

**A PHASE 2, OPEN-LABEL, MULTIPLE ASCENDING  
DOSE STUDY TO EVALUATE THE EFFICACY, SAFETY,  
TOLERABILITY, IMMUNOGENICITY,  
PHARMACOKINETICS, AND PHARMACODYNAMICS  
OF ALXN1210 ADMINISTERED INTRAVENOUSLY TO  
PATIENTS WITH PAROXYSMAL NOCTURNAL  
HEMOGLOBINURIA**

|                            |                  |
|----------------------------|------------------|
| <b>Unique Protocol ID:</b> | ALXN1210-PNH-201 |
| <b>NCT Number:</b>         | NCT02605993      |
| <b>EudraCT Number:</b>     | 2015-002674-20   |
| <b>Date of Protocol:</b>   | 9 May 2018       |

**ALXN1210**  
**ALXN1210-PNH-201**  
**A PHASE 2, OPEN-LABEL, MULTIPLE ASCENDING DOSE STUDY TO**  
**EVALUATE THE EFFICACY, SAFETY, TOLERABILITY,**  
**IMMUNOGENICITY, PHARMACOKINETICS, AND**  
**PHARMACODYNAMICS OF ALXN1210 ADMINISTERED**  
**INTRAVENOUSLY TO PATIENTS WITH PAROXYSMAL NOCTURNAL**  
**HEMOGLOBINURIA**

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Versions  
Original Protocol, dated 14 Jul 2015  
Amendment 1, dated 22 Mar 2016  
Amendment 2, dated 02 Aug 2016  
Amendment 2.1 (UK), dated 04 Aug 2016  
Amendment 3 (Global), 3.1 (UK), dated 07 Mar 2017  
Amendment 4 (Global), 4.1 (UK), dated 18 Dec 2017  
Amendment 5 (Global), 5.1 (UK), dated 09 May 2018

IND Number: 128367

EudraCT Number: 2015-002674-20

This protocol contains confidential information and is provided for exclusive use of Investigators. This information may only be

disclosed to those persons involved in this study who have a need to know with the obligation not to further disseminate this information. This information may not be disclosed to other individuals unless such disclosure is required by federal or state law or regulations subject to the foregoing. These restrictions on disclosure will apply equally to all future oral or written information supplied to you by Alexion which is designated as “privileged” or “confidential.”

## SPONSOR SIGNATURE PAGE

**PROTOCOL TITLE:** A Phase 2, Open-label, Multiple Ascending Dose Study to Evaluate the Efficacy, Safety, Tolerability, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of ALXN1210 Administered Intravenously to Patients with Paroxysmal Nocturnal Hemoglobinuria

**PROTOCOL NUMBER:** ALXN1210-PNH-201, Amendment 5

PPD

\_\_\_\_\_  
PPD, MD, PhD  
Director, Global Medical Sciences  
Alexion Pharmaceuticals, Inc.

11 May 2018

\_\_\_\_\_  
Date

## INVESTIGATOR'S AGREEMENT

I have received and read the current Investigator's Brochure for ALXN1210. I have read the ALXN1210-PNH-201, Amendment 5 study protocol and agree to conduct the study in accordance with this protocol (A Phase 2, Open-label, Multiple Ascending Dose Study to Evaluate the Efficacy, Safety, Tolerability, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of ALXN1210 Administered Intravenously to Patients with Paroxysmal Nocturnal Hemoglobinuria), all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (E6), 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.

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Printed Name of Investigator

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Signature of Investigator

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Date

## PROCEDURES IN CASE OF EMERGENCY

**Table 1: Emergency Contact Information**

| Role in Study         | Name  | Address and Telephone Number  |
|-----------------------|---|---|
| Clinical Project Lead | PPD [REDACTED]<br>Associate Director,<br>Global Clinical Operations | Alexion Pharma GmbH<br>PPD [REDACTED]<br>8045 Zurich<br>Telephone: PPD [REDACTED]<br>Mobile: PPD [REDACTED]<br>Email:<br>PPD [REDACTED]                       |
| Responsible Physician | PPD [REDACTED] MD, PhD<br>Director,<br>Global Medical Sciences      | Alexion Pharmaceuticals, Inc.<br>PPD [REDACTED]<br>New Haven, CT 06510<br>USA<br>Telephone: PPD [REDACTED]<br>Mobile: PPD [REDACTED]<br>Email: PPD [REDACTED] |

## 1. SYNOPSIS

|  |                                       |
|--|---------------------------------------|
| <b>Name of Sponsor/Company:</b> Alexion Pharmaceuticals, Inc.  |                                       |
| <b>Name of Investigational Product:</b> ALXN1210   |                                       |
| <b>Name of Active Ingredient:</b> ALXN1210   |                                       |
| <b>Title of Study:</b> A Phase 2, Open-label, Multiple Ascending Dose Study to Evaluate the Efficacy, Safety, Tolerability, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of ALXN1210 Administered Intravenously to Patients with Paroxysmal Nocturnal Hemoglobinuria   |                                       |
| <b>Protocol No:</b> ALXN1210-PNH-201, Amendment 5  | <b>EudraCT Number:</b> 2015-002674-20 |
| <b>Study Center(s):</b><br>The study will be conducted in patients with paroxysmal nocturnal hemoglobinuria (PNH) at multiple centers in multiple countries.   |                                       |
| <b>Studied Period (years):</b><br>Estimated date first patient enrolled: Q4 2015<br>Estimated date last patient completed: Q2 2020   | <b>Phase of Development:</b> 2        |
| <b>Objectives:</b><br><b>Primary:</b> <ul style="list-style-type: none"> <li>To evaluate the efficacy, safety, and tolerability of multiple doses of ALXN1210 administered intravenously (IV) to complement inhibitor treatment-naïve patients with PNH</li> </ul> <b>Secondary:</b> <ul style="list-style-type: none"> <li>To characterize the pharmacokinetic (PK) and pharmacodynamic (PD) effects of multiple doses of ALXN1210 administered IV to complement inhibitor treatment-naïve patients with PNH</li> <li>To investigate the immunogenicity of ALXN1210 administered IV to complement inhibitor treatment-naïve patients with PNH</li> </ul>  |                                       |
| <b>Study Rationale:</b><br>This is a dose ranging and dose-regimen ranging study designed based on the PK/PD-safety data generated from the single-ascending dose (SAD) and multiple-ascending dose (MAD) studies to help design a dose and dose regimen for the Phase 3 study(ies). It is anticipated that the planned starting and maintenance doses in this study will maintain drug levels above the current target efficacious trough level in addition to including the higher end of drug exposures to accumulate sufficient safety data prior to the start of Phase 3 study(ies). The dose regimens selected for the study are based on the emerging PK/PD data from the ongoing studies.  |                                       |
| <b>Dose Rationale:</b><br>Initial analyses supporting dose and dose regimen selection for Study ALXN1210-PNH-201 utilized data from the SAD study (ALXN1210-HV-101) in healthy volunteers. The PK data following single subtherapeutic doses (200 mg and 400 mg) of ALXN1210 to healthy volunteers (ALXN1210-HV-101) yielded an estimated mean (range) elimination half-life of ALXN1210 of ~31 (27-38) days. The initial PK/PD data estimated a target efficacious trough level of $\geq 100$ $\mu\text{g/mL}$ to design dose regimens for this study. The targeted efficacious trough level is defined as concentration achieving complete complement inhibition ( $\geq 99\%$ ) in all patients ( $\geq 97.5\%$ ). Subsequent population PK analyses, utilizing emerging PK data from both healthy volunteers and patients with PNH across a wider range of doses, exposures, and durations, suggest the median (95% confidence interval) elimination half-life of ALXN1210 is ~43 days (39-48). This change in the estimate of elimination half-life of ALXN1210 following multiple dose administrations in healthy volunteers and patients with PNH has resulted in an increase in the estimated target trough concentrations in Cohorts 1-3 and has presented the opportunity to explore dosing ALXN1210 less frequently. It is also desirable to target a trough level that will achieve complete complement inhibition in all PNH patients. Therefore, to provide safety and PK/PD support for an optimized Phase 3 dosing regimen characterization, it is necessary to evaluate the dose regimen ranging in this protocol from once every month dosing to once every 3 month dosing as enabled by the increased estimated elimination half-life, taking into account the current estimates of targeted efficacious ALXN1210 trough level.<br><br>It was anticipated that the planned starting and maintenance doses in this study would maintain the drug levels above the current target efficacious trough level in addition to including the higher end of drug exposures to accumulate sufficient safety data prior to the start of Phase 3 study(ies). The weight-based dosages of ALXN1210 for the extension phase are premised on PK/PD data from the induction and maintenance phases of this study as well as from |                                       |

early development studies in healthy adult volunteers and an ongoing Phase 1b study (ALXN1210-PNH-103) in patients with PNH. The selection of ALXN1210 dose regimen is based on targeting immediate, complete, and sustained inhibition of terminal complement activity in patients with PNH.

**Methodology:**

ALXN1210-PNH-201 is an open-label, multiple ascending dose study to evaluate the efficacy, safety, tolerability, immunogenicity, PK, and PD of multiple doses of ALXN1210 administered IV to patients with PNH who have not previously been treated with a complement inhibitor.

Four treatment cohorts and up to 26 patients (at least 6 per cohort) are planned for enrollment, with at least 20 patients planned for evaluation. All patients are to be screened for study eligibility after providing written informed consent to participate. Patients who fail to meet any of the eligibility criteria may be rescreened once for study participation, at the discretion of the Investigator.

Patients enrolled in Cohort 1 will receive induction doses of ALXN1210 of 1400 mg on Day 1 and 1000 mg on Day 15. On Day 29 they will receive the first of 8 maintenance doses of 1000 mg of ALXN1210 (administered every 28 days or 4 weeks) (Table s1). Patients enrolled in Cohort 2 will receive induction doses of ALXN1210 of 2000 mg on Day 1 and 1600 mg on Day 22. On Day 43 they will receive the first of 5 maintenance doses of 1600 mg of ALXN1210 (administered every 42 days or 6 weeks). Patients enrolled in Cohort 3 will receive induction doses of ALXN1210 of 1600 mg on Day 1 and 1600 mg on Day 15. On Day 29 they will receive the first of 4 maintenance doses of 2400 mg of ALXN1210 (administered every 56 days or 8 weeks). Patients enrolled in Cohort 4 will receive an induction dose of ALXN1210 of 3000 mg on Day 1. On Day 29 they will receive the first of 3 maintenance doses of 5400 mg of ALXN1210 (administered every 84 days or 12 weeks). The first 2 patients in Cohort 4 will receive their induction dose (3000 mg) at least 1 day apart. The third patient will receive the induction dose at least 7 days after the second patient has received the induction dose.

An independent Data Monitoring Committee (DMC) will review and evaluate the study data for patient safety and make recommendations on dose escalation, continuing dosing within the cohort, modification, or termination of the study. The DMC will conduct a review of the available safety data at the following scheduled time points:

- Fifteen days after the second patient in Cohort 1 receives the second induction dose to determine whether Cohort 2 can be opened.
- Fifteen days after the second patient in Cohort 2 receives the second induction dose to determine whether Cohort 3 can be opened.
- Fifteen days after the second patient in Cohort 3 receives the first maintenance dose to determine whether Cohort 4 can be opened.
- Approximately 7 days after the second patient in Cohort 4 receives the 3000 mg dose to review safety.
- Approximately 7 days after the second patient in Cohort 4 receives the first 5400 mg dose to review safety.

If additional patients are screened and are eligible for enrollment before a dose-escalation decision has been made by the DMC for any cohort, those patients will be assigned to the active cohort with the lowest dose level.

On Day 253 patients will continue treatment in a long-term Extension Period of the study, at the same maintenance dose and frequency as their final dose of ALXN1210 administered during the Treatment 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 463 for patients in Cohort 2, Day 477 for patients in Cohort 3, and Day 533 for patients in Cohort 1, patients will switch from their current dose regimen to a q8w, weight-based regimen, as follows: 3000 mg for patients weighing  $\geq 40$  to  $< 60$  kg, 3300 mg for patients weighing  $\geq 60$  to  $< 100$  kg, and 3600 mg for patients weighing  $\geq 100$  kg. The dose regimen will not change for patients in Cohort 4. Beginning on Day 953 for patients in Cohort 4, Day 981 for patients in Cohort 3, Day 1023 for patients in Cohort 2, and Day 1037 for patients in Cohort 1 patients will switch from the 10 mg/mL ALXN1210 unit dose formulation to the 100 mg/mL ALXN1210 unit dose formulation, while remaining on their current dose regimen. This transition will reduce the number of vials needed for each infusion and the duration of the infusion.

Up to 30 days will be allowed for screening procedures. The total duration of treatment (which includes an Induction Period and a Maintenance Period) is approximately 253 days. The total duration of the Extension Period is up to



approximately 5 years.

The dosing schedule is provided in Table s1 and the overall study design is presented in Figure s1.

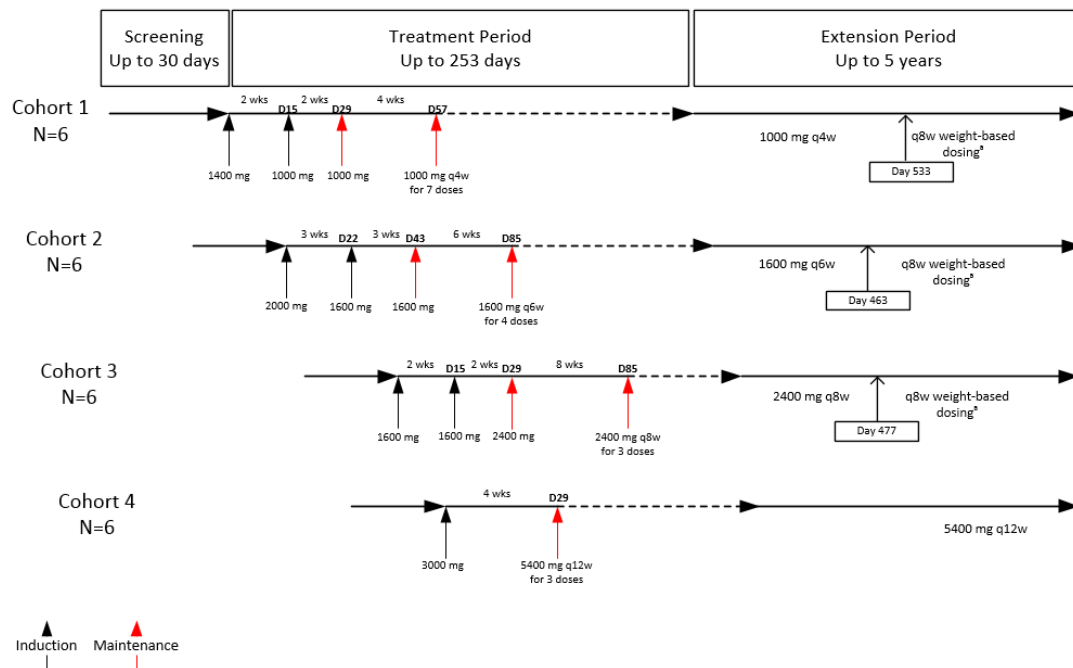
**Table s1: Dosing Schedule**

| Cohort | Patients | Induction                             | Maintenance  |
|--------|----------|---------------------------------------|--|
| 1      | 6        | 1400 mg on Day 1<br>1000 mg on Day 15 | <ul style="list-style-type: none"> <li>1000 mg on Day 29 and then every 28 days or 4 weeks (Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477)</li> <li>Weight-based<sup>a</sup> dose on Day 533 and then every 8 weeks (Days 589, 645, 701, 757, 813, 869, 925, 981, 1037<sup>b</sup>, 1093, 1149, 1205, 1261, 1317, 1373, 1429, 1485, 1541, 1597, 1653, 1709, 1765, 1821, 1877, 1933, 1989, 2045, 2101)</li> </ul> |
| 2      | 6        | 2000 mg on Day 1<br>1600 mg on Day 22 | <ul style="list-style-type: none"> <li>1600 mg on Day 43 and then every 42 days or 6 weeks (Days 85, 127, 169, 211, 253, 295, 337, 379, 421)</li> <li>Weight-based<sup>a</sup> dose on Day 463 and then every 8 weeks (Days 519, 575, 631, 687, 743, 799, 855, 911, 967, 1023<sup>b</sup>, 1079, 1135, 1191, 1247, 1303, 1359, 1415, 1471, 1527, 1583, 1639, 1695, 1751, 1807, 1863, 1919, 1975, 2031, 2087)</li> </ul>                              |
| 3      | 6        | 1600 mg on Day 1<br>1600 mg on Day 15 | <ul style="list-style-type: none"> <li>2400 mg on Day 29 and then every 56 days or 8 weeks (Days 85, 141, 197, 253, 309, 365, 421)</li> <li>Weight-based<sup>a</sup> dose on Day 477 and then every 8 weeks (Days 533, 589, 645, 701, 757, 813, 869, 925, 981<sup>b</sup>, 1037, 1093, 1149, 1205, 1261, 1317, 1373, 1429, 1485, 1541, 1597, 1653, 1709, 1765, 1821, 1877, 1933, 1989, 2045, 2101)</li> </ul>  |
| 4      | 6 to 8   | 3000 mg on Day 1                      | <ul style="list-style-type: none"> <li>5400 mg on Day 29 and then every 84 days or 12 weeks (Days 113, 197, 281, 365, 449, 533, 617, 701, 785, 869, 953<sup>b</sup>, 1037, 1121, 1205, 1289, 1373, 1457, 1541, 1625, 1709, 1793, 1877, 1961, 2045)</li> </ul>  |

<sup>a</sup> 3000 mg for patients weighing  $\geq 40$  to  $< 60$  kg, 3300 mg for patients weighing  $\geq 60$  to  $< 100$  kg, and 3600 mg for patients weighing  $\geq 100$  kg.

<sup>b</sup> Beginning on Day 953 for patients in Cohort 4, Day 981 for patients in Cohort 3, Day 1023 for patients in Cohort 2, and Day 1037 for patients in Cohort 1, patients will switch from the 10 mg/mL ALXN1210 unit dose formulation to the 100 mg/mL ALXN1210 unit dose formulation, while remaining on their current dose regimen.

**Figure s1: ALXN1210-PNH-201 Study Schematic**



<sup>a</sup> Beginning at Day 463 (Cohort 2), Day 477 (Cohort 3), and Day 533 (Cohort 1), weight-based maintenance doses will be administered as follows: 3000 mg for patients weighing  $\geq 40$  to  $< 60$  kg, 3300 mg for patients weighing  $\geq 60$  to  $< 100$  kg, and 3600 mg for patients weighing  $\geq 100$  kg.

**Number of Patients (planned):**

Up to 26 patients (at least 6 per cohort) are planned for enrollment, with at least 20 patients planned for evaluation.

**Diagnosis and Main Criteria for Inclusion:**

Patients must meet all inclusion and no exclusion criteria. Patients who fail any of the eligibility criteria may be rescreened once for participation, at the Investigator's discretion.

**Inclusion Criteria:**

1. Male or female patients  $\geq 18$  years of age
2. PNH diagnosis confirmed by documented high-sensitivity flow cytometry (red blood cells [RBCs] and/or granulocytes)
3. Mean lactate dehydrogenase (LDH)  $\geq 3 \times$  upper limit of normal, based on 2 measurements from separate blood samples collected at least 1 day apart during screening
4. Willing and able to give written informed consent and comply with the study visit schedule
5. Documented meningococcal vaccination not more than 3 years prior to dosing
6. Female patients who consider themselves postmenopausal must provide evidence at screening of menopause status, based on a combination of amenorrhea for at least 1 year and increased serum follicle-stimulating hormone level ( $> 30$  IU/L) on at least 2 occasions (eg, in the absence of hormone replacement therapy, dietary phytoestrogens) or estradiol concentration  $< 10$  pg/mL.
7. Female patients of childbearing potential must use highly effective contraception as defined below, starting at screening and continuing until at least 8 months after the last dose of ALXN1210. Highly effective contraceptive methods are as follows:
  - a. Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation:

- i. Oral
    - ii. Intravaginal
    - iii. Transdermal
  - b. Progesterone-only hormonal contraception associated with inhibition of ovulation
    - i. Oral
    - ii. Injectable
    - iii. Implantable
  - c. Intrauterine device
  - d. Intrauterine hormone-releasing system
  - e. Bilateral tubal occlusion
  - f. Vasectomized partner, provided that the partner is the patient's sole sexual partner
  - g. Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject
  - h. Combination of male condom with appropriate barrier methods for the female patient (double barrier methods)
8. Male patients with a female spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use barrier contraception (male condom) during the Treatment Period and for at least 8 months after the last dose of ALXN1210. Barrier contraception is required even with documented medical assessment of surgical success of a vasectomy. Female spouses/partners of male patients who are of childbearing potential must use highly effective contraception (as defined in inclusion criterion #7) or acceptable contraception, as defined below, starting at screening and continuing until at least 8 months after the last dose of ALXN1210. Male patients must not donate sperm during the Screening and Treatment Periods and for at least 8 months after the last dose of ALXN1210.
  - a. Acceptable contraceptive methods are as follows:
    - i. Simultaneous use of male condom and appropriate barrier methods for the female partner

**Exclusion Criteria:**

1. Treatment with a complement inhibitor at any time
2. Platelet count  $< 30,000/\text{mm}^3$  ( $30 \times 10^9 /\text{L}$ ) at screening
3. Absolute neutrophil count  $< 500/\mu\text{L}$  ( $0.5 \times 10^9 /\text{L}$ ) at screening
4. History of bone marrow transplantation
5. History of *Neisseria meningitidis* infection or history of unexplained, recurrent infection
6. Female patients who are planning to become pregnant, or are pregnant or breastfeeding
7. Positive pregnancy test at screening or Day 1
8. Patients are excluded if they are taking any of the following medications and are not on a stable regimen (as judged by the Investigator) for the time period indicated prior to screening:
  - a. Erythropoietin or immunosuppressants for at least 8 weeks
  - b. Corticosteroids for at least 4 weeks
  - c. Vitamin K antagonists (eg, warfarin) with a stable international normalized ratio (per Investigator discretion) for 4 weeks
  - d. Iron supplements or folic acid for at least 4 weeks
  - e. Low molecular weight heparin for at least 4 weeks
9. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer)
10. Acute or chronic hepatitis B virus infection (evidenced by the presence of hepatitis B surface antigen or immunoglobulin M antibodies against hepatitis B core antigen).
11. Acute or chronic hepatitis C virus infection (evidenced by hepatitis C virus antibody)
12. Active systemic bacterial, viral, or fungal infection within 14 days prior to dosing on Day 1
13. Immunization with a live-attenuated vaccine 1 month prior to dosing on Day 1
14. Participation in an interventional clinical study within 30 days before initiation of dosing on Day 1, or use of any experimental therapy within 30 days prior to dosing on Day 1, or within 5 half-lives of the investigational product, whichever is greater
15. Major surgery within 90 days prior to dosing on Day 1
16. Presence of fever  $\geq 38^\circ\text{C}$  within 2 weeks prior to the first dosing on Day 1
17. Patients with a history of malignancy within 5 years of screening with the exception of a nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
18. Known history of severe allergic or anaphylactic reactions to any drug (including vaccines) or allergen

19. History of allergy to excipients of ALXN1210 (eg, polysorbate 80)
20. Known allergy to Chinese hamster ovary cell proteins
21. History of any clinically significant cardiac, hepatic, immunologic, pulmonary, or rheumatoid disease that, in the Investigator's judgment, would preclude participation
22. Inability to comply with study requirements
23. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the patient unsuitable for enrollment

**Withdrawal from the Study:**

Patients who discontinue dosing or are withdrawn from the study for any reason after receiving any dose of study drug should be encouraged to return for the remainder of the scheduled protocol visits.

**Investigational Product, Dosage, and Mode of Administration:**

ALXN1210 is formulated at 10 mg/mL and 100 mg/mL concentrations. Both ALXN1210 formulations are presented as sterile, preservative-free solutions for IV administration, will be diluted in 0.9% sodium chloride injection, and administered by IV infusion.

**Table s2: Composition of Investigational Product**

| ALXN1210 Formulation    | Composition   |
|-------------------------|---|
| 10 mg/mL concentration  | 10 mg/mL ALXN1210 antibody in 10 mM sodium phosphate containing 150 mM sodium chloride, 0.02% polysorbate 80, and pH 7.0      |
| 100 mg/mL concentration | 100 mg/mL ALXN1210 antibody in 50 mM sodium phosphate containing 25 mM arginine, 5% sucrose, 0.05% polysorbate 80, and pH 7.4 |

**Duration of Treatment:**

Up to 30 days will be allowed for screening procedures. The total duration of treatment (which includes an Induction Period and a Maintenance Period) is approximately 253 days. The total duration of the Extension Period is up to approximately 5 years.

**Reference Therapy, Dosage, and Mode of Administration:**

None

**Endpoints and Criteria for Evaluation:**

**Primary Efficacy:**

- Change in LDH levels from baseline to Day 253

**Secondary Efficacy:**

- Changes in hemolysis-related hematologic parameters: free hemoglobin, haptoglobin, reticulocyte count, PNH red blood cell clone, and D-dimer
- Changes in clinical manifestations: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction

**Exploratory Efficacy:**

- Change from baseline in the need for blood transfusions
- Change from baseline in disease-associated biomarkers (markers of chronic kidney disease; ie, estimated glomerular filtration rate, spot urine albumin:creatinine ratio, and plasma brain natriuretic peptide for pulmonary hypertension)
- Change from baseline in quality of life, assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, version 4 and the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale, version 3.0

- Change from baseline in major adverse vascular events (MAVEs)

**Immunogenicity:**

- Measurement of antidrug antibodies (ADA)

**Pharmacokinetic/Pharmacodynamic:**

- Changes in serum ALXN1210 concentration over time
- Changes in cRBC hemolytic activity
- Changes in free and total C5 concentrations

**Safety:**

- Changes from baseline in physical examination assessments and vital signs
- Change from baseline in electrocardiogram parameters
- Change from baseline in laboratory assessments
- Incidence of adverse events (AEs) and serious adverse events (SAEs)

**Safety Evaluation:**

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 grading scale. Laboratory evaluations include chemistry panel, coagulation panel, complete blood count with differential, and urinalysis. Potential risks of ALXN1210, specifically the risk of infection, will be reviewed with patients at screening and on a regular basis throughout the study. Patients will be contacted by the Investigator or designee to discuss potential safety risks of ALXN1210, and the Investigator or designee will address any safety concerns the patient has at defined times throughout the study.

**Pharmacokinetic and Pharmacodynamic Evaluations:**

Using noncompartmental PK methods, the serum concentration-versus-time data will be used to derive the following PK parameters: maximum observed serum concentration ( $C_{max}$ ) after each dose, time to maximum observed serum concentration ( $t_{max}$ ), the minimum observed serum concentration ( $C_{min}$ ), the observed serum concentration at the end of the dosage interval  $\tau$  ( $C_{trough}$ ), area under the serum concentration-versus-time curve from time 0 (dosing) to the last quantifiable concentration ( $AUC_{\tau}$ ) after each dose, area under the concentration-versus-time curve from time 0 (dosing) to the end of the dosing interval ( $AUC_{\infty}$ ), apparent terminal-phase elimination rate constant ( $\lambda_z$ ), terminal elimination half-life ( $t_{1/2}$ ), and, if possible, total clearance (CL), and volume of distribution at steady-state ( $V_{ss}$ ). In addition, attainment of steady-state and accumulation at steady-state will be determined. The relationship between ALXN1210 exposure and PD markers may be assessed, and dose proportionality and time linearity in PK parameters may be assessed.

Serum concentrations of ALXN1210 and blood samples for analyses of C5 levels (total and free), cRBC hemolysis, and quantitative measures of C5 activation will be collected at the time points specified in Table s2. Serum samples will be stored for additional PK/PD analyses. Assessments of PK/PD relationships may be explored using data from this study or in combination with data from other studies.

**Table s3: Collection Time Points for Serum Concentrations of ALXN1210 and Analysis of Hemolytic Activity**

| Cohort | Period    | Dose Number and Study Day  | Collection Windows   |
|--------|-----------|--|--|
| 1      | Treatment | Dose 1 on Day 1<br>Dose 2 on Day 15                                | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 22 (<math>\pm 1</math> day)</li> </ul> |
|        |           | Doses 3 to 11 on Days 29, 57, 85, 113, 141, 169, 197, 225, and 253 | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> </ul>  |

|   |           |   |  |
|---|-----------|---|--|
|   |           |   | <ul style="list-style-type: none"> <li>• Day 43 (<math>\pm 1</math> day)</li> <li>• Days 127 and 211 (<math>\pm 2</math> days)</li> <li>• Day 253 (up to 0.5 hour before Dose 11)</li> </ul>   |
|   | Extension | Doses 14, 19, 22, 25, 27, 28, 29, 30, 31, 33, 35, 37, 39, 41, 43, 45, and 47 on Days 337, 477, 645, 813, 925, 981, 1037, 1093, 1149, 1261, 1373, 1485, 1597, 1709, 1821, 1933, and 2045         | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• When a patient discontinues the study or at the last study visit (Day 2157)</li> </ul>   |
| 2 | Treatment | Dose 1 on Day 1<br>Dose 2 on Day 22   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 29 (<math>\pm 1</math> day)</li> </ul>   |
|   |           | Doses 3 to 8 on Days 43, 85, 127, 169, 211, and 253   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 57 (<math>\pm 1</math> day)</li> <li>• Days 113, 141, 197, and 225 (<math>\pm 2</math> days)</li> <li>• Day 253 (up to 0.5 hour before Dose 8)</li> </ul>              |
|   | Extension | Doses 10, 14, 17, 20, 22, 23, 24, 25, 26, 28, 30, 32, 34, 36, 38, 40, and 42 on Days 337, 519, 687, 855, 967, 1023, 1079, 1135, 1191, 1303, 1415, 1527, 1639, 1751, 1863, 1975, and 2087        | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• When a patient discontinues the study or at the last study visit (Day 2143)</li> </ul>   |
| 3 | Treatment | Dose 1 on Day 1<br>Dose 2 on Day 15   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Days 22 (<math>\pm 1</math> day)</li> </ul>  |
|   |           | Doses 3 to 7 on Days 29, 85, 141, 197, and 253  | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Days 43 and 57 (<math>\pm 1</math> day)</li> <li>• Days 113, 127, 169, 211, and 225 (<math>\pm 2</math> days)</li> <li>• Day 253 (up to 0.5 hour before Dose 7)</li> </ul> |
|   | Extension | Doses 8, 11, 14, 16, 18, 19, 20, 21, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40 on Days 309, 477, 645, 757, 869, 925, 981, 1037, 1093, 1205, 1317, 1429, 1541, 1653, 1765, 1877, 1989, and 2101 | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• When a patient discontinues the study or at the last study visit (Day 2157)</li> </ul>   |
| 4 | Treatment | Dose 1 on Day 1   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 15 (<math>\pm 1</math> day)</li> </ul>   |
|   |           | Doses 2 to 4 on Days 29, 113, and 197   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 6 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 57 (<math>\pm 1</math> day)</li> <li>• Days 141 and 225 (<math>\pm 2</math> days)</li> <li>• Day 253</li> </ul>  |
|   | Extension | Doses 5, 7, 9, 11, 12, 13, 14, 16, 18, 20, 22, 24, and 26 on Days 281, 449, 617, 785, 869, 953, 1037, 1205, 1373, 1541, 1709, 1877, and 2045  | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• When a patient discontinues the study or at the last study visit (Day 2129)</li> </ul>   |

Abbreviations: EOI = end of infusion; SOI = start of infusion

**Immunogenicity Evaluation:**

Blood samples for the analyses of ADA to ALXN1210 will be collected at the time points listed in [Table s4](#). Please refer to the Laboratory Study Manual for time windows for collection and detailed instructions for collecting, processing, storing, and shipping blood samples for immunogenicity analysis. The total volume of blood collected per patient for clinical laboratory, PK, PD, and immunogenicity assessments will not exceed 300 mL in any 16-week period. All sample analyses will be performed by Alexion or designee.

**Table s4: Collection Time Points for Serum Samples for Immunogenicity Analyses of Antidrug Antibodies to ALXN1210**

|          |   |
|----------|---|
| Cohort 1 | Predose on Days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, 253, 337, 477, 645, 813, 925, 981, 1037, 1093, 1149, 1261, 1373, 1485, 1597, 1709, 1821, 1933, 2045, and 2157 or ET |
| Cohort 2 | Predose on Days 1, 22, 43, 85, 127, 169, 211, 253, 337, 519, 687, 855, 967, 1023, 1079, 1135, 1191, 1303, 1415, 1527, 1639, 1751, 1863, 1975, 2087, and 2143 or ET              |
| Cohort 3 | Predose on Days 1, 15, 29, 85, 141, 197, 253, 309, 477, 645, 757, 869, 925, 981, 1037, 1093, 1205, 1317, 1429, 1541, 1653, 1765, 1877, 1989, 2101, and 2157 or ET               |
| Cohort 4 | Predose on Days 1, 29, 113, 197, 281, 449, 617, 785, 869, 953, 1037, 1205, 1373, 1541, 1709, 1877, 2045, and 2129 or ET   |

<sup>1</sup> This is not a dosing day, therefore collection can occur at any time.

**Statistical Methods:**

All data collected in this study will be documented using summary tables, figures, and data listings. For categorical variables, frequencies and percentages will be presented for each cohort and for the combined cohorts. For continuous variables, descriptive statistics (n, mean, median, standard deviation [SD], minimum, maximum) will be presented for each cohort and for the combined cohorts. Safety analyses will be performed on the Safety Set, which includes all patients who receive at least 1 dose of ALXN1210. Efficacy analyses will be performed on the Full Analysis Set, which includes the Safety Set subset with a baseline and at least 1 postbaseline LDH measurement.

Immunogenicity: Immunogenicity, as measured by ADA, will be summarized in tabular form by treatment.

Efficacy: The absolute LDH level, and the change and percent change from baseline will be summarized at all study visits. Baseline is defined as the average of all available assessments on or prior to first infusion with ALXN1210. A mixed model for repeated measures, with the fixed, categorical effect of visit and fixed, continuous effect of baseline LDH levels as covariates will be fit to test whether the changes and percent changes differ from zero at each time point. An unstructured covariance analysis will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion: first-order autoregressive, compound symmetry, and Toeplitz method. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The secondary endpoints will be similarly analyzed, as appropriate.

Change from baseline in the quality of life instrument scores, FACIT-Fatigue scale and the EORTC scale, will be summarized descriptively at all visits.

Transfusion rates and the incidence rate of MAVEs will be summarized.

**Pharmacokinetics:** Mean serum ALXN1210 concentrations versus nominal time and individual serum ALXN1210 concentrations versus actual time will be graphically presented. Descriptive statistics (mean, SD, coefficient of variance [CV], median, minimum, maximum, geometric mean, and geometric percent [CV]) of the serum concentrations will be provided, as appropriate.

Using noncompartmental PK methods, the serum concentration-versus-time data will be used to derive the following PK parameters:  $C_{max}$  after each dose,  $t_{max}$ ,  $C_{min}/C_{trough}$ ,  $AUC_t$  after each dose,  $AUC_{0-t}$ ,  $\lambda_z$ ,  $t_{1/2}$ ,  $CL_z$ , and  $V_{ss}$ . Descriptive statistics (mean, SD, CV, median, minimum, maximum, geometric mean, and geometric %CV) of the PK parameters will be provided, as appropriate. Attainment of steady state and accumulation at steady state also will be determined. Additional PK analyses, such as assessment of PK linearity and dose proportionality, may be conducted.

Safety: The incidence of treatment-emergent adverse events and SAEs will be summarized by System Organ Class and Preferred Term overall, by severity, and by relationship to study drug. Changes from baseline in electrocardiograms, vital signs, and laboratory assessments (chemistry, hematology, and urinalysis) will be summarized. Shifts from baseline in laboratory assessments as well as physical examination findings will be summarized for all study visits.

**Pharmacodynamics:** The PD effects of ALXN1210 administered IV will be evaluated by assessing changes and

percent changes in serum total and/or free C5 concentrations and cRBC hemolysis over time. Exploratory analyses of PK/PD parameters may be performed.

Additional details of statistical analyses will be described in the statistical analysis plan.

**Sample Size Estimation:**

A sample size of 20 patients from the combined cohorts will provide an approximately 95% power to detect a mean paired difference in LDH from baseline of -40% at Day 253, with an estimated SD of 45%. This is based on a 2-sided, paired t-test, with a 5% type I error rate. To account for a possible 15% dropout rate and additional patients in screening, up to 26 patients will be enrolled.



## 2. TABLE OF CONTENTS, LISTS OF TABLES, AND LIST OF FIGURES

### TABLE OF CONTENTS

|  |    |
|--|----|
| TITLE PAGE .....   | 1  |
| 1. SYNOPSIS .....  | 6  |
| 2. TABLE OF CONTENTS, LISTS OF TABLES, AND LIST OF FIGURES.....                            | 16 |
| 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....                                     | 21 |
| 4. INTRODUCTION .....  | 23 |
| 4.1. Background.....   | 23 |
| 4.1.1. Clinical Studies.....   | 23 |
| 4.1.2. Nonclinical Studies .....   | 24 |
| 4.1.3. Potential Risks .....   | 24 |
| 4.1.3.1. Infections ( <i>Neisseria meningitidis</i> and other encapsulated organisms)..... | 24 |
| 4.1.3.2. Immunogenicity and Hypersensitivity.....  | 25 |
| 4.2. Study Rationale.....  | 25 |
| 5. STUDY OBJECTIVES AND ENDPOINTS.....   | 26 |
| 5.1. Primary Objective .....   | 26 |
| 5.2. Secondary Objectives .....  | 26 |
| 5.3. Endpoints .....   | 26 |
| 5.3.1. Efficacy Endpoints.....   | 26 |
| 5.3.1.1. Primary Efficacy .....  | 26 |
| 5.3.1.2. Secondary Efficacy .....  | 26 |
| 5.3.1.3. Exploratory Efficacy.....   | 26 |
| 5.3.2. Immunogenicity Endpoints.....   | 27 |
| 5.3.3. Pharmacokinetic/Pharmacodynamic Endpoints .....                                     | 27 |
| 5.3.4. Safety Endpoints.....   | 27 |
| 6. OVERALL STUDY DESIGN.....   | 28 |
| 6.1. Number of Patients .....  | 30 |
| 6.2. Dose Rationale.....   | 30 |
| 6.3. Criteria for Dose Continuation and Escalation.....                                    | 31 |
| 6.4. Criteria for Study Termination/Site Termination .....                                 | 31 |
| 7. SCHEDULE OF ASSESSMENTS.....  | 33 |

|         |   |    |
|---------|---|----|
| 8.      | SELECTION AND WITHDRAWAL OF PATIENTS .....            | 50 |
| 8.1.    | Patient Inclusion Criteria .....                      | 50 |
| 8.2.    | Patient Exclusion Criteria .....                      | 51 |
| 8.3.    | Patient Withdrawal Criteria .....                     | 52 |
| 9.      | TREATMENT OF PATIENTS .....                           | 54 |
| 9.1.    | Management of Potential Drug Infusion Reactions.....  | 54 |
| 9.2.    | Infection Risk.....                                   | 55 |
| 9.3.    | Prior and Concomitant Medications and Procedures..... | 56 |
| 9.4.    | Treatment Compliance.....                             | 56 |
| 9.5.    | Randomization and Blinding .....                      | 57 |
| 10.     | STUDY DRUG MATERIALS AND MANAGEMENT .....             | 58 |
| 10.1.   | Description of Study Drug.....                        | 58 |
| 10.2.   | Study Drug Packaging and Labeling .....               | 58 |
| 10.3.   | Study Drug Storage.....                               | 58 |
| 10.4.   | Study Drug Preparation .....                          | 58 |
| 10.4.1. | ALXN1210 Dose Preparation.....                        | 59 |
| 10.4.2. | In-use Shelf Life .....                               | 60 |
| 10.5.   | Study Drug Administration.....                        | 60 |
| 10.6.   | Study Drug Accountability .....                       | 60 |
| 10.7.   | Study Drug Handling and Disposal .....                | 61 |
| 11.     | PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS ..... | 62 |
| 11.1.   | Blood Sample Collection.....                          | 62 |
| 11.2.   | PK/PD Sample Analysis .....                           | 63 |
| 12.     | IMMUNOGENICITY ASSESSMENTS.....                       | 64 |
| 12.1.   | Immunogenicity Sample Analysis.....                   | 64 |
| 13.     | ASSESSMENTS OF EFFICACY .....                         | 65 |
| 13.1.   | Blood Samples for Pharmacodynamic Analysis.....       | 65 |
| 13.1.1. | Lactate Dehydrogenase.....                            | 65 |
| 13.1.2. | Biomarkers of PNH .....                               | 65 |
| 13.1.3. | Hemolysis-related Hematological Parameters.....       | 65 |
| 13.2.   | Quality of Life .....                                 | 65 |
| 13.3.   | PNH Symptomatology.....                               | 65 |
| 13.4.   | Exploratory Markers of PNH.....                       | 66 |

|           |   |    |
|-----------|---|----|
| 13.5.     | Major Adverse Vascular Events .....                     | 66 |
| 14.       | ASSESSMENT OF SAFETY .....                              | 67 |
| 14.1.     | Safety Parameters .....                                 | 67 |
| 14.1.1.   | Demographic/Medical History .....                       | 67 |
| 14.1.2.   | Weight and Height .....                                 | 67 |
| 14.1.3.   | Physical Examination .....                              | 67 |
| 14.1.4.   | Vital Signs .....                                       | 67 |
| 14.1.5.   | Electrocardiogram.....                                  | 67 |
| 14.1.6.   | Laboratory Assessments .....                            | 68 |
| 14.1.6.1. | Pregnancy Screen.....                                   | 68 |
| 14.1.6.2. | Hematology.....   | 68 |
| 14.1.6.3. | Blood Chemistry .....                                   | 68 |
| 14.1.6.4. | Coagulation.....  | 68 |
| 14.1.6.5. | Urinalysis and Urine Chemistry .....                    | 69 |
| 14.1.6.6. | Virus Serology .....                                    | 69 |
| 14.1.6.7. | Brain Natriuretic Protein.....                          | 69 |
| 14.1.7.   | Infusion Site Reaction.....                             | 69 |
| 15.       | ADVERSE EVENT MANAGEMENT .....                          | 70 |
| 15.1.     | Definition of an Adverse Event .....                    | 70 |
| 15.2.     | Definition of a Serious Adverse Event .....             | 71 |
| 15.3.     | Severity Assessments.....                               | 72 |
| 15.4.     | Causality Assessment .....                              | 72 |
| 15.5.     | Outcome.....  | 73 |
| 15.6.     | Recording Adverse Events .....                          | 73 |
| 15.7.     | Reporting Serious Adverse Event(s) to the Sponsor ..... | 74 |
| 15.8.     | Exposure During Pregnancy and Lactation .....           | 74 |
| 15.9.     | Reporting Requirements .....                            | 75 |
| 15.9.1.   | Sponsor .....   | 75 |
| 15.9.2.   | Investigator .....                                      | 75 |
| 16.       | STATISTICS .....  | 76 |
| 16.1.     | General Considerations.....                             | 76 |
| 16.2.     | Analysis Populations .....                              | 76 |
| 16.3.     | Sample Size and Power .....                             | 76 |

|       |   |    |
|-------|---|----|
| 16.4. | Demographics, Baseline Characteristics, and Patient Disposition ..... | 76 |
| 16.5. | Safety Analysis .....   | 77 |
| 16.6. | Efficacy Analysis.....  | 77 |
| 16.7. | Pharmacokinetic Analysis .....  | 78 |
| 16.8. | Pharmacodynamic and Immunogenicity Analyses.....                      | 78 |
| 17.   | DIRECT ACCESS TO SOURCE DATA/DOCUMENTS.....                           | 79 |
| 17.1. | Study Monitoring.....   | 79 |
| 17.2. | Audits and Inspections.....   | 79 |
| 18.   | ETHICS .....  | 80 |
| 18.1. | Data Monitoring Committee.....  | 80 |
| 18.2. | Ethics Review .....   | 80 |
| 18.3. | Ethical Conduct of the Study .....                                    | 80 |
| 18.4. | Written Informed Consent .....  | 80 |
| 19.   | DATA HANDLING AND RECORDKEEPING .....                                 | 82 |
| 19.1. | Data Collection .....   | 82 |
| 19.2. | Inspection of Records .....   | 82 |
| 19.3. | Retention of Records .....  | 82 |
| 20.   | PUBLICATION POLICY .....  | 83 |
| 21.   | LIST OF REFERENCES.....   | 84 |
| 22.   | APPENDIX.....   | 85 |
|       | APPENDIX A. CLINICAL LABORATORY TESTS .....                           | 86 |

### LIST OF TABLES

|          |  |    |
|----------|--|----|
| Table 1: | Emergency Contact Information.....   | 5  |
| Table 2: | Abbreviations and Special Terms.....   | 21 |
| Table 3: | Dosing Schedule .....  | 29 |
| Table 4: | Schedule of Assessments: Induction and Maintenance Dosing During the<br>Treatment Period: Cohort 1 ..... | 34 |
| Table 5: | Schedule of Assessments: Induction and Maintenance Dosing During the<br>Treatment Period: Cohort 2 ..... | 36 |
| Table 6: | Schedule of Assessments: Induction and Maintenance Dosing During the<br>Treatment Period: Cohort 3 ..... | 38 |
| Table 7: | Schedule of Assessments: Induction and Maintenance Dosing During the<br>Treatment Period: Cohort 4 ..... | 40 |

|           |  |    |
|-----------|--|----|
| Table 8:  | Schedule of Assessments: Extension Period and Early Termination: Cohort 1 .....  | 42 |
| Table 9:  | Schedule of Assessments: Extension Period and Early Termination: Cohort 2 .....  | 44 |
| Table 10: | Schedule of Assessments: Extension Period and Early Termination: Cohort 3 .....  | 46 |
| Table 11: | Schedule of Assessments: Extension Period and Early Termination: Cohort 4 .....  | 48 |
| Table 12: | Clinical Criteria for Diagnosing Anaphylaxis .....   | 55 |
| Table 13: | Composition of Investigational Product .....   | 58 |
| Table 14: | Dosing Reference Chart for 10 mg/mL ALXN1210 Formulation Dose<br>Preparation .....   | 59 |
| Table 15: | Weight-based Dosing Reference Chart for 10 mg/mL ALXN1210<br>Formulation Dose Preparation Beginning on Day 463 (Cohort 2), Day 477<br>(Cohort 3), and Day 533 (Cohort 1) ..... | 59 |
| Table 16: | Dosing Reference Chart for 100 mg/mL ALXN1210 Formulation Dose<br>Preparation .....  | 60 |
| Table 17: | Collection Time Points for Serum Concentrations of ALXN1210 and<br>Analysis of Hemolytic Activity .....  | 62 |
| Table 18: | Collection Time Points for Serum Samples for Immunogenicity Analyses of<br>Antidrug Antibodies to ALXN1210 .....   | 64 |

## LIST OF FIGURES

|           |  |    |
|-----------|--|----|
| Figure 1: | ALXN1210-PNH-201 Study Schematic ..... | 30 |
|-----------|--|----|

### 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

**Table 2: Abbreviations and Special Terms**

| Abbreviation or Term | Explanation  |
|----------------------|--|
| $\lambda_z$          | apparent terminal-phase elimination rate constant  |
| %CV                  | percent coefficient of variance  |
| ADA                  | antidrug antibody/ies  |
| ADCC                 | antibody-dependent cell-mediated cytotoxicity  |
| AE                   | adverse event  |
| Alexion              | Alexion Pharmaceuticals, Inc.  |
| AUC <sub>t</sub>     | area under the serum concentration-versus-time curve from time 0 (dosing) to the last quantifiable concentration     |
| AUC <sub>τ</sub>     | area under the concentration-versus-time curve from time 0 (dosing) to the end of the dosing interval                |
| AUC <sub>0-x</sub>   | area under the concentration-versus-time curve from time 0 (dosing) to X days postdosing                             |
| AUC <sub>∞</sub>     | area under the concentration-versus-time curve from time 0 (dosing) extrapolated to infinity                         |
| BMI                  | body mass index  |
| BNP                  | brain natriuretic peptide  |
| BP                   | blood pressure   |
| C5                   | complement component 5   |
| CDC                  | complement-dependent cytotoxicity  |
| CL                   | total clearance  |
| C <sub>max</sub>     | maximum observed serum concentration   |
| C <sub>min</sub>     | minimum observed serum concentration   |
| C <sub>trough</sub>  | the serum concentration at the end of the dosage interval τ  |
| cRBC                 | chicken red blood cell   |
| CTCAE                | Common Terminology Criteria for Adverse Events   |
| CV                   | coefficient of variance  |
| DMC                  | Data Monitoring Committee  |
| ECG                  | electrocardiogram  |
| eCRF                 | electronic case report form  |
| eGFR                 | estimated glomerular filtration rate   |
| EOI                  | end of infusion  |
| EORTC                | European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale, version 3.0 |
| FACIT-Fatigue        | Functional Assessment of Chronic Illness Therapy-Fatigue Scale, version 4  |
| FAS                  | Full Analysis Set  |
| GCP                  | Good Clinical Practice   |
| HIV                  | human immunodeficiency virus   |
| IC <sub>99</sub>     | 99% inhibitory concentration   |
| ICF                  | informed consent form  |
| ICH                  | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use                  |
| IEC                  | Independent Ethics Committee   |
| IRB                  | Institutional Review Board   |
| IV                   | intravenous(ly)  |
| LDH                  | lactate dehydrogenase  |
| mAb                  | monoclonal antibody  |
| MAVE                 | major adverse vascular event   |
| PD                   | pharmacodynamic(s)   |
| PEF                  | peak expiratory flow   |

**Table 2: Abbreviations and Special Terms (Continued)**

|           |  |
|-----------|--|
| PNH       | paroxysmal nocturnal hemoglobinuria          |
| PK        | pharmacokinetic(s)                           |
| QoL       | quality of life                              |
| RBC       | red blood cell                               |
| SAE       | serious adverse event                        |
| SD        | standard deviation                           |
| SOI       | start of infusion                            |
| $t_{1/2}$ | terminal elimination half-life               |
| $t_{max}$ | time to maximum observed serum concentration |
| $V_{ss}$  | volume of distribution at steady state       |

## 4. INTRODUCTION

ALXN1210 is a humanized monoclonal antibody (mAb) that is structurally related to eculizumab (Soliris<sup>®</sup>), and is being developed by Alexion Pharmaceuticals, Inc. (Alexion). ALXN1210 selectively binds to human complement protein C5, inhibiting its cleavage to C5a and C5b during complement activation. This inhibition prevents the release of the proinflammatory mediator C5a and the formation of the cytolytic pore-forming membrane attack complex C5b-9 while preserving the proximal or early components of complement activation (eg, C3 and C3b) essential for the opsonization of microorganisms and clearance of immune complexes. The mechanism of action of ALXN1210 provides a rationale for the potential therapeutic use in diseases where complement activation is involved (eg, paroxysmal nocturnal hemoglobinuria [PNH] or atypical hemolytic uremic syndrome). These disorders of uncontrolled complement activation are chronic and progressive, with severe morbidities and significant premature mortality.

Paroxysmal nocturnal hemoglobinuria is a condition in which uncontrolled complement activity leads to systemic complications, principally through intravascular hemolysis and platelet activation (Socie, 1996; Brodsky, 2014). Persistent intravascular hemolysis may be triggered by various stressors such as infection or physical exertion, and this leads to smooth muscle contraction (free hemoglobin), chronic anemia, and an increased risk of severe thromboembolism. Thromboembolism is the most common cause of mortality in patients with PNH, and pulmonary hypertension and end-organ damage of vital organs, such as the liver, kidneys, brain, and intestines, are sequelae of such events (Hillmen, 2010). Due to these adverse pathologic processes, patients with PNH have a decreased quality of life (QoL), which may include debilitating fatigue, chronic pain, poor physical function, shortness of breath, abdominal pain, erectile dysfunction, a need for anticoagulation, blood transfusions and, in some instances, need for dialysis (Weitz, 2012).

The purpose of the study is to evaluate the efficacy, safety, tolerability, immunogenicity, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple doses of ALXN1210 administered intravenously (IV) to patients with PNH who have not previously been treated with a complement inhibitor.

### 4.1. Background

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

#### 4.1.1. Clinical Studies

ALXN1210 was administered in single doses of 200 mg and 400 mg IV to healthy volunteers in a Phase 1, randomized, blinded, placebo-controlled, single ascending-dose (SAD) study designed to evaluate the safety, tolerability, PK, and PD of ALXN1210 (Study ALXN1210-HV-101, n=14). There were no drug-related serious adverse events (SAEs) and no AEs leading to study discontinuation or individual subject withdrawal. The overall conclusions of the study were as follows:



- ALXN1210 exhibited prolonged PK exposure with mean geometric half-life estimates of 32.4 days and 30.8 days following single doses of 200 and 400 mg, respectively.
- The PK parameters ( $AUC_t$ ,  $AUC_{\infty}$ , and  $C_{max}$ ) were essentially dose proportional over the studied dose range.
- At the EOI, the mean free C5 serum concentrations and cRBC hemolysis activity were inhibited by > 99% and > 97%, respectively. The duration of the effect was dose dependent. All subjects were negative for ADA through Day 150.

ALXN1210 has been administered in multiple doses of 400 mg and 800 mg monthly to healthy volunteers in a Phase 1, randomized, blinded, placebo-controlled, multiple ascending dose (MAD) study designed to evaluate the safety, tolerability, PK, and PD of ALXN1210 (Study ALXN1210-HV-102). The study is currently ongoing.

ALXN1210 has been administered to patients with PNH in an open-label, inpatient, dose-escalation study designed to evaluate the safety, tolerability, PK, and PD of ALXN1210 (Study ALXN1210-PNH-103). The study is currently ongoing.

Please refer to the current edition of the ALXN1210 Investigator's Brochure for more information.

#### **4.1.2. Nonclinical Studies**

The binding characteristics, potency, and effector functions of ALXN1210 have been studied in vitro and compared with its parent molecule, eculizumab. ALXN1210, like eculizumab, binds with high affinity to human C5, but does not bind to C5 from nonhuman primate or nonprimate mammalian species tested or exhibit pharmacological activity in any nonhuman species tested.

Effector function of ALXN1210 was also studied. Since ALXN1210 is directed against a soluble antigen, a direct assessment of the capacity to initiate antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) is not possible. Instead, direct measurements of ALXN1210 binding to Fcγ receptors (FcγRs) and complement component C1q were performed and inferred that in the absence of binding, they cannot mediate ADCC or CDC, respectively. Having both a soluble antigen and weak binding to effector molecules, ALXN1210 is unlikely to be capable of ADCC or CDC in vivo. Supporting this assertion is that no indication of ADCC or CDC was observed in Study ALXN1210-HV-101.

Please refer to the current edition of the ALXN1210 Investigator's Brochure for detailed results.

#### **4.1.3. Potential Risks**

##### **4.1.3.1. Infections (*Neisseria meningitidis* and other encapsulated organisms)**

Complement C5 inhibition is known to increase the susceptibility to infections caused by encapsulated bacteria, particularly *Neisseria meningitidis* (*N. meningitidis*). To address this risk, all study participants must be vaccinated against *N. meningitidis*. Refer to [Section 9.2](#) for further details.

#### **4.1.3.2. Immunogenicity and Hypersensitivity**

Treatment with any therapeutic protein (human, humanized, chimeric) may induce an immune response. Occasionally, this immune response is clinically meaningful. The consequences of an immune reaction to a therapeutic protein range from transient appearance of antibodies, without any clinical consequence, to severe, life-threatening conditions. Potential clinical consequences also may include severe hypersensitivity-type reactions, decrease in efficacy, and induction of autoimmunity, including antibodies to the endogenous form of the protein (Casadevall, 2002; Li, 2001).

Some subjects and patients treated with IV infusions of mAbs have experienced concurrent infusion-related reactions, with signs or symptoms that can be classified as acute allergic/hypersensitivity reactions or cytokine release syndrome (Sampson, 2006). 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. In addition, readministration of some mAbs has been associated with serum sickness-like reactions, manifesting 1 to 14 days after drug administration.

#### **4.2. Study Rationale**

This is a dose ranging and dose-regimen ranging study designed based on the PK/PD-safety data generated from the single-ascending dose (SAD) and multiple-ascending dose (MAD) studies to help design a dose and dose regimen for the Phase 3 study(ies). It is anticipated that the planned starting and maintenance doses in this study will maintain drug levels above the current target efficacious trough level in addition to including the higher end of drug exposures to accumulate sufficient safety data prior to the start of Phase 3 study(ies). The dose regimens selected for the study are based on the emerging PK/PD data from the ongoing studies.

## **5. STUDY OBJECTIVES AND ENDPOINTS**

### **5.1. Primary Objective**

The primary objective of this study is to evaluate the efficacy, safety, and tolerability of multiple doses of ALXN1210 administered IV to complement inhibitor treatment-naïve patients with PNH.

### **5.2. Secondary Objectives**

The secondary objectives are to characterize the PK and PD effects of multiple doses of ALXN1210 administered IV to complement inhibitor treatment-naïve patients with PNH, and to investigate the immunogenicity of ALXN1210 administered IV to complement inhibitor treatment-naïve patients with PNH.

### **5.3. Endpoints**

Efficacy, safety, immunogenicity, PK, and PD endpoints are described in the sections to follow. Timing of assessments is displayed in the Schedule of Assessments ([Section 7](#)).

#### **5.3.1. Efficacy Endpoints**

##### **5.3.1.1. Primary Efficacy**

The primary efficacy endpoint is:

- Change in lactate dehydrogenase (LDH) levels from baseline to Day 253

##### **5.3.1.2. Secondary Efficacy**

The secondary efficacy endpoints are:

- Changes in hemolysis-related hematologic parameters: free hemoglobin, haptoglobin, reticulocyte count, PNH red blood cell (RBC) clone, and D-dimer
- Changes in clinical manifestations: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction

##### **5.3.1.3. Exploratory Efficacy**

The exploratory efficacy endpoints are:

- Change from baseline in the need for blood transfusions
- Change from baseline in disease-associated biomarkers (markers of chronic kidney disease; ie, estimated glomerular filtration rate [eGFR]; spot urine albumin:creatinine, and plasma brain natriuretic peptide [BNP] for pulmonary hypertension)
- Change from baseline in QoL, assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, version 4 and European Organisation for

Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale,  
Version 3.0 (EORTC) scales

- Change from baseline in major adverse vascular events (MAVEs)

**5.3.2. Immunogenicity Endpoints**

- Measurement of ADA

**5.3.3. Pharmacokinetic/Pharmacodynamic Endpoints**

- Changes in serum ALXN1210 concentration over time
- Change in cRBC hemolytic activity
- Change in free and total C5 concentration

**5.3.4. Safety Endpoints**

- Changes from baseline in physical examination assessments and vital signs
- Change from baseline in electrocardiogram (ECG) parameters
- Change from baseline in laboratory assessments
- Incidence of AEs and SAEs

## 6. OVERALL STUDY DESIGN

ALXN1210-PNH-201 is a Phase 2, open-label, multiple ascending dose study to evaluate the efficacy, safety, tolerability, immunogenicity, PK, and PD of multiple doses of ALXN1210 administered IV to patients with PNH who have not been previously treated with a C5 complement inhibitor.

Four treatment cohorts and up to 26 patients (at least 6 per cohort) are planned for enrollment, with at least 20 patients planned for evaluation. All patients are to be screened for study eligibility after providing written informed consent to participate. Patients who fail to meet any of the eligibility criteria may be rescreened once for study participation, at the discretion of the Investigator.

Patients enrolled in Cohort 1 will receive induction doses of ALXN1210 of 1400 mg on Day 1 and 1000 mg on Day 15. On Day 29 they will receive the first of 8 maintenance doses of 1000 mg of ALXN1210 (administered every 28 days or 4 weeks) (Table 3). Patients enrolled in Cohort 2 will receive induction doses of ALXN1210 of 2000 mg on Day 1 and 1600 mg on Day 22. On Day 43 they will receive the first of 5 maintenance doses of 1600 mg of ALXN1210 (administered every 42 days or 6 weeks). Patients enrolled in Cohort 3 will receive induction doses of ALXN1210 of 1600 mg on Day 1 and 1600 mg on Day 15. On Day 29 they will receive the first of 4 maintenance doses of 2400 mg of ALXN1210 (administered every 56 days or 8 weeks). Patients enrolled in Cohort 4 will receive an induction dose of ALXN1210 of 3000 mg on Day 1. On Day 29 they will receive the first of 3 maintenance doses of 5400 mg of ALXN1210 (administered every 84 days or 12 weeks). The first 2 patients in Cohort 4 will receive their induction dose (3000 mg) at least 1 day apart. The third patient will receive the induction dose at least 7 days after the second patient has received the induction dose.

An independent Data Monitoring Committee (DMC) will review and evaluate the study data for patient safety and make recommendations on dose escalation, continuing dosing within the cohort, modification, or termination of the study. The DMC will conduct a review of the available safety data at the following scheduled time points:

- Fifteen days after the second patient in Cohort 1 receives the second induction dose to determine whether Cohort 2 can be opened.
- Fifteen days after the second patient in Cohort 2 receives the second induction dose to determine whether Cohort 3 can be opened.
- Fifteen days after the second patient in Cohort 3 receives the first maintenance dose to determine whether Cohort 4 can be opened.
- Approximately 7 days after the second patient in Cohort 4 receives the 3000 mg dose to review safety.
- Approximately 7 days after the second patient in Cohort 4 receives the first 5400 mg dose to review safety.

If additional patients are screened and are eligible for enrollment before a dose-escalation decision has been made by the DMC for any cohort, those patients will be assigned to the active cohort with the lowest dose level.

On Day 253, patients will continue treatment in a long-term Extension Period of the study, at the same maintenance dose and frequency as their final dose of ALXN1210 administered during the Treatment 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 463 for patients in Cohort 2, Day 477 for patients in Cohorts 3, and Day 533 for patients in Cohort 1, patients will switch from their current dose regimen to a q8w, weight-based regimen, as follows: 3000 mg for patients weighing  $\geq 40$  to  $< 60$  kg, 3300 mg for patients weighing  $\geq 60$  to  $< 100$  kg, and 3600 mg for patients weighing  $\geq 100$  kg. The dose regimen will not change for patients in Cohort 4. Beginning on Day 953 for patients in Cohort 4, Day 981 for patients in Cohort 3, Day 1023 for patients in Cohort 2, and Day 1037 for patients in Cohort 1, patients will switch from the 10 mg/mL ALXN1210 unit dose formulation to the 100 mg/mL ALXN1210 unit dose formulation, while remaining on their current dose regimen. This transition will reduce the number of vials needed for each infusion and the duration of the infusion.

Up to 30 days will be allowed for screening procedures. The total duration of treatment (which includes an Induction Period and a Maintenance Period) is approximately 253 days. The total duration of the Extension Period is up to approximately 5 years (Figure 1).

All patients will be monitored closely for signs of infection throughout the study. Treatment with prophylactic antibiotics will be at the discretion of the Investigator and per the site/country standard of care.

The dosing schedule is provided in Table 3 and the overall study design is presented in Figure 1.

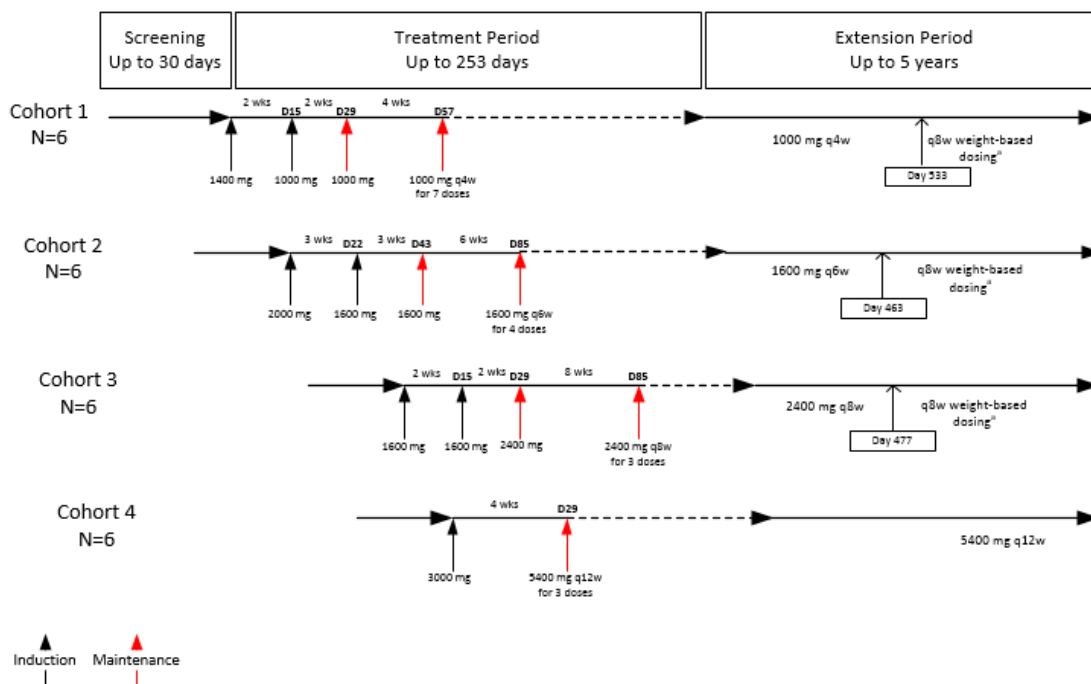
**Table 3: Dosing Schedule**

| Cohort | Patients | Induction                             | Maintenance  |
|--------|----------|---------------------------------------|--|
| 1      | 6        | 1400 mg on Day 1<br>1000 mg on Day 15 | <ul style="list-style-type: none"> <li>1000 mg on Day 29 and then every 28 days or 4 weeks (Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477)</li> <li>Weight-based<sup>a</sup> dose on Day 533 and then every 8 weeks (Days 589, 645, 701, 757, 813, 869, 925, 981, 1037<sup>b</sup>, 1093, 1149, 1205, 1261, 1317, 1373, 1429, 1485, 1541, 1597, 1653, 1709, 1765, 1821, 1877, 1933, 1989, 2045, 2101)</li> </ul> |
| 2      | 6        | 2000 mg on Day 1<br>1600 mg on Day 22 | <ul style="list-style-type: none"> <li>1600 mg on Day 43 and then every 42 days or 6 weeks (Days 85, 127, 169, 211, 253, 295, 337, 379, 421)</li> <li>Weight-based<sup>a</sup> dose on Day 463 and then every 8 weeks (Days 519, 575, 631, 687, 743, 799, 855, 911, 967, 1023<sup>b</sup>, 1079, 1135, 1191, 1247, 1303, 1359, 1415, 1471, 1527, 1583, 1639, 1695, 1751, 1807, 1863, 1919, 1975, 2031, 2087)</li> </ul>                              |
| 3      | 6        | 1600 mg on Day 1<br>1600 mg on Day 15 | <ul style="list-style-type: none"> <li>2400 mg on Day 29 and then every 56 days or 8 weeks (Days 85, 141, 197, 253, 309, 365, 421)</li> <li>Weight-based<sup>a</sup> dose on Day 477 and then every 8 weeks (Days 533, 589, 645, 701, 757, 813, 869, 925, 981<sup>b</sup>, 1037, 1093, 1149, 1205, 1261, 1317, 1373, 1429, 1485, 1541, 1597, 1653, 1709, 1765, 1821, 1877, 1933, 1989, 2045, 2101)</li> </ul>  |
| 4      | 6 to 8   | 3000 mg on Day 1                      | <ul style="list-style-type: none"> <li>5400 mg on Day 29 and then every 84 days or 12 weeks (Days 113, 197, 281, 365, 449, 533, 617, 701, 785, 869, 953<sup>b</sup>, 1037, 1121, 1205, 1289, 1373, 1457, 1541, 1625, 1709, 1793, 1877, 1961, 2045)</li> </ul>  |

<sup>a</sup> 3000 mg for patients weighing  $\geq 40$  to  $< 60$  kg, 3300 mg for patients weighing  $\geq 60$  to  $< 100$  kg, and 3600 mg for patients weighing  $\geq 100$  kg.

- <sup>b</sup> Beginning on Day 953 for patients in Cohort 4, Day 981 for patients in Cohort 3, Day 1023 for patients in Cohort 2, and Day 1037 for patients in Cohort 1, patients will switch from the 10 mg/mL ALXN1210 unit dose formulation to the 100 mg/mL ALXN1210 unit dose formulation, while remaining on their current dose regimen.

**Figure 1: ALXN1210-PNH-201 Study Schematic**



<sup>a</sup> Beginning at Day 463 (Cohort 2), Day 477 (Cohort 3), and Day 533 (Cohort 1), weight-based maintenance doses will be administered as follows: 3000 mg for patients weighing  $\geq 40$  to  $< 60$  kg, 3300 mg for patients weighing  $\geq 60$  to  $< 100$  kg, and 3600 mg for patients weighing  $\geq 100$  kg.

## 6.1. Number of Patients

Up to 26 patients (at least 6 per cohort) are planned for enrollment, with at least 20 patients planned for evaluation.

## 6.2. Dose Rationale

Initial analyses supporting dose and dose regimen selection for Study ALXN1210-PNH-201 utilized data from the SAD study (ALXN1210-HV-101) in healthy volunteers. The PK data following single sub-therapeutic doses (200 mg and 400 mg) of ALXN1210 to healthy volunteers (ALXN1210-HV-101) yielded an estimated mean (range) elimination half-life of ALXN1210 of  $\sim 31$  (27-38) days. The initial PK/PD data estimated a target efficacious trough level of  $\geq 100$   $\mu\text{g/mL}$  to design dose regimens for this study. The targeted efficacious trough level is defined as concentration achieving complete complement inhibition ( $\geq 99\%$ ) in all patients ( $\geq 97.5\%$ ). Subsequent population PK analyses, utilizing emerging PK data from both healthy volunteers and patients with PNH across a wider range of doses, exposures, and durations,

suggest the median (95% confidence interval) elimination half-life of ALXN1210 is ~43 days (39-48). This change in the estimate of elimination half-life of ALXN1210 following multiple dose administrations in healthy volunteers and patients with PNH has resulted in an increase in the estimated target trough concentrations in Cohorts 1-3 and has presented the opportunity to explore dosing ALXN1210 less frequently. It is also desirable to target a trough level that will achieve complete complement inhibition in all PNH patients. Therefore, to provide safety and PK/PD support for an optimized Phase 3 dosing regimen characterization, it is necessary to evaluate the dose regimen ranging in this protocol from once every month dosing to once every 3 month dosing as enabled by the increased estimated elimination half-life, taking into account the current estimates of targeted efficacious ALXN1210 trough level.

It was anticipated that the planned starting and maintenance doses in this study would maintain the drug levels above the current target efficacious trough level in addition to including the higher end of drug exposures to accumulate sufficient safety data prior to the start of Phase 3 study(ies).

The weight-based dosages of ALXN1210 (Table 15) for the extension phase are premised on PK/PD data from the induction and maintenance phases of this study as well as from early development studies in healthy adult volunteers and an ongoing Phase 1b study (ALXN1210-PNH-103) in patients with PNH. The selection of ALXN1210 dose regimen is based on targeting immediate, complete, and sustained inhibition of terminal complement activity in patients with PNH.

### **6.3. Criteria for Dose Continuation and Escalation**

An independent DMC will oversee safety monitoring in this study and will operate according to a separate DMC charter. This committee will be comprised of experts in relevant biomedical fields who have no direct relationship with this study. The DMC will conduct a review of the available safety data at the following scheduled time points:

- Fifteen days after the second patient in Cohort 1 receives the second induction dose to determine whether Cohort 2 can be opened.
- Fifteen days after the second patient in Cohort 2 receives the second induction dose to determine whether Cohort 3 can be opened.
- Fifteen days after the second patient in Cohort 3 receives the first maintenance dose to determine whether Cohort 4 can be opened.
- Approximately 7 days after the second patient in Cohort 4 receives the 3000 mg dose to review safety.
- Approximately 7 days after the second patient in Cohort 4 receives the first 5400 mg dose to review safety.

The DMC will meet quarterly thereafter for the remainder of the study.

### **6.4. Criteria for Study Termination/Site Termination**

The Sponsor or Competent 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 regulatory authorities

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

## **7. SCHEDULE OF ASSESSMENTS**

The Schedules of Assessments are provided for Cohorts 1, 2, and 3 and 4, respectively, in [Table 4](#), [Table 5](#), [Table 6](#), and [Table 7](#) for Induction and Maintenance dosing, and in [Table 8](#), [Table 9](#), [Table 10](#), and [Table 11](#) for the Extension Period and Early Termination.

**Table 4: Schedule of Assessments: Induction and Maintenance Dosing During the Treatment Period: Cohort 1**

| Period                                     | Screening | Treatment                        |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
|--|-----------|----------------------------------|----|----|----|-------------|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|---|
|  |           | Induction                        |    |    |    | Maintenance |    |    |    |     |     |     |     |     |     |     |     |   |
| Study Day                                  | -30 to -1 | 1                                | 7  | 15 | 22 | 29          | 43 | 57 | 85 | 113 | 127 | 141 | 169 | 197 | 211 | 225 | 253 |   |
| Window (day)                               | N/A       | ±1                               | ±1 | ±1 | ±1 | ±1          | ±1 | ±1 | ±2 | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  |   |
| Informed consent                           | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Confirmation of meningococcal vaccination  | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Medical history and demographics           | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Virus serology                             | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| PNH clone size                             | X         | X                                |    |    |    |             |    | X  |    | X   |     |     | X   |     |     |     | X   |   |
| Height, weight, BMI                        | X         | X                                |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Pregnancy test                             | X         | X                                |    | X  |    | X           |    | X  | X  | X   |     | X   | X   | X   |     | X   | X   |   |
| PNH symptomatology                         | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |   |
| Physical examination                       | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     | X   |   |
| Abbreviated physical exam                  |           | X                                |    | X  |    | X           |    | X  | X  | X   |     | X   | X   | X   |     | X   |     |   |
| Vital signs                                | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |   |
| 12-Lead ECG                                | X         | X                                |    |    |    |             |    |    |    |     |     |     |     |     |     |     | X   |   |
| Chemistry, including LDH                   | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |   |
| Hematology                                 | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |   |
| Coagulation                                | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |   |
| Urinalysis and urine chemistry, spot urine | X         | X                                |    |    |    |             |    |    | X  |     |     |     |     | X   |     |     |     | X |
| eGFR calculation                           | X         | X                                |    |    |    |             |    |    | X  |     |     |     |     | X   |     |     |     | X |
| Brain natriuretic peptide                  |           | X                                |    |    |    | X           |    |    | X  |     |     |     | X   |     | X   |     |     | X |
| <b>ALXN1210 administration</b>             |           | X                                |    | X  |    | X           |    | X  | X  | X   |     | X   | X   | X   |     | X   | X   | X |
| PK sampling                                |           | X                                |    | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X |
| Serum PD panel                             |           | X                                |    | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X |
| Immunogenicity (ADA)                       |           | X                                |    | X  |    | X           |    | X  | X  | X   |     | X   | X   | X   |     | X   | X   | X |
| QoL assessments                            |           | X                                |    | X  |    |             |    | X  |    | X   | X   |     |     | X   |     | X   | X   | X |
| Infusion site evaluation                   |           | X                                |    | X  |    | X           |    | X  | X  | X   |     | X   | X   | X   |     | X   | X   | X |
| VAS for infusion site pain                 |           | X                                |    | X  |    | X           |    | X  | X  | X   |     | X   | X   | X   |     | X   | X   | X |
| Review safety card                         |           | ← ← ← Review continuously → → →  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Concomitant medications                    |           | ← ← ← Monitor continuously → → → |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Adverse events                             |           | ← ← ← Monitor continuously → → → |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |

Abbreviations: ADA = antidrug antibody; BMI = body mass index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; QoL = quality of life; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; VAS = visual analog scale

- <sup>1</sup> All assessments will be performed predose and are part of the Maintenance Period. The dose administered on Day 253 is the first dose in the Extension Period.
- <sup>2</sup> Meningococcal vaccination may be completed on Day 1 prior to dosing with ALXN1210. Prophylactic antibiotics must be used if 14 days has not elapsed (see [Section 9.2](#)).
- <sup>3</sup> Hepatitis B and C, human immunodeficiency virus types 1 and 2.
- <sup>4</sup> Granulocyte and red blood cell clone size at screening and red blood cell clone size only during the Treatment Period.
- <sup>5</sup> Measure height at screening only.
- <sup>6</sup> Female patients of childbearing potential only. Serum pregnancy test at screening only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ALXN1210 to female patients on dosing days.
- <sup>7</sup> Investigator assessment of the following events: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. Symptoms of disease burden will be captured through the QoL questionnaires.
- <sup>8</sup> Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and subject symptoms.
- <sup>9</sup> Obtain triplicate 12-lead ECGs at screening and prior to the first dose on Day 1, and single 12-lead ECGs on Day 253.
- <sup>10</sup> Clinical safety laboratory measurements will be collected predose on dosing days. Follicle-stimulating hormones and estradiol levels will be measured at least twice during screening, only in order to confirm postmenopausal status.
- <sup>11</sup> At least two samples must be collected at least one day apart during the screening period for LDH testing.
- <sup>12</sup> Assessment for safety, as well as the following parameters as secondary endpoints: free hemoglobin, haptoglobin, reticulocyte count, and D-dimer.
- <sup>13</sup> Obtain predose on Days 1, 29, 85, 141, 197, and 253.
- <sup>14</sup> Please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>15</sup> To include serum for exploratory PD assays; please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>16</sup> Immunogenicity samples will be collected predose on dosing days. Please refer to [Table 18](#) for cohort-specific sampling time points.
- <sup>17</sup> Functional Assessment of Chronic Illness Therapy-Fatigue Scale, version 4.0 and European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale, Version 3.0.
- <sup>18</sup> An induration or reaction of <10 mm will not be listed as an adverse event unless it persists for more than 24 hours, at which time the patient must inform the study staff immediately and proceed to the nearest hospital emergency department.
- <sup>19</sup> Patient should assess infusion site pain using a 100 mm VAS. The VAS should be completed as soon as practical after completion of the infusion.

**Table 5: Schedule of Assessments: Induction and Maintenance Dosing During the Treatment Period: Cohort 2**

| Period                                     | Screening | Treatment                        |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |
|--|-----------|----------------------------------|----|----|----|-------------|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|
|  |           | Induction                        |    |    |    | Maintenance |    |    |    |     |     |     |     |     |     |     |     |
| Study Day                                  | -30 to -1 | 1                                | 7  | 15 | 22 | 29          | 43 | 57 | 85 | 113 | 127 | 141 | 169 | 197 | 211 | 225 | 253 |
| Window (day)                               | N/A       | ±1                               | ±1 | ±1 | ±1 | ±1          | ±1 | ±1 | ±2 | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  |
| Informed consent                           | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |
| Confirmation of meningococcal vaccination  | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |
| Medical history and demographics           | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |
| Virus serology                             | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |
| PNH clone size                             | X         | X                                |    |    |    |             |    | X  |    | X   |     |     | X   |     |     |     | X   |
| Height, weight, BMI                        | X         | X                                |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |
| Pregnancy test                             | X         | X                                |    |    | X  |             | X  |    | X  |     | X   |     | X   |     | X   |     | X   |
| PNH symptomatology                         | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| Physical examination                       | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     | X   |
| Abbreviated physical exam                  |           | X                                |    |    | X  |             | X  |    | X  |     | X   |     | X   |     | X   |     |     |
| Vital signs                                | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| 12-Lead ECG                                | X         | X                                |    |    |    |             |    |    |    |     |     |     |     |     |     |     | X   |
| Chemistry, including LDH                   | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| Hematology                                 | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| Coagulation                                | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| Urinalysis and urine chemistry, spot urine | X         | X                                |    |    |    |             |    |    | X  |     |     |     | X   |     |     |     | X   |
| eGFR calculation                           | X         | X                                |    |    |    |             |    |    | X  |     |     |     | X   |     |     |     | X   |
| Brain natriuretic peptide                  |           | X                                |    |    | X  |             |    |    | X  |     | X   |     | X   |     |     |     | X   |
| <b>ALXN1210 administration</b>             |           | X                                |    |    | X  |             | X  |    | X  |     | X   |     | X   |     | X   |     | X   |
| PK sampling                                |           | X                                |    |    | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| Serum PD panel                             |           | X                                |    |    | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| Immunogenicity (ADA)                       |           | X                                |    |    | X  |             | X  |    | X  |     | X   |     | X   |     | X   |     | X   |
| QoL assessments                            |           | X                                |    | X  |    |             |    | X  |    | X   | X   |     |     | X   |     | X   | X   |
| Infusion site evaluation                   |           | X                                |    |    | X  |             | X  |    | X  |     | X   |     | X   |     | X   |     | X   |
| VAS for infusion site pain                 |           | X                                |    |    | X  |             | X  |    | X  |     | X   |     | X   |     | X   |     | X   |
| Review safety card                         |           | ← ← ← Review continuously → → →  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |
| Concomitant medications                    |           | ← ← ← Monitor continuously → → → |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |
| Adverse events                             |           | ← ← ← Monitor continuously → → → |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |

Abbreviations: ADA = antidrug antibody; BMI = body mass index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; QoL = quality of life; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; VAS = visual analog scale  
<sup>1</sup> All assessments will be performed predose and are part of the Maintenance Period. The dose administered on Day 253 is the first dose in the Extension Period.

- <sup>2</sup> Meningococcal vaccination may be completed on Day 1 prior to dosing with ALXN1210. Prophylactic antibiotics must be used if 14 days has not elapsed (see [Section 9.2](#)).
- <sup>3</sup> Hepatitis B and C, human immunodeficiency virus types 1 and 2.
- <sup>4</sup> Granulocyte and red blood cell clone size at screening and red blood cell clone size only during the Treatment Period.
- <sup>5</sup> Measure height at screening only.
- <sup>6</sup> Female patients of childbearing potential only. Serum pregnancy test at screening only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ALXN1210 to female patients on dosing days.
- <sup>7</sup> Investigator assessment of the following events: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. Symptoms of disease burden will be captured through the QoL questionnaires.
- <sup>8</sup> Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and subject symptoms.
- <sup>9</sup> Obtain triplicate 12-lead ECGs at screening and prior to the first dose on Day 1, and single 12-lead ECGs on Day 253.
- <sup>10</sup> Clinical safety laboratory measurements will be collected predose on dosing days. Follicle-stimulating hormones and estradiol levels will be measured at least twice during screening, only in order to confirm postmenopausal status.
- <sup>11</sup> At least two samples must be collected at least one day apart during the screening period for LDH testing.
- <sup>12</sup> Assessment for safety, as well as the following parameters as secondary endpoints: free hemoglobin, haptoglobin, reticulocyte count, and D-dimer.
- <sup>13</sup> Obtain predose on Days 1, 22, 85, 127, 169, and 253.
- <sup>14</sup> Please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>15</sup> To include serum for exploratory PD assays; please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>16</sup> Immunogenicity samples will be collected predose on dosing days. Please refer to [Table 18](#) for cohort-specific sampling time points.
- <sup>17</sup> Functional Assessment of Chronic Illness Therapy-Fatigue Scale, version 4.0 and European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale, Version 3.0.
- <sup>18</sup> An induration or reaction of < 10 mm will not be listed as an adverse event unless it persists for more than 24 hours, at which time the patient must inform the study staff immediately and proceed to the nearest hospital emergency department.
- <sup>19</sup> Patient should assess infusion site pain using a 100 mm VAS. The VAS should be completed as soon as practical after completion of the infusion.

**Table 6: Schedule of Assessments: Induction and Maintenance Dosing During the Treatment Period: Cohort 3**

| Period                                     | Screening | Treatment                        |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
|--|-----------|----------------------------------|----|----|----|-------------|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|---|
|  |           | Induction                        |    |    |    | Maintenance |    |    |    |     |     |     |     |     |     |     |     |   |
| Study Day                                  | -30 to -1 | 1                                | 7  | 15 | 22 | 29          | 43 | 57 | 85 | 113 | 127 | 141 | 169 | 197 | 211 | 225 | 253 |   |
| Window (day)                               | N/A       | ±1                               | ±1 | ±1 | ±1 | ±1          | ±1 | ±1 | ±2 | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  |   |
| Informed consent                           | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Confirmation of meningococcal vaccination  | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Medical history and demographics           | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Virus serology                             | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| PNH clone size                             | X         | X                                |    |    |    |             |    | X  |    | X   |     |     | X   |     |     | X   | X   |   |
| Height, weight, BMI                        | X         | X                                |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Pregnancy test                             | X         | X                                |    | X  |    | X           |    | X  |    | X   |     | X   |     | X   |     | X   | X   |   |
| PNH symptomatology                         | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |   |
| Physical examination                       | X         |                                  |    |    |    |             |    |    |    |     |     |     |     |     |     |     | X   |   |
| Abbreviated physical exam                  |           | X                                |    | X  |    | X           |    |    | X  |     |     | X   |     | X   |     |     |     |   |
| Vital signs                                | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |   |
| 12-Lead ECG                                | X         | X                                |    |    |    |             |    |    |    |     |     |     |     |     |     |     | X   |   |
| Chemistry, including LDH                   | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |   |
| Hematology                                 | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |   |
| Coagulation                                | X         | X                                | X  | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |   |
| Urinalysis and urine chemistry, spot urine | X         | X                                |    |    |    |             |    |    | X  |     |     |     |     | X   |     |     |     | X |
| eGFR calculation                           | X         | X                                |    |    |    |             |    |    | X  |     |     |     |     | X   |     |     |     | X |
| Brain natriuretic peptide                  |           | X                                |    |    |    | X           |    |    | X  |     |     |     | X   |     | X   |     |     | X |
| <b>ALXN1210 administration</b>             |           | X                                |    | X  |    | X           |    |    | X  |     |     |     | X   |     | X   |     |     | X |
| PK sampling                                |           | X                                |    | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X |
| Serum PD panel                             |           | X                                |    | X  | X  | X           | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X |
| Immunogenicity (ADA)                       |           | X                                |    | X  |    | X           |    |    | X  |     |     |     | X   |     | X   |     |     | X |
| QoL assessments                            |           | X                                |    | X  |    |             |    |    | X  |     | X   | X   |     |     | X   |     | X   | X |
| Infusion site evaluation                   |           | X                                |    | X  |    | X           |    |    | X  |     |     |     | X   |     | X   |     |     | X |
| VAS for infusion site pain                 |           | X                                |    | X  |    | X           |    |    | X  |     |     |     | X   |     | X   |     |     | X |
| Review safety card                         |           | ← ← ← Review continuously → → →  |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Concomitant medications                    |           | ← ← ← Monitor continuously → → → |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |
| Adverse events                             |           | ← ← ← Monitor continuously → → → |    |    |    |             |    |    |    |     |     |     |     |     |     |     |     |   |

Abbreviations: ADA = antidrug antibody; BMI = body mass index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; QoL = quality of life; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; VAS = visual analog scale  
<sup>1</sup> All assessments will be performed predose and are part of the Maintenance Period. The dose administered on Day 253 is the first dose in the Extension Period.

- <sup>2</sup> Meningococcal vaccination may be completed on Day 1 prior to dosing with ALXN1210. Prophylactic antibiotics must be used if 14 days has not elapsed (see [Section 9.2](#)).
- <sup>3</sup> Hepatitis B and C, human immunodeficiency virus types 1 and 2.
- <sup>4</sup> Granulocyte and red blood cell clone size at screening and red blood cell clone size only during the Treatment Period.
- <sup>5</sup> Measure height at screening only.
- <sup>6</sup> Female patients of childbearing potential only. Serum pregnancy test at screening only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ALXN1210 to female patients on dosing days.
- <sup>7</sup> Investigator assessment of the following events: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. Symptoms of disease burden will be captured through the QoL questionnaires.
- <sup>8</sup> Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and subject symptoms.
- <sup>9</sup> Obtain triplicate 12-lead ECGs at screening and prior to the first dose on Day 1, and single 12-lead ECGs on Day 253.
- <sup>10</sup> Clinical safety laboratory measurements will be collected predose on dosing days. Follicle-stimulating hormones and estradiol levels will be measured at least twice during screening, only in order to confirm postmenopausal status.
- <sup>11</sup> At least two samples must be collected at least one day apart during the screening period for LDH testing.
- <sup>12</sup> Assessment for safety, as well as the following parameters as secondary endpoints: free hemoglobin, haptoglobin, reticulocyte count, and D-dimer.
- <sup>13</sup> Obtain predose on Days 1, 29, 85, 141, 197, and 253.
- <sup>14</sup> Please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>15</sup> To include serum for exploratory PD assays; please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>16</sup> Immunogenicity samples will be collected predose on dosing days. Please refer to [Table 18](#) for cohort-specific sampling time points.
- <sup>17</sup> Functional Assessment of Chronic Illness Therapy-Fatigue Scale, version 4.0 and European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale, Version 3.0.
- <sup>18</sup> An induration or reaction of < 10 mm will not be listed as an adverse event unless it persists for more than 24 hours, at which time the patient must inform the study staff immediately and proceed to the nearest hospital emergency department.
- <sup>19</sup> Patient should assess infusion site pain using a 100 mm VAS. The VAS should be completed as soon as practical after completion of the infusion.



**Table 7: Schedule of Assessments: Induction and Maintenance Dosing During the Treatment Period: Cohort 4**

| Period                                     | Screening | Treatment                        |    |    |    |    |             |    |    |     |     |     |     |     |     |     |     |
|--|-----------|----------------------------------|----|----|----|----|-------------|----|----|-----|-----|-----|-----|-----|-----|-----|-----|
|  |           | Induction                        |    |    |    |    | Maintenance |    |    |     |     |     |     |     |     |     |     |
| Study Day                                  | -30 to -1 | 1                                | 7  | 15 | 22 | 29 | 43          | 57 | 85 | 113 | 127 | 141 | 169 | 197 | 211 | 225 | 253 |
| Window (day)                               | N/A       | ±1                               | ±1 | ±1 | ±1 | ±1 | ±1          | ±1 | ±2 | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  | ±2  |
| Informed consent                           | X         |                                  |    |    |    |    |             |    |    |     |     |     |     |     |     |     |     |
| Confirmation of meningococcal vaccination  | X         |                                  |    |    |    |    |             |    |    |     |     |     |     |     |     |     |     |
| Medical history and demographics           | X         |                                  |    |    |    |    |             |    |    |     |     |     |     |     |     |     |     |
| Virus serology                             | X         |                                  |    |    |    |    |             |    |    |     |     |     |     |     |     |     |     |
| PNH clone size                             | X         | X                                |    |    |    |    |             | X  |    | X   |     |     | X   |     |     | X   | X   |
| Height, weight, BMI                        | X         | X                                |    |    |    |    |             |    |    |     |     |     |     |     |     |     |     |
| Pregnancy test                             | X         | X                                |    |    |    | X  |             |    |    | X   |     |     |     | X   |     |     |     |
| PNH symptomatology                         | X         | X                                | X  | X  | X  | X  | X           | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| Physical examination                       | X         |                                  |    |    |    |    |             |    |    |     |     |     |     |     |     |     | X   |
| Abbreviated physical exam                  |           | X                                |    | X  |    | X  |             | X  |    | X   |     | X   |     | X   |     | X   |     |
| Vital signs                                | X         | X                                | X  | X  | X  | X  | X           | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| 12-Lead ECG                                | X         | X                                |    |    |    |    |             |    |    |     |     |     |     |     |     |     | X   |
| Chemistry, including LDH                   | X         | X                                | X  | X  | X  | X  | X           | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| Hematology                                 | X         | X                                | X  | X  | X  | X  | X           | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| Coagulation                                | X         | X                                | X  | X  | X  | X  | X           | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   |
| Urinalysis and urine chemistry, spot urine | X         | X                                |    |    |    |    |             |    | X  |     |     |     | X   |     |     |     | X   |
| eGFR calculation                           | X         | X                                |    |    |    |    |             |    | X  |     |     |     | X   |     |     |     | X   |
| Brain natriuretic peptide                  |           | X                                |    |    |    | X  |             |    |    | X   |     |     |     | X   |     |     | X   |
| <b>ALXN1210 administration</b>             |           | X                                |    |    |    | X  |             |    |    | X   |     |     |     | X   |     |     | X   |
| PK sampling                                |           | X                                |    | X  |    | X  |             | X  |    | X   |     | X   |     | X   |     | X   | X   |
| Serum PD panel                             |           | X                                |    | X  |    | X  |             | X  |    | X   |     | X   |     | X   |     | X   | X   |
| Immunogenicity (ADA)                       |           | X                                |    |    |    | X  |             |    |    | X   |     |     |     | X   |     |     |     |
| QoL assessments                            |           | X                                |    | X  |    |    |             | X  |    | X   | X   |     |     | X   |     | X   | X   |
| Infusion site evaluation                   |           | X                                |    |    |    | X  |             |    |    | X   |     |     |     | X   |     |     |     |
| VAS for infusion site pain                 |           | X                                |    |    |    | X  |             |    |    | X   |     |     |     | X   |     |     |     |
| Review safety card                         |           | ← ← ← Monitor continuously → → → |    |    |    |    |             |    |    |     |     |     |     |     |     |     |     |
| Concomitant medications                    |           | ← ← ← Monitor continuously → → → |    |    |    |    |             |    |    |     |     |     |     |     |     |     |     |
| Adverse events                             |           | ← ← ← Monitor continuously → → → |    |    |    |    |             |    |    |     |     |     |     |     |     |     |     |

Abbreviations: ADA = antidrug antibody; BMI = body mass index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; QoL = quality of life; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; VAS = visual analog scale

- <sup>1</sup> All assessments will be performed predose and are part of the Maintenance Period. The last dose administered during Maintenance is on Day 197; the next dose administered on Day 281 (see [Table 11](#)) is the first dose in the Extension Period.
- <sup>2</sup> Meningococcal vaccination may be completed on Day 1 prior to dosing with ALXN1210. Prophylactic antibiotics must be used if 14 days has not elapsed (see [Section 9.2](#)).
- <sup>3</sup> Hepatitis B and C, human immunodeficiency virus types 1 and 2.
- <sup>4</sup> Granulocyte and red blood cell clone size at screening and red blood cell clone size only during the Treatment Period.
- <sup>5</sup> Measure height at screening only.
- <sup>6</sup> Female patients of childbearing potential only. Serum pregnancy test at screening only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ALXN1210 to female patients on dosing days.
- <sup>7</sup> Investigator assessment of the following events: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. Symptoms of disease burden will be captured through the QoL questionnaires.
- <sup>8</sup> Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and subject symptoms.
- <sup>9</sup> Obtain triplicate 12-lead ECGs at screening and prior to the first dose on Day 1, and single 12-lead ECGs on Day 253.
- <sup>10</sup> Clinical safety laboratory measurements will be collected predose on dosing days. Follicle-stimulating hormones and estradiol levels will be measured at least twice during screening, only in order to confirm postmenopausal status.
- <sup>11</sup> At least two samples must be collected at least one day apart during the screening period for LDH testing.
- <sup>12</sup> Assessment for safety, as well as the following parameters as secondary endpoints: free hemoglobin, haptoglobin, reticulocyte count, and D-dimer.
- <sup>13</sup> Obtain predose.
- <sup>14</sup> Please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>15</sup> To include serum for exploratory PD assays; please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>16</sup> Immunogenicity samples will be collected predose on dosing days. Please refer to [Table 18](#) for cohort-specific sampling time points.
- <sup>17</sup> Functional Assessment of Chronic Illness Therapy-Fatigue Scale, version 4.0 and European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale, Version 3.0.
- <sup>18</sup> An induration or reaction of < 10 mm will not be listed as an adverse event unless it persists for more than 24 hours, at which time the patient must inform the study staff immediately and proceed to the nearest hospital emergency department.
- <sup>19</sup> Patient should assess infusion site pain using a 100 mm VAS. The VAS should be completed as soon as practical after completion of the infusion.

**Table 8: Schedule of Assessments: Extension Period and Early Termination: Cohort 1**

| Period  | Extension                        |     |     |     |        |     |     |     |                |     |     |     |        |     |     |     |        |                   |      |      |        |      |      |      |      |      | ET <sup>1</sup> |      |      |      |      |      |      |      |      |      |      |      |    |
|---|----------------------------------|-----|-----|-----|--------|-----|-----|-----|----------------|-----|-----|-----|--------|-----|-----|-----|--------|-------------------|------|------|--------|------|------|------|------|------|-----------------|------|------|------|------|------|------|------|------|------|------|------|----|
|   | Year 1                           |     |     |     | Year 2 |     |     |     | Year 3         |     |     |     | Year 4 |     |     |     | Year 5 |                   |      |      | Year 6 |      |      |      |      |      |                 |      |      |      |      |      |      |      |      |      |      |      |    |
| Study Day                                     | 281                              | 309 | 337 | 365 | 393    | 421 | 449 | 477 | 533            | 589 | 645 | 701 | 757    | 813 | 869 | 925 | 981    | 1037 <sup>2</sup> | 1093 | 1149 | 1205   | 1261 | 1317 | 1373 | 1429 | 1485 | 1541            | 1597 | 1653 | 1709 | 1765 | 1821 | 1877 | 1933 | 1989 | 2045 | 2101 | 2157 |    |
| Window (day)                                  | ±5                               | ±5  | ±5  | ±5  | ±5     | ±5  | ±5  | ±5  | ±5             | ±5  | ±5  | ±5  | ±5     | ±5  | ±5  | ±5  | ±5     | ±5                | ±5   | ±5   | ±5     | ±5   | ±5   | ±5   | ±5   | ±5   | ±5              | ±5   | ±5   | ±5   | ±5   | ±5   | ±5   | ±5   | ±5   | ±5   | ±5   | ±5   | ±5 |
| ALXN1210 administration                       | X                                | X   | X   | X   | X      | X   | X   | X   | X <sup>3</sup> | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Weight  |                                  |     |     |     |        |     | X   | X   | X              | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| PNH clone size <sup>4</sup>                   |                                  |     | X   |     |        |     |     | X   |                |     | X   |     |        | X   |     | X   |        | X                 |      | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Pregnancy test <sup>5</sup>                   | X                                | X   | X   | X   | X      | X   | X   | X   | X              | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| PNH symptomatology <sup>6</sup>               | X                                | X   | X   | X   | X      | X   | X   | X   | X              | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Physical examination                          |                                  |     |     |     |        |     |     |     |                |     |     |     |        |     |     |     |        |                   |      |      |        |      |      |      |      |      |                 |      |      |      |      |      |      |      |      |      |      |      |    |
| Abbreviated physical examination <sup>7</sup> |                                  |     | X   |     |        | X   | X   |     | X              |     | X   |     | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Vital signs                                   | X                                | X   | X   | X   | X      | X   | X   | X   | X              | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| 12-Lead ECG <sup>8</sup>                      |                                  |     |     |     |        |     |     |     |                |     |     |     |        |     |     |     |        |                   |      |      |        |      |      |      |      |      |                 |      |      |      |      |      |      |      |      |      |      |      |    |
| Chemistry, including LDH                      | X                                | X   | X   | X   | X      | X   | X   | X   | X              | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Hematology <sup>9</sup>                       | X                                | X   | X   | X   | X      | X   | X   | X   | X              | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Coagulation                                   | X                                | X   | X   | X   | X      | X   | X   | X   | X              | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Urinalysis and urine chemistry                | X                                | X   | X   | X   | X      | X   | X   | X   | X              | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| PK sampling <sup>10</sup>                     |                                  |     | X   |     |        |     | X   |     | X              |     | X   |     | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Serum PD panel <sup>11</sup>                  |                                  |     | X   |     |        |     | X   |     | X              |     | X   |     | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Immunogenicity (ADA) <sup>12</sup>            |                                  |     | X   |     |        |     | X   |     | X              |     | X   |     | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| QoL assessments                               |                                  |     | X   |     |        | X   |     | X   | X              | X   | X   |     | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Infusion site evaluation <sup>13</sup>        | X                                | X   | X   | X   | X      | X   | X   | X   | X              | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| VAS for infusion site pain <sup>14</sup>      | X                                | X   | X   | X   | X      | X   | X   | X   | X              | X   | X   | X   | X      | X   | X   | X   | X      | X                 | X    | X    | X      | X    | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X    | X  |
| Review safety card                            | ← ← ← Review continuously → → →  |     |     |     |        |     |     |     |                |     |     |     |        |     |     |     |        |                   |      |      |        |      |      |      |      |      |                 |      |      |      |      |      |      |      |      |      |      |      |    |
| Concomitant medications                       | ← ← ← Monitor continuously → → → |     |     |     |        |     |     |     |                |     |     |     |        |     |     |     |        |                   |      |      |        |      |      |      |      |      |                 |      |      |      |      |      |      |      |      |      |      |      |    |
| Adverse events                                | ← ← ← Monitor continuously → → → |     |     |     |        |     |     |     |                |     |     |     |        |     |     |     |        |                   |      |      |        |      |      |      |      |      |                 |      |      |      |      |      |      |      |      |      |      |      |    |

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ET = early termination; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; QoL = quality of life; VAS = visual analog scale

<sup>1</sup> The ET visit should only be performed for patients who discontinue or are withdrawn early from the study.

- <sup>2</sup> Beginning on Day 1037, patients in Cohort 1 will switch from the 10 mg/mL ALXN1210 unit dose formulation to the 100 mg/mL ALXN1210 unit dose formulation, while remaining on their current dose regimen.
- <sup>3</sup> Weight-based maintenance doses of ALXN1210 every 8 weeks (q8w), as follows: 3000 mg for patients weighing  $\geq 40$  to  $< 60$  kg, 3300 mg for patients weighing  $\geq 60$  to  $< 100$  kg, 3600 mg for patients weighing  $\geq 100$  kg. The final dose of study drug will be administered on Day 2101.
- <sup>4</sup> Red blood cell clone size only during the Extension Period.
- <sup>5</sup> Female patients of childbearing potential only. Serum pregnancy test end of study (Day 2157) or ET visit only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ALXN1210 to female patients on dosing days.
- <sup>6</sup> Investigator assessment of the following events: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. Symptoms of disease burden will be captured through the QoL questionnaires.
- <sup>7</sup> Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and subject symptoms.
- <sup>8</sup> Obtain triplicate 12-lead ECGs during the end of study (Day 2157) or at ET visit.
- <sup>9</sup> Assessment for safety as well as the following parameters as secondary endpoints: free hemoglobin, haptoglobin, reticulocyte count, and D-dimer.
- <sup>10</sup> Please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>11</sup> To include serum for exploratory PD assays; please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>12</sup> Immunogenicity samples will be collected predose on dosing days. Please refer to [Table 18](#) for cohort-specific sampling time points.
- <sup>13</sup> An induration or reaction of  $< 10$  mm will not be listed as an adverse event unless it persists for more than 24 hours, at which time the patient must inform the study staff immediately and proceed to the nearest hospital emergency department.
- <sup>14</sup> Patient should assess infusion site pain using a 100 mm VAS. The VAS should be completed as soon as practical after completion of the infusion.

**Table 9: Schedule of Assessments: Extension Period and Early Termination: Cohort 2**

| Period  | Extension                        |     |        |     |                |     |     |     |        |     |     |     |     |     |                   |      |      |      |      |      |        |      |      |      |      |      |        |      | ET <sup>1</sup> |      |      |      |      |      |      |   |   |
|---|----------------------------------|-----|--------|-----|----------------|-----|-----|-----|--------|-----|-----|-----|-----|-----|-------------------|------|------|------|------|------|--------|------|------|------|------|------|--------|------|-----------------|------|------|------|------|------|------|---|---|
|   | Year 1                           |     | Year 2 |     |                |     |     |     | Year 3 |     |     |     |     |     | Year 4            |      |      |      |      |      | Year 5 |      |      |      |      |      | Year 6 |      |                 |      |      |      |      |      |      |   |   |
| Study Day                                     | 295                              | 337 | 379    | 421 | 463            | 519 | 575 | 631 | 687    | 743 | 799 | 855 | 911 | 967 | 1023 <sup>2</sup> | 1079 | 1135 | 1191 | 1247 | 1303 | 1359   | 1415 | 1471 | 1527 | 1583 | 1639 | 1695   | 1751 | 1807            | 1863 | 1919 | 1975 | 2031 | 2087 | 2143 |   |   |
| Window (day)                                  | ±5                               | ±5  | ±5     | ±5  | ±5             | ±5  | ±5  | ±5  | ±5     | ±5  | ±5  | ±5  | ±5  | ±5  | ±5                | ±5   | ±5   | ±5   | ±5   | ±5   | ±5     | ±5   | ±5   | ±5   | ±5   | ±5   | ±5     | ±5   | ±5              | ±5   | ±5   | ±5   | ±5   | ±5   | ±5   |   |   |
| ALXN1210 administration                       | X                                | X   | X      | X   | X <sup>3</sup> | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    |      |   |   |
| Weight  |                                  |     |        | X   | X              | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    | X    | X |   |
| PNH clone size <sup>4</sup>                   |                                  | X   |        |     |                | X   |     |     | X      |     |     | X   |     | X   |                   | X    |      | X    |      | X    |        | X    |      | X    |      | X    |        | X    |                 | X    |      | X    |      | X    | X    |   |   |
| Pregnancy test <sup>5</sup>                   | X                                | X   | X      | X   | X              | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    | X    | X |   |
| PNH symptomatology <sup>6</sup>               | X                                | X   | X      | X   | X              | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    | X    | X |   |
| Physical examination                          |                                  |     |        |     |                |     |     |     |        |     |     |     |     |     |                   |      |      |      |      |      |        |      |      |      |      |      |        |      |                 |      |      |      |      |      | X    | X |   |
| Abbreviated physical examination <sup>7</sup> |                                  | X   |        | X   |                | X   | X   |     | X      | X   |     | X   |     | X   |                   | X    |      | X    |      | X    |        | X    |      | X    |      | X    |        | X    |                 | X    |      | X    |      | X    |      |   |   |
| Vital signs                                   | X                                | X   | X      | X   | X              | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    | X    | X |   |
| 12-Lead ECG <sup>8</sup>                      |                                  |     |        |     |                |     |     |     |        |     |     |     |     |     |                   |      |      |      |      |      |        |      |      |      |      |      |        |      |                 |      |      |      |      |      | X    | X |   |
| Chemistry, including LDH                      | X                                | X   | X      | X   | X              | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    | X    | X | X |
| Hematology <sup>9</sup>                       | X                                | X   | X      | X   | X              | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    | X    | X | X |
| Coagulation                                   | X                                | X   | X      | X   | X              | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    | X    | X | X |
| Urinalysis and urine chemistry                | X                                | X   | X      | X   | X              | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    | X    | X | X |
| PK sampling <sup>10</sup>                     |                                  | X   |        |     |                | X   |     |     | X      |     |     | X   |     | X   | X                 | X    | X    | X    |      | X    |        | X    |      | X    |      | X    |        | X    |                 | X    |      | X    |      | X    | X    | X |   |
| Serum PD panel <sup>11</sup>                  |                                  | X   |        |     |                | X   |     |     | X      |     |     | X   |     | X   | X                 | X    | X    | X    |      | X    |        | X    |      | X    |      | X    |        | X    |                 | X    |      | X    |      | X    | X    | X |   |
| Immunogenicity (ADA) <sup>12</sup>            |                                  | X   |        |     |                | X   |     |     | X      |     |     | X   |     | X   | X                 | X    | X    | X    |      | X    |        | X    |      | X    |      | X    |        | X    |                 | X    |      | X    |      | X    | X    | X |   |
| QoL assessments                               |                                  | X   |        | X   |                | X   | X   |     | X      | X   |     | X   |     | X   |                   | X    |      | X    |      | X    |        | X    |      | X    |      | X    |        | X    |                 | X    |      | X    |      | X    | X    | X |   |
| Infusion site evaluation <sup>13</sup>        | X                                | X   | X      | X   | X              | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    | X    | X |   |
| VAS for infusion site pain <sup>14</sup>      | X                                | X   | X      | X   | X              | X   | X   | X   | X      | X   | X   | X   | X   | X   | X                 | X    | X    | X    | X    | X    | X      | X    | X    | X    | X    | X    | X      | X    | X               | X    | X    | X    | X    | X    | X    | X |   |
| Review safety card                            | ← ← ← Review continuously → → →  |     |        |     |                |     |     |     |        |     |     |     |     |     |                   |      |      |      |      |      |        |      |      |      |      |      |        |      |                 |      |      |      |      |      |      |   |   |
| Concomitant medications                       | ← ← ← Monitor continuously → → → |     |        |     |                |     |     |     |        |     |     |     |     |     |                   |      |      |      |      |      |        |      |      |      |      |      |        |      | X               |      |      |      |      |      |      |   |   |
| Adverse events                                | ← ← ← Monitor continuously → → → |     |        |     |                |     |     |     |        |     |     |     |     |     |                   |      |      |      |      |      |        |      |      |      |      |      |        |      | X               |      |      |      |      |      |      |   |   |

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ET = early termination; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; QoL = quality of life; VAS = visual analog scale

<sup>1</sup> The ET visit should only be performed for patients who discontinue or are withdrawn early from the study.

<sup>2</sup> Beginning on Day 1023, patients in Cohort 2 will switch from the 10 mg/mL ALXN1210 unit dose formulation to the 100 mg/mL ALXN1210 unit dose formulation, while remaining on their current dose regimen.

<sup>3</sup> Weight-based maintenance doses of ALXN1210 every 8 weeks (q8w), as follows: 3000 mg for patients weighing  $\geq 40$  to  $< 60$  kg, 3300 mg for patients weighing  $\geq 60$  to  $< 100$  kg, 3600 mg for patients weighing  $\geq 100$  kg. The final dose of study drug will be administered on Day 2087.

<sup>4</sup> Red blood cell clone size only during the Extension Period.

<sup>5</sup> Female patients of childbearing potential only. Serum pregnancy test at end of study (Day 2143) or ET visit only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ALXN1210 to female patients on dosing days.

<sup>6</sup> Investigator assessment of the following events: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. Symptoms of disease burden will be captured through the QoL questionnaires.

<sup>7</sup> Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and subject symptoms.

<sup>8</sup> Obtain triplicate 12-lead ECGs during the end of study (Day 2143) or at ET visit.

<sup>9</sup> Assessment for safety as well as the following parameters as secondary endpoints: free hemoglobin, haptoglobin, reticulocyte count, and D-dimer.

<sup>10</sup> Please refer to [Table 17](#) for cohort-specific sampling time points.

<sup>11</sup> To include serum for exploratory PD assays; please refer to [Table 17](#) for cohort-specific sampling time points.

<sup>12</sup> Immunogenicity samples will be collected predose on dosing days. Please refer to [Table 18](#) for cohort-specific sampling time points.

<sup>13</sup> An induration or reaction of  $< 10$  mm will not be listed as an adverse event unless it persists for more than 24 hours, at which time the patient must inform the study staff immediately and proceed to the nearest hospital emergency department.

<sup>14</sup> Patient should assess infusion site pain using a 100 mm VAS. The VAS should be completed as soon as practical after completion of the infusion.

**Table 10: Schedule of Assessments: Extension Period and Early Termination: Cohort 3**

| Period  | Extension                        |     |        |                |     |     |        |     |     |     |     |        |                  |      |      |      |        |      |      |      |      |        |      |      |      |      | ET <sup>1</sup> |      |      |      |      |      |      |      |   |   |
|---|----------------------------------|-----|--------|----------------|-----|-----|--------|-----|-----|-----|-----|--------|------------------|------|------|------|--------|------|------|------|------|--------|------|------|------|------|-----------------|------|------|------|------|------|------|------|---|---|
|   | Year 1                           |     | Year 2 |                |     |     | Year 3 |     |     |     |     | Year 4 |                  |      |      |      | Year 5 |      |      |      |      | Year 6 |      |      |      |      |                 |      |      |      |      |      |      |      |   |   |
| Study Day                                     | 309                              | 365 | 421    | 477            | 533 | 589 | 645    | 701 | 757 | 813 | 869 | 925    | 981 <sup>2</sup> | 1037 | 1093 | 1149 | 1205   | 1261 | 1317 | 1373 | 1429 | 1485   | 1541 | 1597 | 1653 | 1709 | 1765            | 1821 | 1877 | 1933 | 1989 | 2045 | 2101 | 2157 |   |   |
| Window (day)                                  | ±5                               | ±5  | ±5     | ±5             | ±5  | ±5  | ±5     | ±5  | ±5  | ±5  | ±5  | ±5     | ±5               | ±5   | ±5   | ±5   | ±5     | ±5   | ±5   | ±5   | ±5   | ±5     | ±5   | ±5   | ±5   | ±5   | ±5              | ±5   | ±5   | ±5   | ±5   | ±5   | ±5   | ±5   |   |   |
| ALXN1210 administration                       | X                                | X   | X      | X <sup>3</sup> | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    |   |   |
| Weight  |                                  |     | X      | X              | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X |   |
| PNH clone size <sup>4</sup>                   | X                                |     |        | X              |     |     | X      |     |     |     | X   |        |                  | X    |      |      | X      |      |      | X    |      |        | X    |      |      | X    |                 |      | X    |      |      | X    |      |      |   |   |
| Pregnancy test <sup>5</sup>                   | X                                | X   | X      | X              | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X |   |
| PNH symptomatology <sup>6</sup>               | X                                | X   | X      | X              | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X |   |
| Physical examination                          |                                  |     |        |                |     |     |        |     |     |     |     |        |                  |      |      |      |        |      |      |      |      |        |      |      |      |      |                 |      |      |      |      |      |      |      | X | X |
| Abbreviated physical examination <sup>7</sup> | X                                |     | X      |                | X   |     | X      |     | X   |     | X   |        | X                |      | X    |      | X      |      | X    |      | X    |        | X    |      | X    |      | X               |      | X    |      | X    |      | X    |      |   |   |
| Vital signs                                   | X                                | X   | X      | X              | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X | X |
| 12-Lead ECG <sup>8</sup>                      |                                  |     |        |                |     |     |        |     |     |     |     |        |                  |      |      |      |        |      |      |      |      |        |      |      |      |      |                 |      |      |      |      |      |      |      | X | X |
| Chemistry, including LDH                      | X                                | X   | X      | X              | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X | X |
| Hematology <sup>9</sup>                       | X                                | X   | X      | X              | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X | X |
| Coagulation                                   | X                                | X   | X      | X              | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X | X |
| Urinalysis and urine chemistry                | X                                | X   | X      | X              | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X | X |
| PK sampling <sup>10</sup>                     | X                                |     |        | X              |     |     | X      |     | X   |     | X   | X      | X                | X    | X    |      | X      |      | X    |      | X    |        | X    |      | X    |      | X               |      | X    |      | X    |      | X    | X    | X |   |
| Serum PD panel <sup>11</sup>                  | X                                |     |        | X              |     |     | X      |     | X   |     | X   | X      | X                | X    | X    |      | X      |      | X    |      | X    |        | X    |      | X    |      | X               |      | X    |      | X    |      | X    | X    | X |   |
| Immunogenicity (ADA) <sup>12</sup>            | X                                |     |        | X              |     |     | X      |     | X   |     | X   | X      | X                | X    | X    |      | X      |      | X    |      | X    |        | X    |      | X    |      | X               |      | X    |      | X    |      | X    | X    | X |   |
| QoL assessments                               |                                  | X   |        | X              |     | X   |        | X   | X   |     | X   |        | X                |      | X    |      | X      |      | X    |      | X    |        | X    |      | X    |      | X               |      | X    |      | X    |      | X    | X    | X |   |
| Infusion site evaluation <sup>13</sup>        | X                                | X   | X      | X              | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X |   |
| VAS for infusion site pain <sup>14</sup>      | X                                | X   | X      | X              | X   | X   | X      | X   | X   | X   | X   | X      | X                | X    | X    | X    | X      | X    | X    | X    | X    | X      | X    | X    | X    | X    | X               | X    | X    | X    | X    | X    | X    | X    | X |   |
| Review safety card                            | ← ← ← Review continuously → → →  |     |        |                |     |     |        |     |     |     |     |        |                  |      |      |      |        |      |      |      |      |        |      |      |      |      |                 |      |      |      |      |      |      |      |   |   |
| Concomitant medications                       | ← ← ← Monitor continuously → → → |     |        |                |     |     |        |     |     |     |     |        |                  |      |      |      |        |      |      |      |      |        |      |      |      |      | X               |      |      |      |      |      |      |      |   |   |
| Adverse events                                | ← ← ← Monitor continuously → → → |     |        |                |     |     |        |     |     |     |     |        |                  |      |      |      |        |      |      |      |      |        |      |      |      |      | X               |      |      |      |      |      |      |      |   |   |

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ET = early termination; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; QoL = quality of life; VAS = visual analog scale

<sup>1</sup> The ET visit should only be performed for patients who discontinue or are withdrawn early from the study.

<sup>2</sup> Beginning on Day 981, patients in Cohort 3 will switch from the 10 mg/mL ALXN1210 unit dose formulation to the 100 mg/mL ALXN1210 unit dose formulation, while remaining on their current dose regimen.

- <sup>3</sup> Weight-based maintenance doses of ALXN1210 every 8 weeks (q8w), as follows: 3000 mg for patients weighing  $\geq 40$  to  $< 60$  kg, 3300 mg for patients weighing  $\geq 60$  to  $< 100$  kg, 3600 mg for patients weighing  $\geq 100$  kg. The final dose of study drug will be administered on Day 2101.
- <sup>4</sup> Red blood cell clone size only during the Extension Period.
- <sup>5</sup> Female patients of childbearing potential only. Serum pregnancy test at end of study (Day 2157) or ET visit only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ALXN1210 to female patients on dosing days.
- <sup>6</sup> Investigator assessment of the following events: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. Symptoms of disease burden will be captured through the QoL questionnaires.
- <sup>7</sup> Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and subject symptoms.
- <sup>8</sup> Obtain triplicate 12-lead ECGs during the end of study (Day 2157) or at ET visit.
- <sup>9</sup> Assessment for safety as well as the following parameters as secondary endpoints: free hemoglobin, haptoglobin, reticulocyte count, and D-dimer.
- <sup>10</sup> Please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>11</sup> To include serum for exploratory PD assays; please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>12</sup> Immunogenicity samples will be collected predose on dosing days. Please refer to [Table 18](#) for cohort-specific sampling time points.
- <sup>13</sup> An induration or reaction of  $< 10$  mm will not be listed as an adverse event unless it persists for more than 24 hours, at which time the patient must inform the study staff immediately and proceed to the nearest hospital emergency department.
- <sup>14</sup> Patient should assess infusion site pain using a 100 mm VAS. The VAS should be completed as soon as practical after completion of the infusion.



**Table 11: Schedule of Assessments: Extension Period and Early Termination: Cohort 4**

| Period  | Extension                        |     |        |     |     |     |        |     |     |      |        |      |      |      |        |      |      |      |        |      | ET <sup>1</sup> |      |      |
|---|----------------------------------|-----|--------|-----|-----|-----|--------|-----|-----|------|--------|------|------|------|--------|------|------|------|--------|------|-----------------|------|------|
|   | Year 1                           |     | Year 2 |     |     |     | Year 3 |     |     |      | Year 4 |      |      |      | Year 5 |      |      |      | Year 6 |      |                 |      |      |
| Study Day                                     | 281                              | 365 | 449    | 533 | 617 | 701 | 785    | 869 | 953 | 1037 | 1121   | 1205 | 1289 | 1373 | 1457   | 1541 | 1625 | 1709 | 1793   | 1877 | 1961            | 2045 | 2129 |
| Window (day)                                  | ±5                               | ±5  | ±5     | ±5  | ±5  | ±5  | ±5     | ±5  | ±5  | ±5   | ±5     | ±5   | ±5   | ±5   | ±5     | ±5   | ±5   | ±5   | ±5     | ±5   | ±5              | ±5   | ±5   |
| ALXN1210 administration                       | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    |      |
| PNH clone size <sup>4</sup>                   |                                  | X   |        | X   |     | X   |        | X   |     | X    |        | X    |      | X    |        | X    |      | X    |        | X    |                 | X    |      |
| Pregnancy test <sup>5</sup>                   | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    | X    |
| PNH symptomatology <sup>6</sup>               | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    | X    |
| Physical examination                          |                                  |     |        |     |     |     |        |     |     |      |        |      |      |      |        |      |      |      |        |      |                 |      | X    |
| Abbreviated physical examination <sup>7</sup> | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    |      |
| Vital signs                                   | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    | X    |
| 12-Lead ECG <sup>8</sup>                      |                                  |     |        |     |     |     |        |     |     |      |        |      |      |      |        |      |      |      |        |      |                 |      | X    |
| Chemistry, including LDH                      | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    | X    |
| Hematology <sup>9</sup>                       | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    | X    |
| Coagulation                                   | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    | X    |
| Urinalysis and urine chemistry                | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    | X    |
| PK sampling <sup>10</sup>                     | X                                |     | X      |     | X   |     | X      | X   | X   | X    |        | X    |      | X    |        | X    |      | X    |        | X    |                 | X    | X    |
| Serum PD panel <sup>11</sup>                  | X                                |     | X      |     | X   |     | X      | X   | X   | X    |        | X    |      | X    |        | X    |      | X    |        | X    |                 | X    | X    |
| Immunogenicity (ADA) <sup>12</sup>            | X                                |     | X      |     | X   |     | X      | X   | X   | X    |        | X    |      | X    |        | X    |      | X    |        | X    |                 | X    | X    |
| QoL assessments                               | X                                |     | X      |     | X   |     | X      |     |     | X    |        | X    |      | X    |        | X    |      | X    |        | X    |                 | X    | X    |
| Infusion site evaluation <sup>13</sup>        | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    |      |
| VAS for infusion site pain <sup>14</sup>      | X                                | X   | X      | X   | X   | X   | X      | X   | X   | X    | X      | X    | X    | X    | X      | X    | X    | X    | X      | X    | X               | X    |      |
| Review safety card                            | ← ← ← Review continuously → → →  |     |        |     |     |     |        |     |     |      |        |      |      |      |        |      |      |      |        |      |                 |      |      |
| Concomitant medications                       | ← ← ← Monitor continuously → → → |     |        |     |     |     |        |     |     |      |        |      |      |      |        |      |      |      |        |      |                 |      |      |
| Adverse events                                | ← ← ← Monitor continuously → → → |     |        |     |     |     |        |     |     |      |        |      |      |      |        |      |      |      |        |      |                 |      |      |

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ET = early termination; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; QoL = quality of life; VAS = visual analog scale

<sup>1</sup> The ET visit should only be performed for patients who discontinue or are withdrawn early from the study.

<sup>2</sup> Beginning on Day 953, patients in Cohort 4 will switch from the 10 mg/mL ALXN1210 unit dose formulation to the 100 mg/mL ALXN1210 unit dose formulation, while remaining on their current dose regimen.

- <sup>3</sup> The final dose of study drug will be administered on Day 2045.
- <sup>4</sup> Red blood cell clone size only during the Extension Period.
- <sup>5</sup> Female patients of childbearing potential only. Serum pregnancy test at end of study (Day 2129) or ET visit only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ALXN1210 to female patients on dosing days.
- <sup>6</sup> Investigator assessment of the following events: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. Symptoms of disease burden will be captured through the QoL questionnaires.
- <sup>7</sup> Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and subject symptoms.
- <sup>8</sup> Obtain triplicate 12-lead ECGs during the end of study (Day 2129) or at ET visit.
- <sup>9</sup> Assessment for safety as well as the following parameters as secondary endpoints: free hemoglobin, haptoglobin, reticulocyte count, and D-dimer.
- <sup>10</sup> Please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>11</sup> To include serum for exploratory PD assays; please refer to [Table 17](#) for cohort-specific sampling time points.
- <sup>12</sup> Immunogenicity samples will be collected predose on dosing days. Please refer to [Table 18](#) for cohort-specific sampling time points.
- <sup>13</sup> An induration or reaction of < 10 mm will not be listed as an adverse event unless it persists for more than 24 hours, at which time the patient must inform the study staff immediately and proceed to the nearest hospital emergency department.
- <sup>14</sup> Patient should assess infusion site pain using a 100 mm VAS. The VAS should be completed as soon as practical after completion of the infusion.

## 8. SELECTION AND WITHDRAWAL OF PATIENTS

### 8.1. Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria in order to be eligible for the study:

1. Male or female patients  $\geq 18$  years of age
2. PNH diagnosis confirmed by documented high-sensitivity flow cytometry (RBCs and/or granulocytes)
3. Mean LDH  $\geq 3 \times$  upper limit of normal, based on 2 measurements from separate blood samples collected at least 1 day apart during screening
4. Willing and able to give written informed consent and comply with the study visit schedule
5. Documented meningococcal vaccination not more than 3 years prior to dosing
6. Female patients who consider themselves postmenopausal must provide evidence at screening of menopause status, based on a combination of amenorrhea for at least 1 year and increased serum follicle-stimulating hormone level ( $> 30$  IU/L) on at least 2 occasions (eg, in the absence of hormone replacement therapy, dietary phytoestrogens) or estradiol concentration  $< 10$  pg/mL.
7. Female patients of childbearing potential must use highly effective contraception as defined below, starting at screening and continuing until at least 8 months after the last dose of ALXN1210. Highly effective contraceptive methods are as follows:
  - a. Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
  - b. Progesterone-only hormonal contraception associated with inhibition of ovulation
    - Oral
    - Injectable
    - Implantable
  - c. Intrauterine device
  - d. Intrauterine hormone-releasing system
  - e. Bilateral tubal occlusion
  - f. Vasectomized partner, provided that the partner is the patient's sole sexual partner
  - g. Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

- h. Combination of male condom with appropriate barrier methods for the female patient (double barrier methods)
8. Male patients with a female spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use barrier contraception (male condom) during the Treatment Period and for at least 8 months after the last dose of ALXN1210. Barrier contraception is required even with documented medical assessment of surgical success of a vasectomy. Female spouses/partners of male patients who are of childbearing potential must use highly effective contraception (as defined in inclusion criterion #7) or acceptable contraception, as defined below, starting at screening and continuing until at least 8 months after the last dose of ALXN1210. Male patients must not donate sperm during the Screening and Treatment Periods and for at least 8 months after the last dose of ALXN1210.

Acceptable contraceptive methods are as follows:

- a. Simultaneous use of male condom and appropriate barrier methods for the female partner

## 8.2. Patient Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible to participate in the study:

1. Treatment with a complement inhibitor at any time
2. Platelet count  $< 30,000/\text{mm}^3$  ( $30 \times 10^9 /\text{L}$ ) at screening
3. Absolute neutrophil count  $< 500/\mu\text{L}$  ( $0.5 \times 10^9 /\text{L}$ ) at screening
4. History of bone marrow transplantation
5. History of *N. meningitidis* infection or history of unexplained, recurrent infection
6. Female patients who are planning to become pregnant, or are pregnant or breastfeeding
7. Positive pregnancy test at screening or Day 1
8. Patients are excluded if they are taking any of the following medications and are not on a stable regimen (as judged by the Investigator) for the time period indicated prior to screening:
  - a. Erythropoietin or immunosuppressants for at least 8 weeks
  - b. Corticosteroids for at least 4 weeks
  - c. Vitamin K antagonists (eg, warfarin) with a stable international normalized ratio (per Investigator discretion) for at least 4 weeks
  - d. Iron supplements or folic acid for at least 4 weeks
  - e. Low molecular weight heparin for at least 4 weeks
9. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer)
10. Acute or chronic hepatitis B virus infection (evidenced by the presence of hepatitis B surface antigen or immunoglobulin M antibodies against hepatitis B core antigen).

11. Acute or chronic hepatitis C virus infection (evidenced by hepatitis C virus antibody)
12. Active systemic bacterial, viral, or fungal infection within 14 days prior to dosing on Day 1
13. Immunization with a live-attenuated vaccine 1 month prior to dosing on Day 1
14. Participation in an interventional clinical study within 30 days before initiation of dosing on Day 1, or use of any experimental therapy within 30 days prior to dosing on Day 1, or within 5 half-lives of the investigational product, whichever is greater
15. Major surgery within 90 days prior to dosing on Day 1
16. Presence of fever  $\geq 38$  °C within 2 weeks prior to the first dosing on Day 1
17. Patients with a history of malignancy within 5 years of screening with the exception of a nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
18. Known history of severe allergic or anaphylactic reactions to any drug (including vaccines) or allergen
19. History of allergy to excipients of ALXN1210 (eg, polysorbate 80)
20. Known allergy to Chinese hamster ovary cell proteins
21. History of any clinically significant cardiac, hepatic, immunologic, pulmonary, or rheumatoid disease that, in the Investigator's judgment, would preclude participation
22. Inability to comply with study requirements
23. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the patient unsuitable for enrollment

### **8.3. Patient Withdrawal Criteria**

A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator. Patients who discontinue dosing will be instructed to return for follow-up visits, as described in the Schedule of Assessments ([Section 7](#)), unless they withdraw consent and/or are lost to follow-up.

- If the patient withdraws consent, the Early Termination visit should be completed as soon as possible.
- If the patient is withdrawn from ALXN1210, the Early Termination visit should occur prior to initiation of complement-targeted therapy.
- If the patient is withdrawn from ALXN1210, the patient should be encouraged to return for the remainder of his or her scheduled protocol visits until starting a different complement-targeted therapy.

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 [Section 9.1](#)) 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 deem it is in the best interest of the patient.

## 9. TREATMENT OF PATIENTS

### 9.1. Management of Potential Drug Infusion Reactions

Some patients treated with IV infusions of mAbs have experienced concurrent infusion-related reactions with signs or symptoms that can be classified as acute allergic reactions/hypersensitivity reactions or cytokine release syndrome. The 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 and patients will be monitored closely prior to and through 1 hour following the end of the infusion of ALXN1210. All AEs which may indicate an infusion-related response will be graded according to criteria from the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0.3.

Before infusion is started, the treating physician and other appropriate personnel, medication (adrenaline, inhaled beta agonists, antihistamines, and corticosteroids), and other requirements to treat anaphylaxis must be readily available.

The infusion will be stopped immediately if  $\geq$  Grade 2 allergic/hypersensitivity reaction (including drug fever) or  $\geq$  Grade 3 cytokine release syndrome/acute infusion reaction occurs. Alexion must be notified within 24 hours of any infusion reaction requiring interruption of study drug.

Patients experiencing a reaction during the administration of study drug should be treated according to institutional guidelines.

For a Grade 1 or Grade 2 infusion-related reaction, the infusion should be stopped, and medication with antihistamine (eg, with diphenhydramine, 25 to 50 mg orally or equivalent) and acetaminophen (650 mg orally or equivalent) may be considered. If the signs and symptoms have resolved with the above medications, the infusion may be restarted. If the infusion is slowed, the total infusion time should not exceed 5 hours, including any interruptions for safety or technical reasons. The study drug should be stopped if the infusion reaction recurs. Patients experiencing an infusion reaction should be observed in the clinic until resolution of the reaction, or in the Investigator's best judgment.

If an event of anaphylaxis occurs, according to the criteria listed in [Table 12](#) then subcutaneous epinephrine (1/1000, 0.3 to 0.5 mL or equivalent) should be considered. In the case of bronchospasm, inhaled beta agonist also should be considered. Patients administered antihistamine for the study drug or prevention of infusion reactions should be given appropriate warnings about drowsiness and impairment of driving ability prior to discharge.

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.

**Table 12: Clinical Criteria for Diagnosing Anaphylaxis**

|  |
|--|
| <b>Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:</b>  |
| 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) |
| <b>AND AT LEAST ONE OF THE FOLLOWING:</b>  |
| a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)  |
| b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)  |
| 2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):  |
| a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)   |
| b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)  |
| c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)   |
| d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)  |
| 3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):  |
| a. Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline  |

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

Source: Adapted from [Sampson, 2006](#)

## 9.2. Infection Risk

Due to its mechanism of action, the use of ALXN1210 increases the patient's susceptibility to meningococcal infection (*N. meningitidis*). Patients might be at risk of disease by uncommon serogroups (such as X), although meningococcal disease due to any serogroup may occur. To reduce the risk of infection, all patients must be vaccinated prior to receiving ALXN1210. Patients who are treated with ALXN1210 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).

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given per official guidance and local practice on the appropriate use of antibacterial agents. All 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 take place at specific time points as part of the review of the patient safety card and throughout the study as described in the Schedule of Assessments (Section 7).

### **9.3. Prior and Concomitant Medications and Procedures**

Prior medications (including vitamins and herbal preparations), including those discussed in the exclusion criteria (Section 8.2) and/or procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the patient takes or undergoes within 28 days (or 3 years for documentation of meningococcal vaccination) prior to signing the informed consent form (ICF) until the first dose of ALXN1210 will be recorded on the patient's electronic case report form (eCRF).

All medication use during the study will be recorded in the patient's source/chart and eCRF. This record will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and current medications for PNH. Any changes in concomitant medications also will be recorded in the patient's source/chart and eCRF. Any concomitant medication deemed necessary for the patient's standard of care treatment 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 the medication are recorded in full in the patient's source/chart.

The following concomitant medications are allowed if the following apply, and dose adjustments are not expected during the Treatment Period:

- Patients are taking erythropoietin on a stable dose for at least 8 weeks prior to screening.
- Patients are taking immunosuppressants on a stable dose for at least 8 weeks prior to screening.
- Patients are taking corticosteroids on a stable dose for at least 4 weeks prior to screening.
- Patients are allowed to take vitamin K antagonists (eg, warfarin) but must have had a stable international normalized ratio level (per Investigator discretion) for 4 weeks prior to screening.
- Patients are taking iron supplements or folic acid on a stable dose for at least 4 weeks prior to screening.
- Patients are allowed to take low molecular weight heparin on a stable dose for at least 4 weeks prior to screening.

Adjustments in the frequency or level of dosing in any of the above medications can be made if the Alexion medical monitor or the Investigator deems it is in the best interest of the patient.

### **9.4. Treatment Compliance**

Patients will be administered ALXN1210 in a controlled setting under the Investigator's supervision, thereby ensuring compliance with ALXN1210 administration. Study coordinators at

the investigative site will ensure that all patients are adequately informed on the specific ALXN1210 dosing regimen required for compliance with the study protocol.

Alexion or its designee will periodically monitor study sites to ensure compliance with the protocol, and communicate with sites on a regular basis regarding study protocol deviations. All protocol deviations will be appropriately documented by the Investigator or designee and study monitors.

Unless otherwise specified, procedures, data collection, and evaluation will be conducted as per the clinical site's standard operating procedures.

## **9.5. Randomization and Blinding**

This is an open-label study. Up to 26 patients will be enrolled in the study. The first 2 eligible patients who meet the inclusion/exclusion criteria will be assigned to Cohort 1. The DMC will conduct a review of the available safety data as described in [Section 6.3](#) to determine whether the next cohort may be opened. If additional patients are screened and are eligible for enrollment before a dose-escalation decision has been made by the DMC for any cohort, those patients will be assigned to the active cohort with the lowest dose level.

## 10. STUDY DRUG MATERIALS AND MANAGEMENT

### 10.1. Description of Study Drug

ALXN1210 is formulated at 10 mg/mL and 100 mg/mL concentrations with a pH of 7.0 and 7.4, respectively (Table 13). Both ALXN1210 formulations are presented as sterile, preservative-free solutions for IV administration and are supplied in single-use vials. ALXN1210 will be provided by the Sponsor and is suitable for human use and manufactured under current Good Manufacturing Practices.

Further details are provided in the Investigator's Brochure and in the Pharmacy Manual.

**Table 13: Composition of Investigational Product**

| Name of Ingredient         | 10 mg/mL Concentration (IV)          | 100 mg/mL Concentration (IV)         | Function                         |
|----------------------------|--------------------------------------|--------------------------------------|----------------------------------|
| ALXN1210 antibody          | 10 mg/mL                             | 100 mg/mL                            | Active Ingredient                |
| Sodium phosphate monobasic | 3.34 mM <sup>1</sup><br>(0.46 mg/mL) | 33.1 mM <sup>2</sup><br>(4.42 mg/mL) | Buffering Agent                  |
| Sodium phosphate dibasic   | 6.63 mM <sup>1</sup><br>(1.78 mg/mL) | 16.5 mM <sup>2</sup><br>(4.42 mg/mL) | Buffering Agent                  |
| Sodium chloride            | 150 mM<br>(8.77 mg/mL)               | NA                                   | Tonicity                         |
| L-Arginine                 | NA                                   | 25 mM<br>(4.33 mg/mL)                | Stabilizer                       |
| Sucrose                    | NA                                   | 50 mg/mL                             | Tonicifying agent and stabilizer |
| Polysorbate 80             | 0.02% w/v                            | 0.05% w/v                            | Surfactant                       |
| Water for Injection        | QS                                   | QS                                   | Solvent                          |

Abbreviations: IV = intravenous; NA = not applicable; QS = quantum sufficiat (sufficient quantity).

<sup>1</sup> The sodium phosphate concentration is approximately 10 mM, which is comprised of sodium phosphate monobasic and the sodium phosphate dibasic.

<sup>2</sup> The sodium phosphate concentration is approximately 50 mM, which is comprised of sodium phosphate monobasic and the sodium phosphate dibasic.

### 10.2. Study Drug Packaging and Labeling

ALXN1210 will be supplied in a one-vial-per-kit configuration. Each vial and carton will be labeled according to specific country or region regulatory requirements.

### 10.3. Study Drug Storage

ALXN1210 vials must be stored in refrigerated conditions at 2°C to 8°C (36°F to 46°F) and protected from light. ALXN1210 vials should not be frozen or shaken.

### 10.4. Study Drug Preparation

Preparation of ALXN1210 doses must be performed in accordance with site-specific local standards by qualified and study-trained pharmacy personnel.

Handling and preparation of materials used to prepare and administer study drug must be carried out using aseptic techniques for sterile products.

Pharmacy personnel will prepare doses in accordance with the dose assignment.

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

#### 10.4.1. ALXN1210 Dose Preparation

ALXN1210 will be diluted in 0.9% sodium chloride injection (country-specific pharmacopeia) and administered by IV infusion at a fixed rate by dose, as indicated in [Table 14](#).

For each patient, doses will be prepared as required for each dose cohort, as indicated in [Table 14](#).

**Table 14: Dosing Reference Chart for 10 mg/mL ALXN1210 Formulation Dose Preparation**

| Dose (mg) | Infusion Volume (mL) | Maximum Infusion Rate (mL/hour) | Minimum Infusion Duration minutes (hours) |
|-----------|----------------------|---------------------------------|---|
| 1000      | 200                  | 333                             | 36.0 (0.6)                                |
| 1400      | 280                  | 333                             | 50.4 (0.8)                                |
| 1600      | 320                  | 333                             | 57.6 (1.0)                                |
| 2000      | 400                  | 333                             | 72.1 (1.2)                                |
| 2400      | 480                  | 333                             | 86.4 (1.4)                                |
| 3000      | 600                  | 333                             | 108.1 (1.8)                               |
| 5400*     | 1080                 | 333                             | 194.6 (3.2)                               |

\*To be given in divided dose.

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

These dosing rates apply to patients  $\geq 50$  kg; for patients  $< 50$  kg, please refer to the pharmacy manual.

Beginning on Day 463 for patients in Cohort 2, Day 477 for patients in Cohorts 3, and Day 533 for patients in Cohort 1, patients will switch from their current dose regimen to a q8w, weight-based regimen, as shown in [Table 15](#). The dose regimen will not change for patients in Cohort 4.

**Table 15: Weight-based Dosing Reference Chart for 10 mg/mL ALXN1210 Formulation Dose Preparation Beginning on Day 463 (Cohort 2), Day 477 (Cohort 3), and Day 533 (Cohort 1)**

| Body Weight (kg) <sup>a</sup> | Dose (mg) | ALXN1210 Volume (mL) | Total Volume (mL) | Maximum Infusion Rate (mL/hr) | Minimum Infusion Duration in minutes (hr) |
|-------------------------------|-----------|----------------------|-------------------|-------------------------------|---|
| $\geq 40$ to $< 60$           | 3000      | 300                  | 600               | 250                           | 140 (2.4)                                 |
| $\geq 60$ to $< 100$          | 3300      | 330                  | 660               | 330                           | 120 (2.0)                                 |
| $\geq 100$                    | 3600      | 360                  | 720               | 328                           | 132 (2.2)                                 |

Note: For patients weighing  $< 40$  kg, please see Pharmacy Manual.

<sup>a</sup> 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.

Beginning on Day 953 for patients in Cohort 4, Day 981 for patients in Cohort 3, Day 1023 for patients in Cohort 2, and Day 1037 for patients in Cohort 1, patients will switch from the 10 mg/mL ALXN1210 unit dose formulation to the 100 mg/mL ALXN1210 unit dose formulation ([Table 16](#)), while remaining on their current dose regimen.

**Table 16: Dosing Reference Chart for 100 mg/mL ALXN1210 Formulation Dose Preparation**

| Dose (mg) | ALXN1210 Volume (mL) | Total Volume (mL) | Maximum Infusion Rate (mL/hour) | Minimum Infusion Duration minutes (hours) |
|-----------|----------------------|-------------------|---------------------------------|---|
| 3000      | 30                   | 60                | 65                              | 55 (0.92)                                 |
| 3300      | 33                   | 66                | 98                              | 40 (0.67)                                 |
| 3600      | 36                   | 72                | 144                             | 30 (0.50)                                 |
| 5400      | 54                   | 108               | 67                              | 95 (1.6)                                  |

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

These dosing rates apply to patients  $\geq 50$  kg; for patients  $< 50$  kg, please refer to the Pharmacy Manual.

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

#### 10.4.2. In-use Shelf Life

ALXN1210 will be diluted with 0.9% sodium chloride injection (country-specific pharmacopeia) before administration (dosing solution). The dosing solution is stable for 6 hours at room temperature 15°C to 25°C (59°F to 77°F) or for 24 hours when refrigerated at 2°C to 8°C (36°F to 46°F). The expiration date and time of the dosing solution is calculated from breach of the first vial. The dose must be administered within the expiration date and time.

#### 10.5. Study Drug Administration

All doses of ALXN1210 will be administered by IV infusion using a programmable IV infusion pump and IV sets with in-line filters. Infusion rates are presented in [Section 10.4.1](#). Infusion volume and duration and further information regarding the preparation and administration of study drug are provided in the Pharmacy Manual.

During the Induction and Maintenance Periods (up to Day 253), patients will remain seated or semi-reclined for the duration of ALXN1210 administration and remain in the clinic for an additional 2 hours for safety observations.

Time of dosing ( $t = 0$ ) will be defined as ALXN1210 start of infusion. All procedures will be performed in relation to SOI or EOI as described in the Schedules of Assessments ([Section 7](#)).

#### 10.6. Study Drug Accountability

The study site must maintain accurate records demonstrating dates and amount of study drug received from Alexion, to whom dispensed (patient-by-patient accounting), and accounts of any study drug accidentally or deliberately destroyed.

Accountability logs will be provided to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensation, and disposition of the study drug.

The study monitor will examine the inventory during the study. Accountability records must be readily available and may be subject to regulatory authority review by the local regulatory agency, or an independent auditor's inspection, at any time.

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 site pharmacy standard operating procedures for clinical study drugs. At the end of the study, a

final reconciliation must be made between the amount of study drug supplied, dispensed, and subsequently destroyed or returned to Alexion.

A written explanation will be provided for any discrepancies. After reconciliation, the Investigator must destroy or return to Alexion all unused vials of study drug as instructed by Alexion.

Refer to the Pharmacy Manual for detailed instructions on receipt, storage, preparation, administration, destruction, and return of study drug.

### **10.7. Study Drug Handling and Disposal**

At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all remaining study drug inventory will be reconciled and retained or destroyed according to applicable provincial and federal regulations.

For handling instructions, please refer to the Pharmacy Manual.

## 11. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

### 11.1. Blood Sample Collection

The total volume of blood collected per patient for clinical laboratory, PK, PD, and immunogenicity assessments will not exceed 300 mL in any 16-week period.

Please refer to the Laboratory Study Manual for details on sample collection, including blood volume requirements.

After administration of ALXN1210, blood samples for determination of serum ALXN1210 concentrations will be collected at the time points indicated in the Schedule of Assessments (Section 7), with the actual blood sampling dates and times being recorded and used in PK calculations. The timing of PK sample collection may be altered based on initial PK results to ensure appropriate PK monitoring. The number of PK sampling time points for any given patient will not exceed the currently planned number of time points.

Serum concentrations of ALXN1210 and blood samples for analyses of C5 levels (total and free), cRBC hemolysis, and quantitative measures of C5 activation will be collected at the time points specified in (Table 17). Serum samples will be stored for additional PK/PD analyses.

**Table 17: Collection Time Points for Serum Concentrations of ALXN1210 and Analysis of Hemolytic Activity**

| Cohort | Period    | Dose Number and Study Day   | Collection Windows  |
|--------|-----------|---|---|
| 1      | Treatment | Dose 1 on Day 1<br>Dose 2 on Day 15   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 22 (<math>\pm 1</math> day)</li> </ul>  |
|        |           | Doses 3 to 11 on Days 29, 57, 85, 113, 141, 169, 197, 225, and 253  | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 43 (<math>\pm 1</math> day)</li> <li>• Days 127 and 211 (<math>\pm 2</math> days)</li> <li>• Day 253 (up to 0.5 hour before Dose 11)</li> </ul>           |
|        | Extension | Doses 14, 19, 22, 25, 27, 28, 29, 30, 31, 33, 35, 37, 39, 41, 43, 45, and 47 on Days 337, 477, 645, 813, 925, 981, 1037, 1093, 1149, 1261, 1373, 1485, 1597, 1709, 1821, 1933, and 2045 | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• When a patient discontinues the study or at the last study visit (Day 2157)</li> </ul>  |
| 2      | Treatment | Dose 1 on Day 1<br>Dose 2 on Day 22   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 29 (<math>\pm 1</math> day)</li> </ul>  |
|        |           | Doses 3 to 8 on Days 43, 85, 127, 169, 211, and 253   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 57 (<math>\pm 1</math> day)</li> <li>• Days 113, 141, 197, and 225 (<math>\pm 2</math> days)</li> <li>• Day 253 (up to 0.5 hour before Dose 8)</li> </ul> |

| Cohort | Period    | Dose Number and Study Day   | Collection Windows   |
|--------|-----------|---|--|
|        | Extension | Doses 10, 14, 17, 20, 22, 23, 24, 25, 26, 28, 30, 32, 34, 36, 38, 40, and 42 on Days 337, 519, 687, 855, 967, 1023, 1079, 1135, 1191, 1303, 1415, 1527, 1639, 1751, 1863, 1975, and 2087        | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• When a patient discontinues the study or at the last study visit (Day 2143)</li> </ul>   |
| 3      | Treatment | Dose 1 on Day 1<br>Dose 2 on Day 15   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Days 22 (<math>\pm 1</math> day)</li> </ul>  |
|        |           | Doses 3 to 7 on Days 29, 85, 141, 197, and 253  | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Days 43 and 57 (<math>\pm 1</math> day)</li> <li>• Days 113, 127, 169, 211, and 225 (<math>\pm 2</math> days)</li> <li>• Day 253 (up to 0.5 hour before Dose 7)</li> </ul> |
|        | Extension | Doses 8, 11, 14, 16, 18, 19, 20, 21, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40 on Days 309, 477, 645, 757, 869, 925, 981, 1037, 1093, 1205, 1317, 1429, 1541, 1653, 1765, 1877, 1989, and 2101 | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• When a patient discontinues the study or at the last study visit (Day 2157)</li> </ul>   |
| 4      | Treatment | Dose 1 on Day 1   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 4 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 15 (<math>\pm 1</math> day)</li> </ul>   |
|        |           | Doses 2 to 4 on Days 29, 113, and 197   | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• EOI (up to 0.5 hour after)</li> <li>• 6 hours post-SOI (<math>\pm 1</math> hour)</li> <li>• Day 57 (<math>\pm 1</math> day)</li> <li>• Days 141 and 225 (<math>\pm 2</math> days)</li> <li>• Day 253</li> </ul>  |
|        | Extension | Doses 5, 7, 9, 11, 12, 13, 14, 16, 18, 20, 22, 24, and 26 on Days 281, 449, 617, 785, 869, 953, 1037, 1205, 1373, 1541, 1709, 1877, and 2045  | <ul style="list-style-type: none"> <li>• Predose (up to 0.5 hour before)</li> <li>• When a patient discontinues the study or at the last study visit (Day 2129)</li> </ul>   |

Abbreviations: EOI = end of infusion; SOI = start of infusion

## 11.2. PK/PD Sample Analysis

Samples for PK/PD analysis should not be drawn from the same arm as the infusion on dosing days. Detailed instructions on the procedures for collection, processing, storage, and shipment of blood samples for PK and PD analyses will be provided in the Laboratory Study Manual. All sample analysis will be performed by Alexion or designee.



## 12. IMMUNOGENICITY ASSESSMENTS

Blood samples for the analyses of ADA to ALXN1210 will be collected at the time points specified in [Table 18](#).

**Table 18: Collection Time Points for Serum Samples for Immunogenicity Analyses of Antidrug Antibodies to ALXN1210**

|          |   |
|----------|---|
| Cohort 1 | Predose on Days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, 253, 337, 477, 645, 813, 925, 981, 1037, 1093, 1149, 1261, 1373, 1485, 1597, 1709, 1821, 1933, 2045, and 2157 or ET |
| Cohort 2 | Predose on Days 1, 22, 43, 85, 127, 169, 211, 253, 337, 519, 687, 855, 967, 1023, 1079, 1135, 1191, 1303, 1415, 1527, 1639, 1751, 1863, 1975, 2087, and 2143 or ET              |
| Cohort 3 | Predose on Days 1, 15, 29, 85, 141, 197, 253, 309, 477, 645, 757, 869, 925, 981, 1037, 1093, 1205, 1317, 1429, 1541, 1653, 1765, 1877, 1989, 2101, and 2157 or ET               |
| Cohort 4 | Predose on Days 1, 29, 113, 197, 281, 449, 617, 785, 869, 953, 1037, 1205, 1373, 1541, 1709, 1877, 2045, and 2129 or ET   |

<sup>1</sup> This is not a dosing day, therefore collection can occur at any time.

### 12.1. Immunogenicity Sample Analysis

Please refer to the Laboratory Study Manual for time windows for collection and detailed instructions for collecting, processing, storing, and shipping blood samples for immunogenicity analysis.

The total volume of blood collected per patient for clinical laboratory, PK, PD, and immunogenicity assessments will not exceed 300 mL in any 16-week period. All sample analyses will be performed by Alexion or designee.

### **13. ASSESSMENTS OF EFFICACY**

The following assessments will be performed during the study to evaluate the efficacy of ALXN1210 therapy.

#### **13.1. Blood Samples for Pharmacodynamic Analysis**

##### **13.1.1. Lactate Dehydrogenase**

Lactate dehydrogenase levels will be analyzed at the time points specified in the Schedule of Assessments (Section 7).

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

##### **13.1.2. Biomarkers of PNH**

A serum PD panel will be collected for analyses of C5 levels (total and free) and cRBC hemolysis at the time points specified in Table 17. In addition, serum samples will be stored for potential additional analyses.

##### **13.1.3. Hemolysis-related Hematological Parameters**

Hemolysis-related hematological parameters will be assessed by measurements of free hemoglobin, haptoglobin, reticulocyte count, PNH clone size (%), and D-dimer.

Hematology assessments will be obtained at the time points specified in the Schedule of Assessments (Section 7).

#### **13.2. Quality of Life**

The FACIT-Fatigue scale, version 4, is a collection of QoL questionnaires targeted to the management of fatigue symptoms due to a chronic illness.

The EORTC Quality of Life Questionnaire-Core 30 Scale, Version 3.0, is a questionnaire developed to assess the QoL of cancer patients.

Both scales will be administered at the time points specified in the Schedule of Assessments (Section 7). Sample FACIT-Fatigue and EORTC scales will be provided in the Study Manual.

#### **13.3. PNH Symptomatology**

The Investigator will assess patients for the following events: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. Symptoms of disease burden will be captured through the QoL questionnaire.

Investigator assessment of clinical symptoms related to PNH will be made at the time points specified in the Schedule of Assessments (Section 7).

### **13.4. Exploratory Markers of PNH**

Markers of PNH symptoms and comorbidities (ie, chronic kidney disease by urinary spot albumin:creatinine ratio and eGFR, and BNP for pulmonary hypertension) will be evaluated in the study as exploratory efficacy endpoints. Evaluation for changes in kidney function will be based on Investigator assessment and laboratory results of serum and urinary creatinine and eGFR. The estimated glomerular filtration rate will be calculated using the Modification of Diet in Renal Disease formula at the same time blood is drawn for chemistry assessments; specified in the Schedule of Assessments ([Section 7](#)). In addition, total serum LDH levels may be further analyzed as individual LDH isozymes (LDH1-5).

### **13.5. Major Adverse Vascular Events**

Major adverse vascular events (MAVEs) will be assessed as part of the planned evaluation for AEs as described in [Section 15](#). The definition of MAVE is provided below.

The description of event, location, method of diagnosis (magnetic resonance imaging, ultrasound, angiogram, or other), date of diagnosis and date resolved (or ongoing) will be collected in the eCRF as part of the patient's medical history and during the study.

A MAVE can only be one of the following events:

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

## **14. ASSESSMENT OF SAFETY**

### **14.1. Safety Parameters**

Patients will meet with the Investigator or designee to discuss the potential safety risks of ALXN1210 and to allow for the Investigator to address any of the patient's safety concerns at the time points specified in the Schedule of Assessments ([Section 7](#)).

Collection of AEs, including SAEs and MAVEs, will be monitored from the time informed consent is obtained until study completion. Investigators are instructed to follow any AEs through to their conclusion; in the event of patient discontinuation from the study, AE monitoring should continue through the last study visit if possible.

Clinical and laboratory assessments will be performed to assess ALXN1210. Timing of the assessments is specified in the Schedule of Assessments ([Section 7](#)). Any abnormal results should be followed until resolution or stabilization.

#### **14.1.1. Demographic/Medical History**

A review of demographic parameters, including age, gender, race, and ethnicity will be performed, as specified in the Schedule of Assessments ([Section 7](#)). A complete medical history will be taken and documented.

#### **14.1.2. Weight and Height**

Weight, height, and body mass index will be recorded, as described in the Schedule of Assessments ([Section 7](#)).

#### **14.1.3. Physical Examination**

A physical examination assessing general appearance, skin, head/eyes/ears/nose/throat, neck, lymph nodes, chest, heart, abdominal cavity, limbs, central nervous system, and musculoskeletal will be performed at the time points specified in the Schedule of Assessments ([Section 7](#)). An abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and subject symptoms.

#### **14.1.4. Vital Signs**

Vital sign measurements will be taken after the patient has been resting in the supine position for at least 5 minutes, and will include oral or tympanic temperature (°C), respiratory rate, supine blood pressure, and pulse rate. The timing of vital sign assessments is provided in the Schedule of Assessments ([Section 7](#)). Out-of-range blood pressure or pulse measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements will be recorded as AEs.

#### **14.1.5. Electrocardiogram**

The ECG will be obtained after the patient has been resting in a supine position for at least 5 minutes. A triplicate 12-lead ECG will be obtained at screening, prior to the first dose of ALXN1210 on Day 1, and at the end of study (Day 2157 for Cohorts 1 and 3, Day 2143 for

Cohort 2, and Day 2129 for Cohort 4) or Early Termination visit. A single ECG will be obtained at the other time points specified in the Schedule of Assessments ([Section 7](#)).

Heart rate, PR, QRS, RR (when available), and QT will be measured, and corrected QTcF intervals (Fridericia's formula) will be calculated.

#### **14.1.6. Laboratory Assessments**

Blood samples for analysis of hematology, clinical chemistry, coagulation, BNP, urinalysis/urine chemistry, and virus serology parameters will be collected as specified in the Schedule of Assessments ([Section 7](#)). A list of parameters is provided in [Appendix A](#).

Abnormal results should be followed, as appropriate. Handling and shipping of clinical laboratory samples will be outlined in the Laboratory Study Manual. A central laboratory will be used to evaluate all laboratory assessments. If a screening laboratory sample is cancelled by the central laboratory due to hemoglobin interference in a grossly hemolyzed specimen, a local retest may be performed and the results entered into the EDC system. Any on-treatment laboratory samples cancelled centrally will be reviewed by Alexion Medical to determine if local retesting is needed. Sites will be notified if local laboratory retesting is required during a patient's treatment.

##### **14.1.6.1. Pregnancy Screen**

Serum pregnancy testing (beta human chorionic gonadotropin) will be performed in all female patients of childbearing potential at screening and end of study/Early Termination. Urine pregnancy testing (with a minimum human chorionic gonadotropin detection limit of 25 IU/L) will be performed at the time points specified in the Schedule of Assessments ([Section 7](#)).

##### **14.1.6.2. Hematology**

Blood will be analyzed for the parameters listed in [Appendix A](#) and will be performed at the time points specified in the Schedule of Assessments ([Section 7](#)).

##### **14.1.6.3. Blood Chemistry**

Blood samples will be analyzed for the parameters listed in [Appendix A](#). Considering that indirect bilirubin is calculated from total and direct bilirubin values, indirect bilirubin results will not be available if direct bilirubin is below the limit of quantification.

Serum follicle-stimulating hormone level and estradiol concentrations will be measured at least twice 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](#)).

##### **14.1.6.4. Coagulation**

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

Coagulation assessments will be performed at the time points specified in the Schedule of Assessments ([Section 7](#)).

#### **14.1.6.5. Urinalysis and Urine Chemistry**

Urine samples will be analyzed for the parameters listed in [Appendix A](#).

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

Urinalysis and urine chemistry assessments will be performed at the time points specified in the Schedule of Assessments ([Section 7](#)).

#### **14.1.6.6. Virus Serology**

Blood samples will be analyzed for the parameters listed in [Appendix A](#) and will be performed at the time points specified in the Schedule of Assessments ([Section 7](#)).

#### **14.1.6.7. Brain Natriuretic Protein**

Blood samples for BNP analysis will be performed at the time points specified in the Schedule of Assessments ([Section 7](#)).

#### **14.1.7. Infusion Site Reaction**

Patients will be evaluated for infusion site reactions at the time points specified in the Schedule of Assessments ([Section 7](#)). Infusion site reactions will be recorded as an AE using the appropriate coding terms.

An induration or reaction of < 10 mm will not be listed as an AE unless it persists for more than 24 hours, at which time, the patient must inform the study staff immediately and proceed to the nearest hospital emergency department. Pain at the site of infusion will be assessed using a 100 mm visual analog scale (VAS). The VAS should be completed as soon as practical after completion of the infusion.

## 15. ADVERSE EVENT MANAGEMENT

The Investigator is responsible for detecting, assessing, documenting and reporting all AEs. All AEs will be recorded from the signing of informed consent until study completion. There is no time limit for SAEs that are considered causally related.

All observed or volunteered AEs, regardless of causal relationship, must be reported and recorded in the eCRF. Adverse events reported by the patient and/or parent or legal guardian, and/or identified in response to an open-ended question from study personnel, or revealed by observation, physical examination, or other study procedures must be collected and recorded.

### 15.1. Definition of an Adverse Event

An AE is defined as any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or procedure, whether or not considered related to the medicinal product or procedure, which occurs during the course of the clinical study.

Exacerbations of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition, are all to be considered AEs.

Abnormal test findings may be considered AEs. If an abnormal laboratory value is identified, Investigators are strongly encouraged to report a diagnosis, or a sign or symptom, rather than an isolated abnormal test value. An abnormal test finding should be documented as an AE if **any of the following** conditions are met:

- Is associated with a sign or symptom
- Requires additional diagnostic testing (repeat tests are not considered additional testing)
- Requires a medical or surgical intervention
- Leads to a change in study dosing outside of the protocol-defined dosing or leads to discontinuation from the study
- Requires significant additional treatment
- Does not meet any of the conditions above; however, the Investigator or Sponsor considers the result clinically significant or meeting the definition of an AE.

This definition also includes the signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug misuse
- Drug interactions
- Extravasation
- Exposure during pregnancy

- Exposure via breastfeeding
- Medication error
- Occupational exposure

An AE does not necessarily include the following:

- Medical or surgical procedures (eg, surgery, endoscopies, tooth extraction, transfusion); the condition that leads to the procedure is the AE (eg, laparoscopic cholecystectomy is the procedure or treatment for an SAE of necrotic gall bladder)
- Pre-existing diseases or conditions present or detected prior to the screening evaluation that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery if planned prior to the start of the study, social and/or convenience admissions)

## 15.2. Definition of a Serious Adverse Event

Any AE that fulfills any one of the criteria listed below must be recorded as an SAE.

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

- Results in death
- Is life threatening<sup>a</sup>
- Requires hospitalization or prolongation of hospitalization<sup>b</sup>. Hospitalization does not necessarily include the following:
  - Rehabilitation/hospice/nursing facility
  - Emergency room visit less than 24 hours
  - Elective or preplanned admission/surgery/day surgery
  - Protocol-specified admission
  - Admission for a pre-existing condition not associated with either a new AE or with worsening of a pre-existing AE
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event<sup>c</sup>

a The term “life threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

b Hospitalization requires inpatient admission or prolongation of an existing hospitalization. The AEs that are associated with hospitalization or prolongation of hospitalization are considered SAEs.

c Important medical event: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening, or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also



usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Severity and seriousness must be differentiated. Severity describes the intensity of an AE, while the term seriousness refers to an AE that has met the criteria for an SAE, as described above.

### **15.3. Severity Assessments**

All AEs will be graded according to criteria from CTCAE v4.03, published 14 June 2010.

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

Changes in the severity of an AE should be documented to allow an assessment of the AE duration at each level of intensity to be evaluated. Adverse events characterized as intermittent require documentation of onset and duration of each episode, if the severity of the intermittent event changes.

### **15.4. Causality Assessment**

An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. Definitions for causality assessments are as follows:

- Not related (unrelated): This relationship suggests that there is no association between the investigational product and the reported event.
- Unlikely related: This relationship 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 the AE cannot be excluded with complete confidence.
- Possibly related: This relationship 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: This relationship suggests that a reasonable temporal sequence of the event with the investigational product administration exists, as well as the likely 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.

### **15.5. Outcome**

For all AEs, regardless of causal relationships, the Investigator must follow up regarding the outcome of the event until the event or sequelae either resolve or stabilize. Adverse event outcomes must be recorded in the eCRF and on any additional forms, as appropriate.

If a patient experiences an SAE with an outcome of death, the following procedures are to be performed:

- The SAE resulting in death should have an outcome documented as death/fatal, with an end date being the date of death.
- If the patient had additional AE/SAEs that were ongoing at the time of death, these events would be documented as ongoing with no end date.
- Only 1 event should have an outcome of death/fatal, unless an autopsy report or Investigator states otherwise.

### **15.6. Recording Adverse Events**

All observed or volunteered AEs, regardless of dose level or causal relationship, must be reported as described in [Section 15](#).

For all AEs, the Investigator must do the following:

- Determine the AE outcome
- Determine if the event meets criteria for an SAE
- Assess AE severity
- Determine AE causality

Adverse events must be documented in clear, unambiguous medical terms. Study personnel are advised not to use abbreviations or acronyms.

For each AE, record in the eCRF only the diagnosis; do not report the characteristic signs and symptoms of the diagnosis as additional AEs.

If a diagnosis is not available, record each sign and symptom as an AE; when a diagnosis becomes available, study personnel are to update the source document and the eCRF with the relevant diagnosis only.

For medical or surgical procedures (eg, surgery, endoscopies, tooth extraction, transfusion), the condition/diagnosis that leads to the procedure should be recorded as the AE (eg, laparoscopic cholecystectomy is the procedure or treatment for an SAE of necrotic gall bladder).

All AEs that later increase in frequency and or severity (medical and scientific judgment should be exercised by the Investigator) will be considered new AEs, and will be recorded on a new line in the eCRF.

Withdrawal due to an AE or SAE must be clearly differentiated from withdrawal due to other reasons.

## **15.7. Reporting Serious Adverse Event(s) to the Sponsor**

All AEs must be assessed by the Investigator to determine if they meet criteria for an SAE. All SAEs must be reported to Alexion or designee immediately, or within 24 hours of the Investigator and/or study site staff becoming aware of the event, regardless of the presumed relationship to ALXN1210.

The Investigator must verify the accuracy of the information recorded on the SAE pages of the eCRF with the corresponding source documents, and submit the SAE electronically via the Safety Gateway. In the event that the eCRF is not available or the Investigator is unable to submit the SAE electronically, the Investigator must complete the Safety Gateway Contingency form, sign and date the paper SAE pages, and send a copy via e-mail or fax to the contact information provided below:

E-mail: [ClinicalSAE@alexion.com](mailto:ClinicalSAE@alexion.com)

Fax: + 1 203.439.9347

Additional follow-up information, if required or available, should be entered into the eCRF and sent to the Sponsor or designee within 24 hours of the Investigator or study site staff becoming aware of this additional information. These reporting timelines should be followed for all initial and follow-up SAEs.

For all SAEs, the Investigator must provide the following:

- Appropriate and requested follow-up information in the time frame detailed above
- Causality of the serious event(s)
- Outcome of the serious event(s)
- Medical records and laboratory/diagnostic information

## **15.8. Exposure During Pregnancy and Lactation**

Pregnancy data will be collected during this study for all patients. Exposure during pregnancy, also called 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 followed. If a female patient participating in this study, or a male patient's female partner becomes or is found to be pregnant while being treated or exposed to study drug, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding Form" to Alexion or designee via the same method as SAE reporting. Female patients who become pregnant will be discontinued from dosing, but will continue to be followed for safety where

feasible. Male patients may continue in the study if an accidental pregnancy of their female partner occurs, despite adequate contraception.

The female patient should be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the patient discontinues ALXN1210 treatment or discontinues from the study. When the pregnancy outcome becomes known, the pregnancy reporting form should be updated and returned to Alexion or designee. If additional follow-up is required, the Investigator will be requested to provide the information.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that investigational product may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs, and many may meet criteria for an SAE. Complications of pregnancy and abnormal outcomes of pregnancy, such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly, would meet the criteria of an SAE and therefore should be reported as an SAE. Elective abortions without complications should not be handled as an AE.

Exposure of an infant to an Alexion product during breastfeeding should also be reported on the "Pregnancy Reporting and Outcome/Breast Feeding Form." Any AEs an infant experiences following breastfeeding are to be reported to Alexion or designee.

## **15.9. Reporting Requirements**

This protocol will use the current Investigator's Brochure as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by Alexion, based on the Reference Safety Document.

### **15.9.1. Sponsor**

The Sponsor or legal representative is responsible for notifying relevant regulatory authorities of SAEs meeting the reporting criteria.

### **15.9.2. Investigator**

The Investigator must fulfill all local regulatory requirements for Investigators conducting clinical studies. It is the Investigator's responsibility to notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all reportable SAEs that occur. Alexion will notify Investigators of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. The Investigator is responsible for notifying the IRB or IEC of these additional SAEs. Adverse events are recorded in the eCRF, and are retrieved by or submitted to the Sponsor at regular monthly intervals, or more frequently during the course of the investigation.

## **16. STATISTICS**

### **16.1. General Considerations**

All data collected in this study will be documented using summary tables, figures, and data listings. For categorical variables, frequencies and percentages will be presented for each cohort, and for the combined cohorts. For continuous variables, descriptive statistics (n, mean, median, SD, minimum, maximum) will be presented for each cohort, and for the combined cohorts.

Descriptive statistics for PK parameters will include the number of observations, mean, SD, coefficient of variance (CV), median, minimum, maximum, geometric mean, and geometric %CV.

A clinical study report will be produced after the end of the Maintenance Period and will include safety, efficacy, immunogenicity, PK, and PD analyses. A final clinical study report will be produced at study completion and will include data on all patients in the study through the end of the Extension Period. Additional analyses may be performed for the 100 mg/mL formulation.

All calculations will be performed by Alexion or its designee. Additional details of statistical analyses will be described in the statistical analysis plan.

### **16.2. Analysis Populations**

The safety population will consist of all patients who receive at least 1 dose of study drug (Safety Set). Patients in this population will be used for the safety analyses.

The full analysis set (FAS) will consist of all patients in the safety population who had a baseline LDH measurement and at least 1 postbaseline LDH measurement. The FAS will be used for all efficacy analyses.

The PK population will consist of all patients who have sufficient serum concentration data to enable the calculation of PK parameters. The PK population will be used for PK summaries.

The immunogenicity population will consist of all patients who have a predose and postdose immunogenicity sample collected.

### **16.3. Sample Size and Power**

A sample size of 20 patients from the combined cohorts will provide approximately 95% power to detect a mean paired difference in LDH from baseline of -40% at Day 253, with an estimated SD of 45%. This is based on a 2-sided paired t-test, with 5% type I error rate. To account for a possible 15% dropout rate and additional patients in screening, up to 26 patients will be enrolled.

### **16.4. Demographics, Baseline Characteristics, and 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 discontinued from the study, along with reason for discontinuation, by cohort. Demographics and baseline characteristics will be summarized for all patients by each cohort and overall.

## 16.5. Safety Analysis

Safety analyses will be performed on the Safety Set, which consists of all patients who receive at least 1 dose of ALXN1210, and will be reported by cohort and overall. Safety analyses will include all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements, and will be presented using descriptive statistics. No inferential statistical analyses are planned on safety parameters. The incidence of treatment-emergent adverse events and SAEs will be summarized by System Organ Class and Preferred Term for each cohort and overall, by severity, and by relationship to ALXN1210. Adverse events will be coded using the Medical Dictionary for Regulatory Activities, Version 18.0 or higher. Serious AEs and AEs resulting in withdrawal from the study will be listed. Patients having multiple AEs within a category (eg, overall, System Organ Class, Preferred Term) will be counted once in that category. For severity tables, a patient's most severe event within a category will be counted.

Changes from baseline in vital signs and laboratory assessments (chemistry, complete blood count with differential, and urinalysis) will be summarized by cohort. Shift tables of clinical laboratory tests using criteria from CTCAE v4.03 will be produced by cohort. Graphical displays will be presented, as appropriate.

The ECG parameters will be measured at the specified time points, including heart rate, PR, RR, QRS, QT, and corrected QTcF intervals. The average of the triplicate ECG readings at the time points collected will be calculated, and changes from pretreatment baseline values will be assessed by cohort.

All concomitant medications will be coded using the World Health Organization Drug Dictionary, and the frequency and percentage of concomitant medications will be summarized.

## 16.6. Efficacy Analysis

Efficacy analyses will be performed on the FAS, which include the Safety Set subset with a baseline and at least 1 postbaseline LDH measurement.

Absolute LDH levels, and the change and percent change from baseline will be summarized at all study visits. Baseline is defined as the average of all available assessments on or prior to the first ALXN1210 infusion. A mixed model for repeated measures (MMRM) with the fixed, categorical effect of visit and fixed, continuous effect of baseline LDH levels as covariates will be fit to test whether changes and percent changes differ from zero at each time point. An unstructured covariance analysis will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion: first-order autoregressive, compound symmetry, and Toeplitz method. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. As a sensitivity analysis, changes and percent changes from baseline will be analyzed, using the Wilcoxon signed-rank test. Graphical displays will be presented, as appropriate.

The percentage of patients with clinical symptoms will be summarized for all study visits.

Changes in hematologic measures will be similarly analyzed using an MMRM and Wilcoxon signed-rank test.

Scoring guidelines for the FACIT-Fatigue and EORTC scales will be used to calculate QoL scores. Changes from baseline in FACIT-Fatigue and EORTC scale scores will be summarized descriptively for all study visits, and analyzed using MMRM and Wilcoxon signed rank test.

Transfusion rates and the incidence rate of MAVEs will be summarized.

## 16.7. Pharmacokinetic Analysis

Individual serum concentration data for ALXN1210-treated patients, with actual sampling dates and times, will be used to derive the PK parameters by noncompartmental analyses, using Phoenix<sup>®</sup> WinNonlin<sup>®</sup> (Pharsight Corporation, St Louis, Missouri) Version 6.3 or higher. The PK samples collected on or after Day 1149 for Cohort 1, Day 1135 for Cohort 2, Day 1093 for Cohort 3, or Day 1121 for Cohort 4 will be stored and may be assayed if considered necessary for the purpose of medical monitoring.

The following PK parameters will be estimated: maximum observed serum concentration ( $C_{max}$ ) after each dose, time to maximum observed serum concentration ( $t_{max}$ ), minimum observed serum concentration ( $C_{min}$ ), the observed serum concentration at the end of the dosage interval  $\tau$  ( $C_{trough}$ ), area under the serum concentration-versus-time curve from time 0 (dosing) to the last quantifiable concentration ( $AUC_t$ ), area under the concentration-versus-time curve from time 0 (dosing) to the end of the dosing interval ( $AUC_\tau$ ), apparent terminal-phase elimination rate constant ( $\lambda_z$ ), terminal elimination half-life ( $t_{1/2}$ ), and, if possible, total clearance (CL) and volume of distribution at steady state ( $V_{ss}$ ). Attainment of steady state and accumulation at steady state also will be determined. Dose proportionality and time linearity in PK parameters may be assessed.

Mean serum ALXN1210 concentrations versus nominal time and individual serum ALXN1210 concentrations versus actual time will be graphically presented. Descriptive statistics (mean, SD, CV, median, minimum, maximum, geometric mean, and geometric %CV) of the serum concentration and PK parameter summaries will be provided, as appropriate.

## 16.8. Pharmacodynamic and Immunogenicity Analyses

The PD effects of ALXN1210 administered IV will be evaluated by assessing changes and percent changes in serum total and/or free C5 concentrations and cRBC hemolysis over time. Assessments of PK-PD relationships may be explored using data from this study or in combination with data from other studies.

Immunogenicity, as measured by ADA, will be summarized in tabular form by treatment.

The PD and ADA samples collected on or after Day 1149 for Cohort 1, Day 1135 for Cohort 2, Day 1093 for Cohort 3, or Day 1121 for Cohort 4 will be stored and may be assayed if considered necessary for the purpose of medical monitoring.

## **17. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **17.1. Study Monitoring**

Before an investigational site can enter a patient into the study, a representative of Alexion (Sponsor) will visit the investigational study site to:

- Determine the adequacy of the facilities;
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or designee.

During the study, a monitor from the Sponsor or the Sponsor's designee will have regular contact with the investigational site, for the following:

- Provide information and support to the Investigator
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRF, and that ALXN1210 accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRF with the patient's medical records, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts)
- Record and report any protocol deviations not previously sent to the Sponsor or designee
- Confirm AEs and SAEs have been properly documented in the eCRF, and confirm any SAEs have been forwarded to the Sponsor or the Sponsor's designee, and those SAEs that meet criteria for reporting have been forwarded to the IRB/IEC

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

### **17.2. Audits and Inspections**

Authorized representatives of the Sponsor or designee, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of an 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, Good Clinical Practice (GCP) guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor or designee immediately if contacted by a regulatory agency about an inspection.



## **18. ETHICS**

### **18.1. Data Monitoring Committee**

An independent DMC comprised of experts in relevant biomedical fields who have no direct relationship with the study will be appointed by the Sponsor. The DMC will review and evaluate the accumulated study data for patient safety and make recommendations on dose escalation, continuing dosing within the cohort, modification, or termination of the study. The DMC will review study information as outlined in the DMC charter, which is maintained separately from the study protocol.

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

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

### **18.2. Ethics Review**

The final study protocol and the final version of the ICF must be approved or given a favorable opinion in writing by an IRB/IEC, as appropriate. The Investigator must submit written approval to the Sponsor or the Sponsor's designee prior to enrolling any patient into the study.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol, in accordance with local regulatory requirements. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any serious adverse drug reactions from any other study conducted with ALXN1210. The Sponsor or the Sponsor's designee will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC, according to local regulations and guidelines.

### **18.3. Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH, GCP, applicable regulatory requirements, and the Alexion policy on bioethics.

### **18.4. Written Informed Consent**

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent form (ICF) must be obtained before conducting any study procedures, and documented in the patient's study record.

The Investigator 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 must be given to the patient.

## **19. DATA HANDLING AND RECORDKEEPING**

### **19.1. Data Collection**

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or the Sponsor's designee may conduct a quality assurance audit. Please see [Section 17.2](#) for more details regarding the audit process.

All required clinical data will be recorded promptly and accurately, electronically into the study electronic data capture (EDC) system, Medidata RAVE. All source documents will be preserved in order to maintain data integrity. The Investigator or designee will assume the responsibility of ensuring completeness, accuracy, and timeliness of the clinical data entry into the EDC system.

At each scheduled monitoring visit, the Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study source documents to ensure the accuracy and completeness of the data contained within the EDC system.

Electronic checks and manual review will be performed to identify any errors or inconsistencies in the data provided in the EDC system. Queries will be raised in the EDC system to the respective study sites, as applicable.

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

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

### **19.2. Inspection of Records**

The Sponsor or the Sponsor's designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

### **19.3. Retention of Records**

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. 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.

## **20. PUBLICATION POLICY**

The terms for publication are outlined in the Clinical Study Agreement, Statement of Agreement, or the Master Clinical Study Agreement. Refer to these documents for further details and information.

## 21. LIST OF REFERENCES

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## **22. APPENDIX**

## APPENDIX A. CLINICAL LABORATORY TESTS

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| <p><b>Chemistry Testing</b></p> <ul style="list-style-type: none"><li>Alanine aminotransferase</li><li>Albumin</li><li>Alkaline phosphatase</li><li>Aspartate aminotransferase</li><li>Bicarbonate</li><li>Blood urea nitrogen</li><li>Chloride</li><li>Creatinine</li><li>Gamma-glutamyltransferase</li><li>Glucose</li><li>Lactate dehydrogenase</li><li>Magnesium</li><li>Phosphorus</li><li>Potassium</li><li>Sodium</li><li>Total bilirubin (direct and indirect)</li><li>Total calcium</li><li>Total protein</li><li>Uric acid</li></ul> <p><b>Hematology Testing</b></p> <ul style="list-style-type: none"><li>Haptoglobin</li><li>Reticulocyte count</li><li>Free hemoglobin</li><li>Hematocrit</li><li>Hemoglobin</li><li>Mean corpuscular hemoglobin</li><li>Platelet count</li><li>Red blood cell distribution width</li><li>Red blood cell mean corpuscular volume</li><li>Red blood cell count</li><li>White blood cell count</li><li>White blood cell differential</li></ul> | <p><b>Urinalysis</b></p> <ul style="list-style-type: none"><li>Albumin</li><li>Appearance</li><li>Bilirubin</li><li>Blood</li><li>Creatinine</li><li>Glucose</li><li>Ketone</li><li>Nitrite</li><li>pH</li><li>Protein</li><li>Specific gravity</li><li>Urobilinogen</li></ul> <p><b>Coagulation Panel</b></p> <ul style="list-style-type: none"><li>International normalized ratio</li><li>Prothrombin time</li><li>Partial thromboplastin time</li><li>D-dimer</li></ul> <p><b>Virus Serology</b></p> <ul style="list-style-type: none"><li>Hepatitis B core antibody (HBcAb)</li><li>Hepatitis B surface antigen (HBsAg)</li><li>Hepatitis B surface antibody (HBsAb)</li><li>Hepatitis C virus antibody</li><li>HIV-1</li><li>HIV-2</li></ul> <p><b>Other</b></p> <ul style="list-style-type: none"><li>Serum follicle-stimulating hormone (postmenopausal female patients <i>only</i>)</li><li>Brain natriuretic peptide</li><li>Estradiol concentrations (postmenopausal female patients <i>only</i>)</li><li>Beta human chorionic gonadotropin (female patients <i>only</i>)</li><li>PNH clone size (granulocyte or red blood cell assay at screening, red blood cell <i>only</i> at all other time points)</li></ul> |
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