predose (within 0.5 hours prior to the start of infusion) and at end-of-infusion (within 0.5 hours after the end of infusion) on Days 197, 365, 589, 813, and 1037; at end-of-infusion on Day 183; and at any time on Day 225 or ET. The predose PK/PD sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion PK/PD samples will be drawn from the patient's opposite, noninfused arm. All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.

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

[l] If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD samples for analysis will be collected. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD samples.

[m] The dose of ALXN1210 is based on the patient's last recorded study visit body weight.

## Table 5: Schedule of Study Visits and Assessments: Extension Period Day 1093 to Day 2045 – Patients Entering from Eculizumab Group

| **Period** | **Extension Period** | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **1093** | **1149** | **1205** | **1261** | **1317** | **1373** | **1429** | **1485** | **1541** | **1597** | **1653** | **1709** | **1765** | **1821** | **1877** | **1933** | **1989** | **2045 EOS/ ET[n]** |
| **Window (day)** | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 |
| PNH clone size[a] | X | X | X | X | X | X | X | X | X | | | X | | | X | | | X |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test[b] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Record transfusions and transfusion parameters[c] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PNH symptomatology[d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| FACIT-Fatigue[e] | | | X | | | | X | | | | | X | | | X | | | X |
| EORTC QLQ-C30[e] | | | X | | | | X | | | | | X | | | X | | | X |
| Abbreviated physical examination[f] | | X | | X | | X | | X | | X | | X | | | X | | | X |
| Vital signs[g] | X | X | X | X | X | X | X | X | X | | | X | | | X | | | X |
| Safety 12-Lead ECG[h] | | | | | | | | | | | | | | | | | | X |
| Chemistry including LDH[i] | X | X | X | X | X | X | X | X | X | | | X | | | X | | | X |
| Hematology including free hemoglobin and coagulation[i] | X | X | X | X | X | X | X | X | X | | | X | | | X | | | X |
| Urinalysis and urine chemistry[i] | X | X | X | X | X | X | X | X | X | | | X | | | X | | | X |
| PK/PD sampling[j] | | | | X | | | | X | | | | X | | | X | | | X |
| Immunogenicity (ADA)[k] | | X | | X | | X | | X | | | | X | | | X | | | X |
| Review safety card | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Breakthrough hemolysis[l] | ←Monitor continuously→ | | | | | | | | | | | | | | | | | |
| Concomitant medications | ←Monitor continuously→ | | | | | | | | | | | | | | | | | |
| Adverse events | ←Monitor continuously→ | | | | | | | | | | | | | | | | | |
| ALXN1210 administration[m] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

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

[a] Granulocyte and RBC clone size measured by high-sensitivity flow cytometry on Days 1149, 1485, and 1877; RBC clone size only at other visits.

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

[c] Transfusions given during and between visits will be recorded.

[d] Investigator or designee assessment of the following events: fatigue, chest pain, abdominal pain, dyspnea, dysphagia, erectile dysfunction, and red/dark urine or hemoglobinuria.
[e] Physician- and patient-reported assessments will be performed prior to study drug administration.
[f] Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or qualified designee) judgment and patient symptoms. At least one body system must be checked for an abbreviated physical examination.
[g] 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]). Vital signs will be taken before each study drug administration.
[h] Single 12-lead ECG will be collected at Day 2045 or ET. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
[i] Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line.
[j] Serum samples for PK/PD analyses will be collected predose (within 0.5 hours prior to the start of infusion) and at end-of-infusion (within 0.5 hours after the end of infusion) on Days 1261, 1485, 1709, and 1877; and at any time on Day 2045 or ET. The predose PK/PD sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion PK/PD samples will be drawn from the patient's opposite, noninfused arm. All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.
[k] Samples for ADA will be collected predose or at any time when a dose of study drug is not administered.
[l] If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD samples for analysis will be collected. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD samples.
[m] The dose of ALXN1210 is based on the patient's last recorded study visit body weight.
[n] If a patient withdraws early from the study (eg, to begin treatment with marketed product), an ET visit will be performed.

## Table 6: Schedule of Study Visits and Assessments: Patients who Roll-over from Ongoing ALXN1210 IV PNH Studies

| **Study Day** | **1 R** | **56R** | **112R** | **168R** | **224R** | **280R** | **336R** | **392 R** | **448 R** | **504 R EOS/ ET[o,p]** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Window (day)** | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 |
| Informed Consent | X | | | | | | | | | |
| Confirmation or administration of meningococcal vaccination[a] | X | | | | | | | | | |
| Medical History and Demographics | X | | | | | | | | | |
| PNH clone size[b] | X | | | X | | | X | | | X |
| Weight | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test[c] | X | X | X | X | X | X | X | X | X | X |
| Record transfusions and transfusion parameters[d] | X | X | X | X | X | X | X | X | X | X |
| PNH symptomatology[e] | X | X | X | X | X | X | X | X | X | X |
| FACIT-Fatigue[f] | X | | | | | | | | | X |
| EORTC QLQ-C30[f] | X | | | | | | | | | X |
| Abbreviated physical examination[g] | X | | | X | | | X | | | X |
| Vital signs[h] | X | X | X | X | X | X | 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 | X | X | X | X | X | X | X | X | X | X |
| Breakthrough hemolysis[m] | ←Monitor continuously→ | | | | | | | | | |
| Concomitant medications | ←Monitor continuously→ | | | | | | | | | |
| Adverse events | ←Monitor continuously→ | | | | | | | | | |
| ALXN1210 administration[n] | X | X | X | X | X | X | X | X | X | |

Abbreviations: ADA = antidrug antibody; BP = blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale; EOS = end of study; ET = early termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; IV = intravenous; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; R = roll over; RBC = red blood cell; WBC = white blood cell

[a] All patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

[b] WBC (granulocyte and monocyte) and RBC clone size measured by high-sensitivity flow cytometry at Day 1 R; RBC clone size only on Day 168 and Day 336.

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

[d] Transfusions given during and between visits will be recorded.
[e] Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.
[f] Physician- and patient-reported assessments will be performed prior to study drug administration.
[g] Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or qualified designee) judgment and patient symptoms. At least one body system must be checked for an abbreviated physical examination.
[h] Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic BP (millimeters of mercury [mmHg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). Vital signs will be taken before each study drug administration.
[i] Single 12-lead ECG will be collected at Day 504 or ET. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
[j] Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line.
[k] Serum samples for PK/PD analyses will be collected predose (within 0.5 hours prior to the start of infusion) and at end-of-infusion (within 0.5 hours after the end of infusion) on Days 1, 168, 336, and at any time on Day 504 or ET. The predose PK/PD sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion PK/PD samples will be drawn from the patient's opposite, noninfused arm. All collection times will be recorded in the eCRF. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.
[l] Samples for ADA will be collected predose .
[m] If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD samples for analysis will be collected. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD samples.
[n] The dose of ALXN1210 is based on the patient's last recorded study visit body weight.
[o] If a patient withdraws early from the study (eg, to begin treatment with marketed product), an ET visit will be performed.
[p] Depending on when patients roll over, the EOS will be adjusted such that it coincides with the planned EOS for the current protocol (estimated January 2023).

# 8. STUDY POPULATION

Original Study ALXN1210-PNH-301 Cohort: A total of approximately 214 patients with documented PNH will be enrolled and randomly assigned to treatment with either ALXN1210 or eculizumab at approximately 300 investigative sites globally.

Roll-Over Cohort: A maximum number of approximately 56 patients may roll over from other ongoing studies of ALXN1210 IV in patients with PNH into the Extension Period of Study ALXN1210-PNH-301.

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

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

## 8.1. Eligibility Criteria for Original Study ALXN1210-PNH-301 Cohort

### 8.1.1. Inclusion Criteria

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

1. Male or female, 18 years of age or older at the time of consent.
2. Documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry evaluation (Borowitz, 2010) of RBCs and white blood cells (WBCs), with granulocyte or monocyte clone size of ≥ 5%.
3. Presence of 1 or more of the following PNH-related signs or symptoms within 3 months of Screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin < 10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion due to PNH.
4. LDH level ≥ 1.5 × ULN at Screening.
5. To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
6. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance (Section 9.13) for avoiding pregnancy while on treatment and for 8 months after last dose of study drug.
7. Patients must be willing and able to give written informed consent and to comply with all study visits and procedures, including the use of any data collection device(s) to directly record patient data.

### 8.1.2. Exclusion Criteria

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

1. Current or previous treatment with a complement inhibitor.
2. Platelet count < 30,000/$mm^3$ ($30 \times 10^9$/L) at Screening.
3. Absolute neutrophil count < 500/µL ($0.5 \times 10^9$/L) at Screening.
4. History of bone marrow transplantation.
5. Body weight < 40 kg at Screening.
6. History of *N. meningitidis* infection.
7. History of unexplained, recurrent infection.
8. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
9. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study drug administration on Day 1.
10. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer).
11. Immunized with a live-attenuated vaccine 1 month prior to study drug administration on Day 1.
12. History of malignancy within 5 years of Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
13. 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.
14. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of randomization, coexisting chronic anemia unrelated to PNH) that would make them unlikely to tolerate the requirements of the protocol (eg, transfusion guidelines).
15. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.
16. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
17. Females who plan to become pregnant or are currently pregnant or breastfeeding.
18. Females who have a positive pregnancy test result at Screening or on Day 1.
19. 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.

20. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
21. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the 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.

## 8.2. Eligibility Criteria for Roll-over Cohort

1. All patients regardless of age, who are currently receiving ALXN1210 IV in an ongoing ALXN1210 study in patients with PNH
2. Patients must be willing and able to give written informed consent and to comply with all Extension study visits and procedures, including the use of any data collection device(s) to directly record patient data
3. Female patients of childbearing potential 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

## 8.3. Discontinuation

### 8.3.1. Withdrawal of Patients

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

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

- Serious infusion reaction (such as bronchospasm with wheezing or requiring ventilator support or symptomatic hypotension, refer to Appendix A) or serum sickness-like reactions manifesting 1 to 14 days after drug administration;
- Severe uncontrolled infection;
- Pregnancy or planned pregnancy; or
- If the Alexion Medical Monitor or the Investigator deems it 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 adverse event or an unresolved laboratory result that, in the opinion of the Investigator, is significantly outside of the reference

range and clinically significant (Section 11.4), the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

As it is essential to obtain follow-up data on any patient withdrawn due to an AE or SAE, follow-up due diligence documentation will consist of 3 phone calls followed by 1 registered letter to the patient's last known address. In any case, every effort must be made to undertake protocol specified safety follow-up procedures.

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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to local requirements.

## 8.4. End of Study Definition

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

# 9. STUDY TREATMENT

## 9.1. Materials and Supplies

### 9.1.1. Description of Study Drugs

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

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

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

ALXN1210 and eculizumab drug products are supplied for clinical studies as sterile, preservative-free 10-mg/mL solutions in single-use vials and designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via IV infusion.

Refer to Table 7, the current ALXN1210 IB, and the approved eculizumab local labeling or current eculizumab IB for additional information.

**Table 7: Study Drug**

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

### 9.1.2. Study Drug Packaging and Labeling

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

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

### 9.1.3. Study Drug Storage

Upon arrival of the study drug kits at the study site, the pharmacist or designee should promptly remove the study drug kits from the shipping cooler and store them in their original cartons under refrigerated conditions at 2°C to 8°C (36°F to 46°F) and protected from light. ALXN1210 and eculizumab should not be frozen. Study drug must be stored in a secure, limited-access storage area, and the temperature must be monitored daily.

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

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

### 9.1.4. Study Drug Preparation and Infusion

**Eculizumab or ALXN1210 must NOT be administered as an IV push or bolus injection.** Infusions of study drug should be prepared using aseptic technique. The patient's required dose of ALXN1210 or eculizumab will be further diluted into commercially available saline (0.9% sodium chloride; country-specific pharmacopeia) at the volume specified in Table 8 for ALXN1210 or Table 9 for eculizumab (see also approved local labeling or current IB for eculizumab). ALXN1210 or eculizumab admixture will be administered to the patient using an IV tubing administration set via an infusion pump. Use of a 0.2 micron filter is required during infusion of ALXN1210. The permitted duration of an eculizumab infusion (excluding IV flush) ranges from a minimum of 25 minutes to a maximum of 45 minutes for both the 600 mg and 900 mg doses, except in the management of an AE, when the duration may be extended to a maximum of 120 minutes. If an IV flush is included (expected to last no more than 15 minutes), the total infusion duration for eculizumab plus IV flush must not exceed 60 minutes (no more than 135 minutes if slowed or stopped due to AE). The total infusion duration, including an IV flush, will be recorded on the eCRF.

**Table 8: 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 | ≥ 30 to < 40 | 1200 | 120 | 120 | 240 | 78 (1.3) | 184 |
| | ≥ 40 to < 60 | 2400 | 240 | 240 | 480 | 114 (1.9) | 252 |
| | ≥ 60 to < 100 | 2700 | 270 | 270 | 540 | 102 (1.7) | 317 |
| | ≥ 100 | 3000 | 300 | 300 | 600 | 108 (1.8) | 333 |
| Maintenance | ≥ 30 to < 40 | 2700 | 270 | 270 | 540 | 168 (2.8) | 192 |
| | ≥ 40 to < 60 | 3000 | 300 | 300 | 600 | 140 (2.4) | 257 |
| | ≥ 60 to < 100 | 3300 | 330 | 330 | 660 | 120 (2.0) | 330 |
| | ≥ 100 | 3600 | 360 | 360 | 720 | 132 (2.2) | 327 |

Note: Please refer to the Pharmacy Manual for additional dose preparation instructions.
[a] Dose regimen will be based on the last recorded study visit body weight. If the study drug is prepared the night before a visit, the weight from the most recent study visit should be used.

**Table 9: Dosing Reference Chart for Eculizumab Dose Preparation**

| Dose Type | Dose (mg) | Eculizumab Volume (mL) | Saline Volume (mL) | Total Volume (mL) | Approximate Infusion Duration[a] (minutes) | Approximate Infusion Rate (mL/hour) |
|---|---|---|---|---|---|---|
| Induction | 600 | 60 | 60 | 120 | 35 | 200 |
| Maintenance | 900 | 90 | 90 | 180 | 35 | 300 |

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

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

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

### 9.1.5. Study Drug Handling and Disposal

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

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

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

Please refer to the Pharmacy Manual for further information.

## 9.2. Treatments Administered

Original Study ALXN1210-PNH-301 Cohort: This study involves a direct comparison of ALXN1210 versus the active control, eculizumab.

Patients will be randomly assigned in a 1:1 ratio to receive either ALXN1210 or eculizumab for 26 weeks. Study drug will be administered as a slow IV infusion (see Table 8 and Table 9).

The dose regimen for ALXN1210 is a loading dose on Day 1 followed by maintenance doses on Day 15 and q8w thereafter. The dosage of ALXN1210 is based on the patient's last recorded study visit body weight, as indicated in Table 10.

**Table 10: ALXN1210 Weight-Based Dosages**

| ALXN1210 Treatment Group Body Weight | Loading Dose | Maintenance Dose |
|---|---|---|
| ≥ 30 to < 40 kg[b] | 1200 mg | 2700 mg |
| ≥ 40 to < 60 kg | 2400 mg | 3000 mg |
| ≥ 60 to < 100 kg | 2700 mg | 3300 mg |
| ≥ 100 kg | 3000 mg | 3600 mg |

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

[b] In the event that a patient drops below 30 kg during the course of the study, the approved ravulizumab aHUS dosing for patients weighing ≥ 20 to < 30 kg will be used: a loading dose of 900 mg and maintenance dose of 2100 mg.

Patients randomly assigned to the eculizumab group will receive eculizumab according to the approved dosing regimen for the PNH indication, which is 4 weekly induction doses, followed by maintenance doses q2w starting at Week 5 (Table 11).

**Table 11: Eculizumab Dosages**

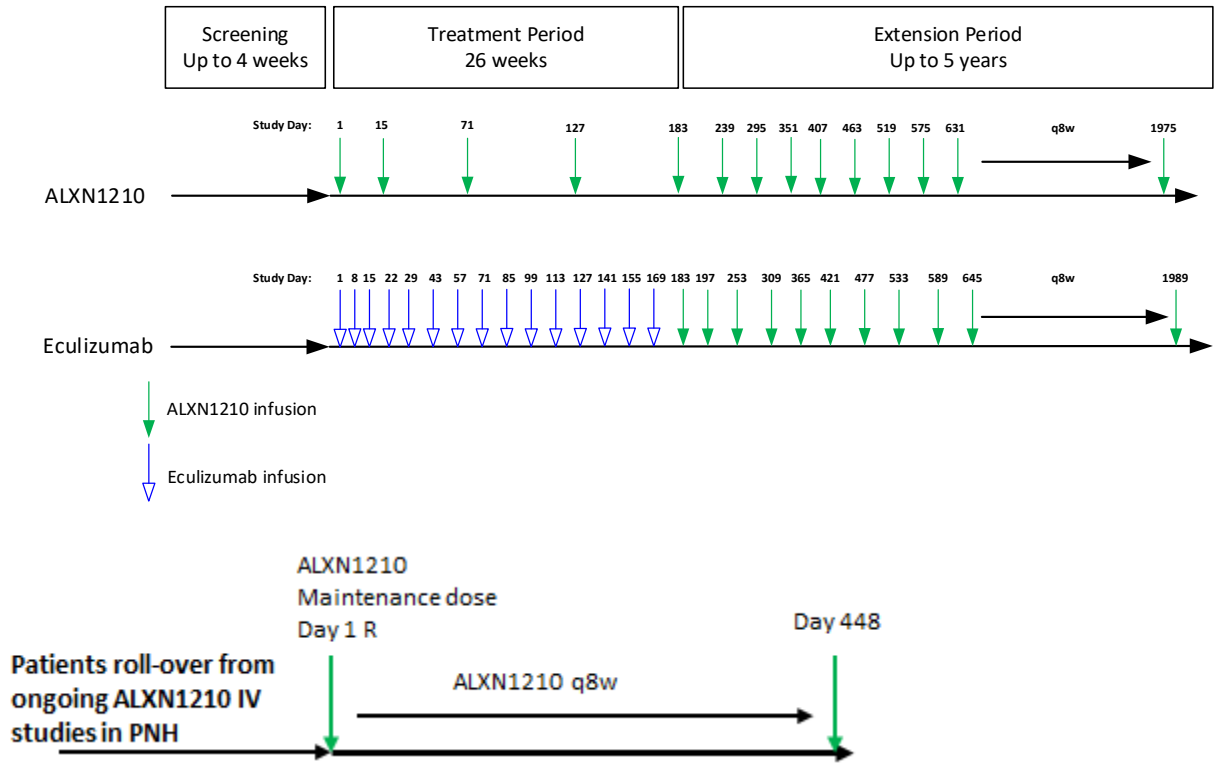
| Eculizumab Treatment Group | Induction Dose | Maintenance Dose |
|---|---|---|
| All patients | 600 mg | 900 mg |

After the randomized treatment period all patients will enter the Extension Period and receive ALXN1210 until the product is registered or approved (in accordance with country-specific regulations) or for up to 5 years, whichever occurs first. Beginning on Day 183, patients who had been randomized to the ALXN1210 treatment group will receive their weight-based maintenance dose of ALXN1210 q8w, and patients who had been randomized to the eculizumab group will receive a weight-based loading dose of ALXN1210 followed 2 weeks later and q8w thereafter by a weight-based maintenance dose of ALXN1210 (Table 10; Figure 2).

In the Roll-over Cohort, patients will receive weight-based maintenance dosing of ALXN1210 q8w from Day 1 of roll over (Table 10, Figure 2).

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

**Figure 2: Dosing Schematic**




Abbreviations: PNH = paroxysmal nocturnal hemoglobinuria; q8w = once every 8 weeks; R = roll over

## 9.3. Method of Assignment to Treatment

Original Study ALXN1210-PNH-301 Cohort: Patients who meet all criteria for enrollment will be randomly assigned to study treatment with ALXN1210 or eculizumab at the Baseline Visit (Day 1). Treatment group assignment will be determined by a computer-generated random sequence using an interactive voice- or web-response system (IxRS). The randomization will be a stratified randomization. Patients will be stratified into 1 of 6 groups based on their transfusion history (0, 1 to 14, or > 14 units of pRBCs in the 1 year prior to first dose of study drug) and screening lactate dehydrogenase (LDH) levels (1.5 to < 3 × ULN or ≥ 3 × ULN). The patients within each of the 6 groups will then be randomly assigned in a 1:1 ratio to receive ALXN1210 or eculizumab during the 26-week randomized treatment period.

All patients in the Roll-over Cohort will receive ALXN1210.

## 9.4. Rationale for Selection of Doses in the Study

The weight-based dosages of ALXN1210 in this study (Table 10) are premised on PK/PD data from early development studies in healthy adult volunteers as well as the available data from patients with PNH in an ongoing Phase 1b dose-finding study (ALXN1210-PNH-103) and an ongoing Phase 2 proof-of-concept study (ALXN1210-PNH-201). The selection of ALXN1210 dose regimen is based on targeting immediate, complete and sustained inhibition of terminal complement in patients with PNH.

The eculizumab dosage is the labelled dose for the treatment of patients with PNH (Soliris® USPI and SmPC).

## 9.5. Special Treatment Considerations

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

## 9.6. Blinding

This is an open-label study.

## 9.7. Prior and Concomitant Medications and Nonpharmacologic Procedures

For the Original Study ALXN1210-PNH-301 Cohort, prior medications (including vitamins and herbal preparations)—including those discussed in the exclusion criteria (Section 8.1.2) and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the patient takes or undergoes within 28 days prior to the start of Screening until the first dose of study drug—will be recorded on the patient's eCRF. In addition, history of meningococcal vaccination must be collected for the 3 years prior to first dose of study drug.

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

For both cohorts, all medication use and procedures undertaken during the study will be recorded in the patient's source document/medical chart and eCRF. This record will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and current medications for PNH. Concomitant medications will be recorded from the first infusion of study drug through 56 days after the patient's last dose of study drug. Any changes in concomitant medications also will be recorded in the patient's source document/medical chart and eCRF. Any concomitant medication deemed necessary for the patient's standard of care during the study, or for the treatment of any AE, along with the allowed medications described below may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full in the patient's source document/medical chart and eCRF.

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

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

## 9.8. Vaccination

Due to their mechanism of action, the use of eculizumab or ALXN1210 increases the patient's susceptibility to meningococcal infection (*N. meningitidis*). To reduce the risk of meningococcal infection, all patients must 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 complement inhibitors (eg, eculizumab). The vaccinations must be reconfirmed after 3 years or according to the current national vaccination guidelines. Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given per official guidance and local practice on the appropriate use of antibacterial agents and vaccination. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the patients during the course of the study, patients will be provided a safety card to carry with them at all times. Additional discussion and explanation of the potential risks, signs, and symptoms will occur at each visit as part of the review of the patient safety card as described in the Schedule of Assessments (Section 7.3). Vaccination status for *N. meningitidis* will be recorded on the patient's eCRF.

## 9.9. Treatment Compliance

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

## 9.10. Home Visits During the Extension Period

During the Extension Period, and only for visits not requiring an abbreviated physical exam, patients may have the opportunity to have ALXN1210 administered at a medical facility that is located near the patient's home if allowed by national legislation. This will also ensure patient safety and treatment continuity during the coronavirus disease 2019 (COVID-19) pandemic. Alternatively, ALXN1210 may be administered at the patient's home under the orders of the Investigator and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. These visits will be conducted by a trained qualified staff member from the medical facility near the patient's home or by qualified home health care professionals. The study drug will be prepared at the Investigator's pharmacy and transported under controlled conditions to the patient's home or the medical facility for administration by a dedicated courier. The use of a courier, specialized in medicinal product shipments, is needed to ensure traceability and temperature controlled delivery for the transfer of drug from Investigator's pharmacy to patient's home or the medical facility for administration, as specified in the home health care manual. During a remote dosing visit, all assessments will be performed according to the schedule of assessments, including recording of AEs and concomitant medications, collection of blood and urine samples, assessment of PNH symptomatology, vital signs, QoL assessments, and review of safety card. Patients must return to the study site for any visit at which an abbreviated physical examination is required, as specified in the Schedule of

Assessments (Section 7.3). Information about AEs concomitant medications, and samples for protocol-defined laboratory parameters must be sent to the Investigator's site for evaluation on the day of the remote visit. In countries where local legislation does not allow infusions outside authorized study sites, the Investigators will be notified in writing that this provision is prohibited.

## 9.11. COVID-19 Risk Assessment

Paroxysmal nocturnal hemoglobinuria can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining an investigational study with a therapeutic treatment is potentially significant. The fact that Study ALXN1210-PNH-301 is open-label and every participant is treated with the study intervention also contributes to the potential benefit a participant may derive from partaking in the study. Given that treatment for PNH does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in participants not receiving immunosuppressants. However, there is no specific data to further inform this risk. The Investigator will therefore balance the risk/benefit considerations for the study participant, taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 12.

**Table 12: Potential Risks and Mitigation Measures due to COVID-19**

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

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

## 9.12. COVID-19 Vaccine Risk Assessment

Following a review of the available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished with concomitant ALXN1210 administration, based on ALXN1210's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ALXN1210. The same precautions should be taken as described in Section 9.8. Vaccination may further activate complement. As a result, patients with complement-mediated

diseases may experience increased signs and symptoms of their underlying disease. Therefore, patients should be closely monitored for disease symptoms after recommended vaccination

Because vaccines may activate complement, if possible, consider vaccination when the underlying complement mediated disease is clinically controlled and when systemic C5 inhibitor concentration (and subsequent complement blockade) is relatively high, shortly after administration.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination. The potential risks identified and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 13.

**Table 13: Potential Risks and Mitigation Measures due to COVID19 Vaccine**

| Risks category | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Potential risks** | | |
| Data quality and integrity | Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules, and increase missed visits and/or participant study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures). | Capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine) |

Abbreviation: COVID-19 = coronavirus disease 2019.

## 9.13. Contraception Guidance

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

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

Highly effective contraceptive methods include:

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

Acceptable contraceptive methods include:

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

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

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

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

# 10. EFFICACY ASSESSMENTS

## 10.1. Transfusions

A pRBC transfusion will be administered when a patient has a

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

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

If a patient meets either transfusion criterion during the study, the Investigator will determine the appropriate number of units of pRBCs to be transfused. It is recommended that the transfusion be performed within 48 hours of the hemoglobin determination responsible for the transfusion. Administration of a transfusion, including the hemoglobin result and symptoms that triggered the transfusion, and the number of units transfused, will be documented in the eCRF.

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

For the original Study ALXN1210-PNH-301 Cohort, prior to randomization and within 5 days prior to study drug administration on Day 1, each patient's hemoglobin must be evaluated by either local or central laboratory. If at that time the patient's hemoglobin value meets these transfusion guidelines, the patient must be transfused with pRBCs to a hemoglobin level above the transfusion threshold in order to be eligible for randomization. The patient's post-transfusion hemoglobin value should be confirmed by local or central laboratory to be above the transfusion threshold.

## 10.2. LDH and Other Disease-Related Laboratory Parameters

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

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

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

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

## 10.3. PNH Symptomatology

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

## 10.4. Patient-Reported Outcome Measures

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

- The FACIT-Fatigue scale, Version 4.0, is a collection of QoL questionnaires pertaining to the management of fatigue symptoms due to a chronic illness. The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days. Patients will score each item on a 5-point scale: 0 (Not at all) to 4 (Very much). Total scores range from 0 to 52, with higher score indicating better QoL.
- The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, is a questionnaire developed to assess the QoL of cancer patients. The questionnaire includes the following subscales: global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social activity), symptom scales (fatigue, nausea and vomiting, and pain), and single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Thirty questions related to QoL, with the first 28 questions scored on a 4-point scale (1 = not at all to 4 = very much) and the final 2 questions that probe the patient's overall health and QoL scored on a scale of 1 (very poor) to 7 (excellent). Each subscale has a range of 0 to 100%, with a high score representing a higher response level. Thus, a high score for a functional scale represents a high level of functioning but a high score for a symptom scale represents a high level of symptomatology/problem.

The FACIT-Fatigue and EORTC QLQ-C30 scales are provided in Appendix B and Appendix C, respectively.

## 10.5. Major Adverse Vascular Events

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

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

A MAVE is defined as follows:

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

# 11. SAFETY ASSESSMENTS

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

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

The timing of the clinical and laboratory assessments to be performed is specified in the Schedule of Assessments (Section 7.3). Any clinically significant abnormal results should be followed until resolution or stabilization. For the Roll-over Cohort, select data referenced in the following sections may be obtained from the prior studies from which the patients rolled over.

## 11.1. Demographic/Medical History

### 11.1.1. Demographics and Baseline Characteristics

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

### 11.1.2. Disease Characteristics

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

### 11.1.3. Medical History

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

## 11.2. Physical Examinations

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

## 11.3. Vital Signs

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

## 11.4. Laboratory Assessments

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

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

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

### 11.4.1. Pregnancy Testing

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

### 11.4.2. Hematology

Blood samples will be analyzed for the hematology parameters listed in Appendix D.

### 11.4.3. Serum Chemistry

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

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

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

### 11.4.4. Coagulation

Blood samples will be analyzed for the coagulation parameters listed in Appendix D.

### 11.4.5. Urinalysis and Urine Chemistry

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

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

### 11.4.6. Virus Serology

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

## 11.5. Electrocardiograms

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

The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and to determine the clinical significance of the results. These assessments will be indicated on the 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 or eculizumab in serum prior to study drug administration as indicated in the Schedule of Assessments (Section 7.3). Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, PK/PD, safety, and activity of ALXN1210 or eculizumab.

## 11.7. Adverse Event Management

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

Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the start of the study, admissions for social reasons or for convenience), and anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen are not AEs.

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

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

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

Cases of pregnancy that occur during maternal or paternal exposure to investigational product are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.

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

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

### 11.7.1. Targeted Adverse Events

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

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

Additional events of interest in this study include the following:

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

### 11.7.2. Severity Assessment

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

Grade refers to the severity of the AE. The CTCAE assigns a grade of 1 through 5, with unique clinical descriptions of severity for each AE (Table 14).

**Table 14: Adverse Event Severity Grading Scale**

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

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

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

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

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

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

### 11.7.3. Causality Assessment

An Investigator must provide a causality assessment (Unrelated, Unlikely, Possible, Probable, or Definite) for all AEs (both serious and nonserious) based upon the Investigator's medical judgment and the observed symptoms associated with the event (Table 15). This assessment must be recorded on the eCRF and any additional forms as appropriate.

**Table 15: Causality Assessment Descriptions**

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

### 11.7.4. Serious Adverse Events

An SAE is any untoward medical occurrence that:

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

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

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

Information pertaining to the collection and reporting of SAEs is provided in Section 11.7.6.

### 11.7.5. Suspected Unexpected Serious Adverse Reactions

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

with global regulations and the associated detailed guidances. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs/IECs 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 ICF for the original Study ALXN1210-PNH-301 Cohort and from Day 1 of roll over for the Roll-over Cohort, 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 EDC or the Safety Gateway is unavailable at the site(s), the SAE must be reported on paper. Facsimile transmission or email may be used in the event of electronic submission failure.

**Email:** clinicalsae@alexion.com

**Facsimile:** + 1.203.439.9347 (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

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

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

If a female patient or a patient's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion 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 and eculizumab concentration over time
- cRBC hemolytic activity over time (exploratory)
- Free and total C5 concentrations over time

# 13. DATA QUALITY ASSURANCE

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

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

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

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

## 13.1. Data Collection and Storage

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

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

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

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

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

## 13.2. Records Retention

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

# 14. STATISTICAL METHODS AND PLANNED ANALYSES

Section 14.2 through Section 14.10 describe the statistical methods and planned analysis for the Original Study ALXN1210-PNH-301 Cohort.

The statistical method for the Roll-over Cohort is described in Section 14.11.

Section 14.1 applies to both cohorts.

## 14.1. General Considerations

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

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

A CSR will be produced based on efficacy, safety, PK, PD, and immunogenicity data collected through the end of the 26-week randomized treatment period (Day 183). 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

Approximately 214 patients will be randomly assigned in a 1:1 ratio to receive ALXN1210 (N = 107) or eculizumab (N = 107) to ensure at least 193 evaluable patients (assumes no more than a 10% drop-out rate). The sample size estimation is based on a noninferiority design comparing patients treated with ALXN1210 to those treated with eculizumab. Coprimary endpoints of hemolysis as directly measured by the normalization of LDH (LDH-N) from Day 29 through Day 183 and the proportion of patients who achieve transfusion avoidance (TA) through Day 183 will be used to assess noninferiority. The sample size is based on the endpoint that requires the larger number of patients.

For the coprimary endpoint of LDH-N, using a noninferiority margin (NIM) based on the relative benefit of eculizumab with respect to placebo of 0.39 and a type I error of 1-sided 2.5%, a minimum of 142 patients will provide 80% power to demonstrate noninferiority of ALXN1210 to eculizumab. The NIM was determined based on a randomized placebo-controlled study (Hillmen, 2006) which showed a relative benefit of eculizumab over placebo with an odds ratio

of 6.5. This was based on several factors. As baseline LDH is a predictor of the rate of normalization, in order to preserve the constancy assumption, the rate of LDH-N was calculated adjusted to the observed baseline LDH of the current ALXN1210 Phase 1b and 2 data. The estimate of LDH-N for eculizumab was then calculated to be a weighted average of the proportions of LDH-N from Day 29 to Day 183 to be consistent with the proposed analysis plan for this study. As the proportion of LDH-N for placebo treated patients was 0% at all visits, the upper bound of the 95% CI was used in order to be able to calculate an odds ratio. The final estimate of benefit was based on a LDH-N proportion of 42% for eculizumab-treated patients and 10% for placebo. A traditional choice of NIM is one with ≤ 50% loss of benefit resulting in a NIM of an odds ratio of 0.39. The calculation of NIM follows (Ng, 2008) in which the NIM is given by $1/\{OR^{0.5}\}$ where OR represents the odds ratio of eculizumab compared to placebo and is given by [0.42/(1-0.42)]/[0.1/(1-0.1)], and 0.5 is the fraction of benefit to be preserved. This approach chooses the NIM on the log odds scale, as described in Section IV of the 2010 Food and Drug Administration (FDA) Guidance for Industry: Non-Inferiority Clinical Trials. While more conservative approaches for constructing NIMs could be used, such as using the lower bound of the 95% CI for eculizumab, the resulting estimated sample size would make this study operationally infeasible in light of the rarity of PNH and the paucity of eculizumab-naïve patients.

For the other coprimary endpoint of proportion of patients not receiving any transfusions through Day 183, using a NIM of -20% and a type I error of 1-sided 2.5%, a minimum of 193 patients will provide 80% power to demonstrate noninferiority between the treatment arms. The NIM was determined based on the global PNH Registry for eculizumab-treated patients enrolling into the registry in 2012 or later (Soliris Type II Variation Procedure No. EMEA/H/C/000791/II/66). History of transfusion is a predictor of on-treatment transfusion so to preserve the constancy assumption, the NIM was assessed based on available data from treated and untreated patients in proportion to enrollment expectations in the current study. Patients treated with eculizumab (TA rate of 57.1%) showed a benefit over untreated patients (TA rate of 18.6%) with a difference of approximately 40% (38.5%) after adjustment for history of transfusions 12 months prior to enrollment. The adjustment comes from an expected proportion of patients without a history of transfusions to be no more than 20%. Enrolled patients for this study will be capped at 20% for patients without a history of transfusions to ensure constancy is satisfied.

A traditional choice of NIM is one with ≤ 50% loss of benefit which gives a NIM of approximately -20%. A more conservative NIM could be used using the lower bound of the 95% CI for the difference in rates, but the resulting estimated sample size would make the study operationally infeasible in light of the rarity of PNH and the paucity of eculizumab-naïve patients with and without a history of transfusions. Further, given the proportion of patients with TA observed in preliminary results from the Phase 1b/2 program, it is expected that noninferiority can be demonstrated with more conservative NIMs for the given sample size with limited loss of power.

Because the sample size estimate based on LDH-N is smaller than that based on TA (Table 16), the final sample size estimate selected for this study is based on the TA endpoint. Adjusting for a possible 10% dropout rate, approximately 214 patients will be enrolled in this study.

**Table 16: Summary of Parameters Used in Estimating Sample Size with Coprimary Endpoints**

| Parameters | LDH Normalization (LDH-N) | Transfusion Avoidance (TA) |
|---|---|---|
| Power | 80% | 80% |
| Type I error | 1-sided 0.025 | 1-sided 0.025 |
| Noninferiority margin | 0.39 | -0.20 |
| Allocation ratio | 1:1 | 1:1 |
| Mean eculizumab response | 0.42[a] | 0.57[b] |
| Standard deviation of eculizumab response | NA | NA |
| Assumed treatment difference | 1 | 0 |
| | | |
| Estimated sample size (SS) | 142 | 193 |
| Adjusted SS for 10% dropouts | 158 | 214 |

Note: Software package: Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, US. www.ncss.com.
a. Response rate from TRIUMPH study adjusted for baseline LDH.
b. Response rate from Global PNH Registry adjusted for history of transfusion.

## 14.3. Analysis Sets

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

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

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

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

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

## 14.4. Demographics and Baseline Characteristics

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

## 14.5. Patient Disposition

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

The numbers of patients who are treated, discontinue treatment (along with reason for treatment discontinuation), complete or withdraw from the Randomized Treatment Period (along with reason for withdrawal), enter the Extension Period, and complete or withdraw from the Extension Period (along with reason for withdrawal) will be tabulated by treatment group and overall.

## 14.6. Prior and Concomitant Medications and Nonpharmacologic Procedures

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

## 14.7. Treatment Compliance

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

## 14.8. Efficacy Analyses

### 14.8.1. Coprimary Efficacy Analysis

The coprimary efficacy endpoints are 1) the difference between treatment groups in the proportion of patients who achieve TA through Day 183, and 2) the relative effect between treatments in LDH-N from Day 29 through Day 183 expressed as an odds ratio.

Transfusion avoidance will be achieved only by those patients who did not receive a transfusion and did not meet the protocol-specified guidelines for transfusion. The percentage of patients who achieve TA with 95% CIs will be computed at Day 183 for both the ALXN1210 and eculizumab treatment groups and the randomization strata. A difference in the percentage of patients achieving TA in the 2 treatment groups will be calculated between ALXN1210 and eculizumab treatment groups, along with a 95% CI for the difference. The difference between the ALXN1210 and eculizumab treatment groups will be computed as a weighted combination of the differences between the ALXN1210 and eculizumab treatment groups within stratification groups (using Mantel-Haenszel). The 95% CI for the difference between ALXN1210 and eculizumab treatment groups will be calculated using the stratified Newcombe confidence interval method.

LDH-N will be analyzed using a generalized estimating equation (GEE) approach which accounts for the repeated measures of LDH-N at each visit (Liang, 1986). The GEE approach provides odds ratios and CIs of treatment effect while controlling for the correlation between visits for a given patient and other baseline factors. LDH-N from Day 29 through Day 183 will

be used as the dependent variable and an indicator variable for treatment, history of transfusion (as a categorical variable based on the stratification factor levels), and baseline LDH level (as a continuous variable) will be included in the model as explanatory variables. The within-patient correlation will assume a first-order autoregressive structure which assumes the highest correlation is between visits that are closest in time. Day 29 is the first scheduled assessment after initiation of maintenance dosing, and experience with eculizumab and Phase 1b/2 ALXN1210 data demonstrate near maximal suppression of LDH by 4 weeks of treatment. Results from the model will be presented as odds ratios with 95% confidence intervals.

In order to conclude ALXN1210 is noninferior to eculizumab, both coprimary endpoints individually need to demonstrate noninferiority. If the lower-bound of the 95% CI for the difference (ALXN1210-eculizumab) is greater than the NIM of -20% for TA and the lower-bound of the 95% CI for the odds ratio of ALXN1210 compared to eculizumab is greater than the NIM of 0.39 for LDH-N, then ALXN1210 treatment will be concluded to be noninferior to eculizumab.

### 14.8.2. Key Secondary Efficacy Analyses

The 4 key secondary efficacy endpoints will be summarized by randomization strata and by treatment group at baseline and at the study visits where these assessments are collected during the 26-week randomized treatment period. Change in FACIT-Fatigue (and percent change in LDH) from baseline to Week 26 will be analyzed using a mixed model for repeated measures (MMRM; Mallinckrodt, 2001, Mallinckrodt, 2004) with the fixed, categorical effects of treatment, the stratification randomization indicators of transfusion history (0, 1 to 14, or > 14 units of pRBCs in the 1 year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 × ULN or ≥ 3 × ULN), study visit and study visit by treatment group interaction as well as the continuous, fixed covariate of baseline FACIT-Fatigue (or LDH). For percent change in LDH, the baseline LDH level as a continuous variable will be included. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. A difference between the ALXN1210 and eculizumab treatment groups along with a 2-sided 95% CI will be calculated.

For breakthrough hemolysis and stabilized hemoglobin, the same approach used for TA will be employed. These key secondary endpoints will be tested in a hierarchical manner provided that noninferiority was declared for the coprimary endpoints.

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

1. If the upper bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the percentage change from Baseline to Week 26 in LDH is less than the NIM of 20%, then ALXN1210 will be declared noninferior for this parameter and the next parameter will be tested.
2. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in change from baseline in FACIT-Fatigue is greater

than the NIM of -5, then ALXN1210 will be declared noninferior for this parameter and the next parameter will be tested.

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

If noninferiority is established for all key secondary endpoints, then superiority will be assessed using a closed-testing procedure with the following order and using a 2-sided 0.05 test for each parameter:

5. Proportion of patients with breakthrough hemolysis through Day 183 (Week 26)
6. Percentage change from baseline to Day 183 (Week 26) in LDH
7. Hemolysis as directly measured by LDH-N from Day 29 through Day183 (Week 26)
8. Change from baseline to Day 183 (Week 26) in FACIT-Fatigue
9. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)
10. Transfusion avoidance

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

### 14.8.3. Other Secondary Efficacy Analyses

Changes from baseline in EORTC-QLQ-C30 will be summarized by treatment group at baseline and at the study visits where these assessments are collected (Section 7.3). Shifts from baseline in clinical manifestations of PNH will be summarized by treatment group and at the study visits where these assessments are collected. The number of any treatment-emergent MAVEs (n) and number of patients with events (n, %) will be displayed by treatment group. Total number of units of pRBCs transfused during treatment will be summarized by treatment group. Kaplan-Meier curves for both treatment groups and estimates of time to first occurrence of LDH-N since first study drug will be produced.

No statistical inference of these parameters is planned.

## 14.9. Safety Analyses

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

### 14.9.1. Adverse Events

The following definitions will be used for AEs:

- Pretreatment AEs: Any AE that starts after providing informed consent, but before the first infusion of study drug
- Treatment-emergent adverse event (TEAE): Any AE that starts during or after the first infusion of study drug.
- Treatment-emergent SAE: A 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 (SOC) 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 and Vital Signs

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

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

By-patient data listings will be provided.

### 14.9.3. Clinical Laboratory Tests

Changes in clinical chemistry, hematology, and urinalysis results from Baseline to postbaseline study time points will be summarized descriptively by treatment group. 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 electrocardiogram intervals (PR, RR, QT, and QTcF) will be provided by treatment group. QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

### 14.9.5. Immunogenicity

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

## 14.10. Pharmacokinetic/Pharmacodynamic Analyses

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

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

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

Descriptive statistics will be presented for all ALXN1210 and eculizumab PD endpoints at each sampling time (Section 7.3). The PD effects of ALXN1210 and eculizumab administered IV will be evaluated by assessing the absolute values and changes and percentage changes from baseline in total and free C5 serum concentrations and cRBC hemolysis over time, as appropriate. Assessments of ALXN1210 PK/PD relationships may be explored using data from this study or in combination with data from other studies.

## 14.11. Analysis of Data in the Roll-Over Cohort

A maximum number of approximately 56 patients may roll over from other ongoing studies of ALXN1210 IV in patients with PNH into the Extension Period of Study ALXN1210-PNH-301.

Analysis of data from patients who are rolled over from other ongoing ALXN1210 IV PNH studies will be performed as a separate cohort. The long-term safety will be evaluated by incidence of TEAEs and SAEs, laboratory assessments, and proportion of patients who develop ADA. The analyses will be performed on the Roll-over Safety Set defined as all patients who receive at least 1 ALXN1210 dose after roll over.

TEAEs are defined as AEs with start dates and start times on or after the date and time of the first ALXN1210 dose after the roll over to ALXN1210-PNH-301.

Similar to the original Study ALXN1210-PNH-301 Cohort, 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 the latest version of MedDRA, and will be summarized by SOC and PT.

Clinical laboratory values and their changes from baseline will be summarized over time by visit.

Vital signs, ECGs, and proportion of ADA-positive patients will be summarized at each study visit. Other assessments, such as EORTC-QLQ-C30 and FACIT-Fatigue will be summarized at each study visit. All endpoints will be presented in listings.

The baseline for the roll-over patients is defined as the last measurement prior to the 1$^{st}$ infusion of study drug after roll over.

Details of the statistical analyses described above will be included in the SAP before study completion. A summary of long-term safety in the Roll-over Cohort will be included in the final CSR.

## 14.12. Other Statistical Issues

### 14.12.1. Missing or Invalid Data

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

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

# 15. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

## 15.1. Informed Consent

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

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

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

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

## 15.2. Safety Review

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

## 15.3. Ethical Review

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

## 15.4. Regulatory Considerations

This study will be conducted in accordance with:

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

- Applicable national and local laws and regulations

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

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

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

### 15.4.1. Changes/Deviations to Protocol

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

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

## 15.5. Publication Policy

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

# 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. Complement in hemolytic anemia. Blood. 2015;126:2459-2465.

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

Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008;111(4):1840-1847.

Canalejo K, Cervantes NR, Felippo M, Sarandria C, Aixala M. Paroxysmal nocturnal haemoglobinuria. Experience over a 10 years period. Int J Lab Hemat. 2013;36(2):1213-1221.

Dale J, Myhre E. Lactate dehydrogenase and mechanical trauma of erythrocytes. Acta Med Scand. 1972;191(1-2):133-136.

Hill A, Kelly RJ, Hillmen, P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;121:4985-4996.

Hill A, Kelly RJ, Kulasekararaj AG, et al. Eculizumab in paroxysmal nocturnal hemoglobinuria (PNH): a report of all 153 patients treated in the UK [abstract]. Poster presented at American Society of Hematology (ASH) Annual Meeting, December 7-10, 2012a. Atlanta, Georgia.

Hill A, Sapsford RJ, Scally A, et al. Under-recognized complications in patients with paroxysmal nocturnal haemoglobinuria: raised pulmonary pressure and reduced right ventricular function. Br J Haematol. 2012b;158:409-414.

Hillmen P, Elebute M, Kelly R, et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria. Am J Hematol. 2010;85(8):553-559. Erratum in Am J Hematol. 2010;85(11):911.

Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006;355:1233-1243.

Lee JW, Jang JH, Kim JS, et al. Clinical signs and symptoms associated with increased risk for thrombosis in patients with paroxysmal nocturnal hemoglobinuria from a Korean Registry. Int J Hematol. 2013;97:749-757.

Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear methods. Biometrika. 1986;73(1):13-22.

Mallinckrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed-effects models. J Biopharm Stat. 2001;11:9-21.

Mallinckrodt CH, Kaiser CJ, Watkin JG, Molenberghs G, Carroll RJ. The effect of correlation structure on treatment contrasts estimated from incomplete clinical trial data with likelihood-based repeated measures compared with last observation carried forward ANOVA. Clinical Trials. 2004;1:477–489.

Matis LA, Rollins SA. Complement-specific antibodies: designing novel anti-inflammatories. Nat Med. 1995;1:839–842.

Ng T-H. Noninferiority hypotheses and choice of noninferiority margin. Statist Med. 2008;27:5392-5406.

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

Prodinger WM, Wurzner R, Erdei A, Dierich MP. Complement. In: Paul WE, editor. Fundamental immunology (4th ed). Philadelphia: Lippincott-Raven Publishers; 1999. P967-995.

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.

# 17. APPENDICES

# APPENDIX A. MANAGEMENT OF POTENTIAL DRUG INFUSION REACTIONS

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

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

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

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

Before any infusion is started, the treating physician and other appropriate personnel must make certain that medication (ie, adrenaline, inhaled beta agonists, antihistamines, corticosteroids) and other equipment to treat anaphylaxis are readily available. The infusion must be stopped immediately if Grade $\geq 2$ allergic/hypersensitivity reactions (including drug fever) or Grade $\geq 3$ 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:<br>a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)<br>b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence) |
| 2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):<br>a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips/tongue/uvula)<br>b. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)<br>c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)<br>d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) |
| 3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):<br>a. Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline |

Source: Sampson, 2006
Abbreviations: BP= blood pressure; PEF = peak expiratory flow

# APPENDIX B. FACIT-FATIGUE SUBSCALE VERSION 4

## FACIT Fatigue Scale (Version 4)

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

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





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

## EORTC QLQ-C30 (version 3)

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

Please fill in your first initial: |____|
Your birth date (Day, Month, Year): |__|__||__|__||__|__|__|__|
Today's date (Day, Month, Year): |__|__||__|__||__|__|__|__|

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

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

Please go on to the next page

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

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

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# APPENDIX D. PROTOCOL LABORATORY TESTS

**Hematology**

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

**Coagulation Panel**

- D-dimer
- International normalized ratio
- Partial thromboplastin time
- Prothrombin time

**Urinalysis**

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

**Clinical Chemistry**

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

**Virus Serology**

- HIV-1
- HIV-2

**Other**

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

Abbreviations: HIV-1 = human immunodeficiency virus type 1; HIV-2 = human immunodeficiency virus type 2; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; WBC = white blood cell