A Phase 1, Open-label, Single Ascending and Multiple Set Dose Study to Evaluate the Safety, Tolerability, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of ALXN1210 Administered Intravenously to Healthy Japanese Subjects

Unique Protocol ID:	ALXN1210-HV-104
NCT Number:	NCT05288816
EudraCT Number:	2015-005468-40
Date of Protocol:	24 August 2016

ALXN1210

ALXN1210-HV-104

A PHASE 1, OPEN-LABEL, SINGLE ASCENDING AND MULTIPLE SET DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ALXN1210 ADMINISTERED INTRAVENOUSLY TO HEALTHY JAPANESE SUBJECTS

Sponsor	Alexion Pharmaceuticals, Inc. 100 College Street New Haven, CT 06510 United States
Sponsor Contact:	PPD Associate Director, Clinical Project Lead, Global Clinical Operations Alexion Pharmaceuticals, Inc. 33 Hayden Avenue Lexington, MA 02421 USA Telephone: PPD Email: PPD
Medical Monitor:	PPD Senior Medical Director, Research Alexion Pharmaceuticals, Inc. 33 Hayden Avenue Lexington, MA 02421 USA Telephone: PPD Email: PPD

Date of Original Protocol:	12 January 2016
Date of Amendment 1:	24 August 2016
IND Number:	128367
EudraCT Number:	2015-005468-40

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ALXN1210. I have read the ALNX1210-HV-104 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to conduct the study in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH)/Good Clinical Practices (GCP) and applicable to regulatory requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTRACT RESEARCH ORGANIZATION:

Richmond Pharmacology Ltd.
St George's University of London
Cranmer Terrace
Tooting
London
SWQ17 ORE
Telephone: PPD

SPONSOR'S SIGNATURE PAGE

PROTOCOL TITLE: A Phase 1, Open-Label, Single Ascending and Multiple Set Dose Study to Evaluate the Safety, Tolerability, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of ALXN1210 Administered Intravenously to Healthy Japanese Subjects

PROTOCOL NUMBER: ALXN1210-HV-104

PPD

Senior Medical Director, Research
Alexion Pharmaceuticals, Inc.
33 Hayden Avenue
Lexington, MA 02421 USA

24-AUG-2016

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Clinical Project Lead	PPD Associate Director, Clinical Project Lead, Global Clinical Operations	Alexion Pharmaceuticals, Inc. 33 Hayden Avenue Lexington, MA 02421 USA Telephone: PPD Mobile: PPD Email: PPD
Responsible Physician	PPD Senior Medical Director, Research	Alexion Pharmaceuticals, Inc. 33 Hayden Avenue Lexington, MA 02421 USA Telephone: PPD Mobile: PPD Email: PPD
24-Hour Emergency Contact	PPD Senior Medical Director, Research	Alexion Pharmaceuticals, Inc. 33 Hayden Avenue Lexington, MA 02421 USA Telephone: PPD Mobile: PPD Email: PPD

2. SYNOPSIS

Name of Sponsor/Company:
Alexion Pharmaceuticals, Inc.

Name of Investigational Product:
ALXN1210

Name of Active Ingredient:
ALXN1210

Title of Study: A Phase 1, Open-Label, Single Ascending and Multiple Set Dose Study to Evaluate the Safety, Tolerability, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of ALXN1210 Administered Intravenously to Healthy Japanese Subjects
Protocol No. ALXN1210-HV-104
EudraCT number: 2015-005468-40

Study center(s):
This study will be conducted by Richmond Pharmacology Ltd. at the following facility:
St George's University of London
Cranmer Terrace
Tooting
London
SWQ17 ORE
Telephone: PPD

Studied period (years):	**Phase of development:** 1
Estimated date first subject enrolled: April 2016 Estimated date last subject completed: April 2017	

Study Rationale:
The purpose of the study is to evaluate the safety, tolerability, immunogenicity, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple doses of ALXN1210 in healthy Japanese subjects. Data from this study will be used to determine whether results obtained in Japanese subjects are comparable to results obtained in non-Japanese subjects.

ALXN1210 is a humanized monoclonal antibody (mAb) that inhibits terminal complement. It specifically binds the terminal complement protein C5 thereby inhibiting its cleavage to C5a and C5b during complement activation. This inhibition not only prevents the release of the pro-inflammatory mediator C5a, but also inhibits the formation of the cytolytic pore C5b-9. The mechanism of action described here provides a mechanistic rationale for the potential therapeutic use of ALXN1210 in diseases where complement activation is involved eg, paroxysmal nocturnal hemoglobinuria (PNH) or atypical hemolytic uremic syndrome (aHUS).

ALXN1210 has been administered safely to healthy subjects in single intravenous (IV) doses of 200 mg and 400 mg in a single ascending dose (SAD) study (Study ALXN1210-HV-101, N = 14) and in multiple IV doses of 400 mg and 800 mg on an every 4 week (Q4W) regimen in an ongoing multiple ascending dose (MAD) study (Study ALXN1210-HV-102, N = 16). The starting doses of ALXN1210 in these two studies were selected to assess safety in healthy volunteers but also to have measurable pharmacologic activity (eg, inhibition of complement activation) based on the therapeutic exposure required with eculizumab. No safety concerns have been identified in either of the Phase 1 studies, both of which were randomized, blinded, and placebo controlled. In the completed Study ALXN1210-HV-101 (SAD), no serious adverse drug reactions, treatment discontinuations, or deaths were reported.

Persons exposed to a terminal complement inhibitor for C5 are known to be at an increased risk of infections caused by encapsulated organisms, in particular *Neisseria meningitidis*. Subjects might be at risk of infection by uncommon serogroups (particularly A, C, Y, W135, and X), although meningococcal disease due to any serogroup may occur. To address this risk, all subjects in this study will be vaccinated against *N meningitidis* with tetravalent meningococcal conjugate vaccine (MCV4), serogroup B meningococcal vaccine, and prophylactic antibiotic treatment will be administered as an additional precaution in this study. A serum bactericidal antibody (SBA) titer

against meningococcus Group A, C, W135, and Y will be performed at screening to exclude subjects without an immune response. Unless the PI and sponsor agree to an alternative regimen, all subjects will take prophylactic antibiotics (oral penicillin V 500 mg twice daily) until complement activity has normalized (as determined by CH50 assay).

Objectives:

Primary:

- To evaluate the safety and tolerability of single and multiple doses of ALXN1210 following IV administration to healthy Japanese subjects.

Secondary:

- To investigate the immunogenicity of ALXN1210 in healthy Japanese subjects.
- To characterize the PK of single and multiple doses of ALXN1210 in healthy Japanese subjects.
- To evaluate the PD effects of ALXN1210 as assessed by total and free C5 concentrations and chicken red blood cell (cRBC) hemolysis in healthy Japanese subjects.

Methodology:

This is a Phase 1, open-label, single ascending and multiple set dose study designed to evaluate the safety, tolerability, immunogenicity, PK, and PD of ALXN1210 in healthy Japanese subjects.

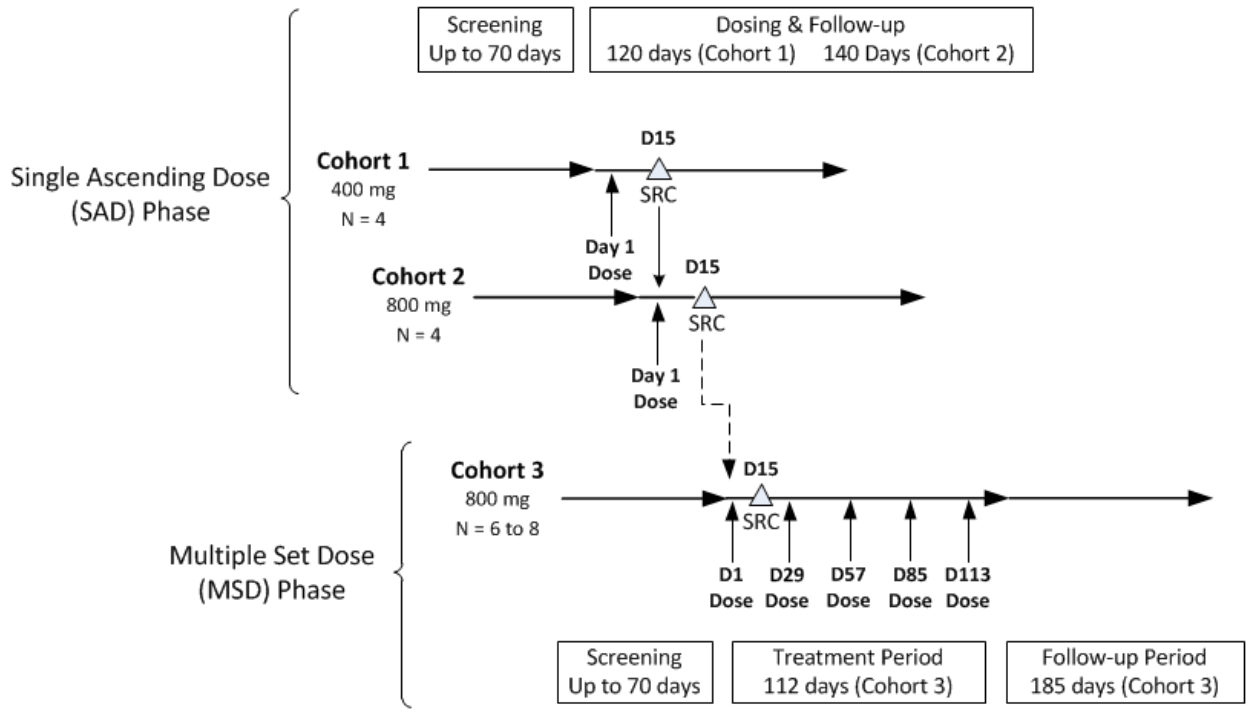
A total of 3 cohorts and up to 16 subjects are planned for evaluation. The cohorts will be enrolled sequentially and all subjects will receive IV ALXN1210:

- Cohort 1, 400 mg single dose (N = 4)
- Cohort 2, 800 mg single dose (N = 4)
- Cohort 3, 800 mg Q4W for a total of 5 doses (N = 6 to 8)

A Safety Review Committee (SRC) will review the available clinical and safety data at the following points in the study to determine whether dose escalation or continuation may proceed: 1) after the last subject in the 400 mg cohort (Cohort 1) has completed Day 15 to determine if dose escalation to 800 mg may proceed (Cohort 2); 2) after the last subject in the 800 mg cohort (Cohort 2) has completed Day 15 to determine if repeat dosing with 800 mg may begin (Cohort 3); and 3) after at least 4 subjects in the 800 mg multiple dose cohort (Cohort 3) have completed Day 15 to determine if dosing in Cohort 3 may continue. Dose escalation or continuation will proceed as scheduled and the study will continue as long as no prespecified toxicity events occur. Dose continuation within Cohort 3 after Period 2 will proceed following review of the available safety and tolerability data by the PI in accordance with the protocol's toxicity rules. Minimum data requirements do not apply for the PI review; however, it is expected to include available data up to 14 days after each dose.

Up to 2 subjects per cohort may be added if 2 or more subjects discontinue before Day 15 (first dose only for Cohort 3) for reasons other than drug-related AEs, and after consultation with the SRC. All enrolled subjects will be included in analyses as appropriate. Subjects who have been dosed and who withdraw from the study will be followed for safety assessments through the last study visit, if possible.

Subjects in Cohorts 1 and 2 (Single Ascending Dose [SAD] Phase) will participate in the study for up to 27 or 30 weeks, respectively, including a screening period of up to 70 days, followed by a 120-day (Cohort 1) or 140-day (Cohort 2) dosing and observation period for safety, immunogenicity, PK, and PD assessments after study drug administration. Subjects in Cohort 3 (Multiple Set Dose [MSD] Phase) will participate in the study for approximately 52 weeks, including a screening period of up to 70 days, a treatment period of 112 days, and a 185-day observation period for safety, immunogenicity, PK, and PD assessments after the fifth dose of study drug. Subjects in Cohort 1 will utilize contraception for a minimum of 6 months after last dose, whereas subjects in Cohorts 2 and 3 will utilize contraception for a minimum of 8 months after last dose.



Number of subjects (planned):
Up to 16 subjects are planned for evaluation of the primary and secondary objectives, and a maximum of 22 subjects could be enrolled and dosed. See the synopsis section "Methodology" regarding addition of subjects who withdraw or are withdrawn from the study after dosing. The total number of subjects dosed (including potential added subjects) will remain within a maximum of 6 subjects each in Cohorts 1 and 2 and 10 subjects in Cohort 3, for a maximum of 22 subjects in this study.

Diagnosis and main criteria for inclusion:
All subjects must adhere to the following inclusion/exclusion criteria. Subjects who fail to meet eligibility criteria may not be rescreened for participation in the study unless the condition is transient, self-limited, and easily treatable, and is expected to be resolved at the time of dosing, as agreed by the investigator and medical monitor.

Inclusion:

1. Healthy Japanese males or females aged 25 through 55 years, inclusive (subjects must have lived outside of Japan for ≤ 10 years and be first generation Japanese, defined as born in Japan and having 4 biologic grandparents who are ethnic Japanese).
2. Body mass index (BMI) from 18 through 29.9 kg/m^2, inclusive, and weight between 50 and 100 kg, inclusive.
3. QT interval (corrected using the Fridericia's formula; QTcF) ≤ 450 msec for males and ≤ 470 msec for females at screening and prior to dosing on Day 1.
4. Willing and able to give written informed consent and comply with the study visit schedule.
5. Documented vaccination with MCV4 at least 56 days and not more than 3 years prior to dosing. Documentation must include a positive SBA to confirm an immune response before study drug administration.
6. Vaccination with serogroup B meningococcal vaccine at least 56 days prior to dosing on Day 1, with a booster administered at least 28 days prior to dosing on Day 1, with at least 28 days between the first and second injections.
7. Female subjects of childbearing potential must use highly effective contraception as defined below, starting at screening and continuing until at least 6 months (Cohort 1) or 8 months (Cohorts 2 and 3) after the last dose of ALXN1210.

   Highly effective contraceptive methods for females are as follows*:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

*It is recommended that heterosexually active female subjects of childbearing age who take oral contraceptives and penicillin V, or any other antibiotics with the potential to reduce the effectiveness of hormonal contraception, should use a barrier method (eg, condom or diaphragm and spermicide) in addition to the oral contraceptive medication.

Male subjects 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 6 months (Cohort 1) or 8 months (Cohorts 2 and 3) after the last dose of ALXN1210. Barrier contraception is required even with documented medical assessment of surgical success of a vasectomy. Female spouses or partners of male subjects who are of childbearing potential must use highly effective contraception as defined above, or acceptable contraception as defined below, starting at screening and continuing until at least 6 months (Cohort 1) or 8 months (Cohorts 2 and 3) after the last dose of ALXN1210. Male subjects must not donate sperm during the screening and treatment periods and for at least 6 months (Cohort 1) or 8 months (Cohorts 2 and 3) after the last dose of ALXN1210.

Acceptable contraceptive methods are as follows:

- Simultaneous use of male condom and, for the female partner, occlusive cap (diaphragm or cervical/vault caps) with intravaginally applied spermicide

Exclusion:

1. Subjects who are in intimate and prolonged contact with (defined as living under the same roof or providing personal care) people younger than 2 years of age or older than 65 years of age, or who are either immunocompromised or have one of the following underlying medical conditions: anatomic or functional asplenia (including sickle cell disease); congenital complement, properdin, factor D, or primary antibody deficiencies; acquired complement deficiencies (eg, those receiving eculizumab); or human immunodeficiency virus (HIV)
2. Subjects who are one of the following:
   - Professionals who are exposed to environments of greater risk for meningococcal disease
   - Research, industrial, and clinical laboratory personnel who are routinely exposed to *N meningitidis*
   - Military personnel during recruit training (military personnel may be at increased risk of meningococcal infection when accommodated in close quarters)
   - Daycare center workers
   - Those living on a college or university campus
   - Those who plan to travel during the course of the study to or have travelled to endemic areas for meningococcal meningitis (eg, India, Sub-Saharan Africa, pilgrimage to Saudi Arabia for Hajj) within the past 6 months
3. History of any *Neisseria* infection
4. History of unexplained, recurrent infection, or infection requiring treatment with systemic antibiotics within the last 90 days prior to dosing.

5. HIV infection (evidenced by HIV-1 or HIV-2 antibody titer).
6. Acute or chronic hepatitis B virus (HBV) infection. Hepatitis B surface antigen (HBsAg) testing is required for all subjects prior to enrollment. Subjects with positive HBsAg will not be enrolled. For subjects with negative HBsAg, the following testing algorithm will be required:
    - If hepatitis B core antibody (HBcAb) is negative, the subject is eligible to enroll;
    - If HBcAb is positive, the hepatitis B surface antibody (HBsAb) will be tested.
        - If both HBcAb and HBsAb are positive, the subject is eligible to enroll.
        - If HBcAb is positive and HBsAb is negative, the subject will not be enrolled.
7. Acute or chronic hepatitis C virus (HCV) infection (evidenced by antibody titer).
8. Active systemic viral or fungal infection within 14 days prior to dosing.
9. Positive or indeterminate QuantiFERON®-TB test indicating possible tuberculosis infection.
10. History of latent or active tuberculosis or exposure to endemic areas within 8 weeks prior to the screening visit.
11. Female subjects who are breastfeeding or are unwilling to practice contraception and are not postmenopausal. Postmenopausal is defined as amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle-stimulating hormone level ≥ 40 mIU/mL and estradiol concentration ≤ 110 pmol/L within the 6 months prior to drug administration.
12. Positive serum pregnancy test at screening or Day –1.
13. Serum creatinine greater than the upper limit of normal (ULN) of the reference range of the testing laboratory at screening or Day –1.
14. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > ULN of the reference range of the testing laboratory at screening or > 1.5 × ULN of the reference range of the testing laboratory at Day –1.
15. Any of the following hematology results: hemoglobin < 130 g/L for males and < 115 g/L for females; hematocrit < 0.37 L/L for males and < 0.33 L/L for females; white blood cells (WBC) < $3.0 \times 10^3/\mu L$; absolute neutrophils < $2.0 \times 10^3/\mu L$; and platelets < 150 or > $400 \times 10^3/\mu L$ at screening or Day –1. Complete blood count (CBC) clinical laboratory results that are considered clinically relevant and unacceptable by the investigator at Day –1.
16. History of complement deficiency or complement activity below normal reference range as evaluated by complement alternative pathway (CAP) ELISA at screening.
17. History of malignancy 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. Participation in a clinical study within 30 days before initiation of dosing on Day 1 or use of any experimental small-molecule therapy within 30 days prior to dosing on Day 1.
19. Participation in more than one clinical study of a mAb, or participation in a clinical study of a mAb within the 12 months prior to screening, during which the subject was exposed to the active study drug. Subjects who have participated in only one study of a mAb may be considered for enrollment if they completed that study more than 12 months prior to screening
20. Major surgery or hospitalization within 90 days prior to dosing.
21. Contraindication to receiving MCV4 and/or serogroup B vaccine, including severe allergic reaction to a previous dose of MCV4 and/or serogroup B vaccine; severe allergy to any vaccine component; or previous diagnosis of Guillain-Barré syndrome.
22. History of allergy to excipients of ALXN1210 (eg, polysorbate 80).
23. Documented history of allergy to penicillin or cephalosporin.
24. History of significant allergic reaction (anaphylaxis, angioedema) to any product (food, pharmaceutical, etc.).
25. Currently smokes > 10 cigarettes daily (former smokers may be permitted to enroll at the investigator's discretion).
26. History of illicit drug abuse, history of significant alcohol abuse within 1 year prior to the screening visit, or regular use of alcohol within 6 months prior to the screening visit (more than 14 units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]).
27. Positive urine drug toxicology screen at screening or Day –1.
28. Alcohol consumption within 48 hours prior to study drug administration or positive alcohol breath test on Day –1.
29. Donation of plasma within 7 days prior to dosing. Donation or loss (excluding volume drawn at screening) of more than 50 mL of blood within 30 days of dosing or more than 499 mL of blood within

56 days of dosing.

30. History of continuous topical/inhaled or systemic steroid use > 1 month or history of any inhaled or topical immunosuppressive therapy within 90 days prior to study drug administration.
31. Use of prescription medications (excluding oral contraceptives) within 14 days prior to study drug administration, except with prior approval of the sponsor.
32. Regular use of nonprescription, over-the-counter medications, including herbal remedies/supplements, within 14 days prior to study drug administration. Multivitamins, acetaminophen ≤ 2 g per day, and topical skin products without significant systemic absorption are allowed.
33. Clinical diagnosis of any autoimmune or rheumatologic disease (eg, systemic lupus erythematosus, rheumatoid arthritis).
34. Immunization with a live-attenuated vaccine 1 month prior to dosing or planned vaccination during the course of the study (except for the vaccination planned by the study protocol). Immunization with inactivated or recombinant influenza vaccine is permitted.
35. Presence of fever (confirmed body temperature > 37.6°C) (eg, a fever associated with a symptomatic viral or bacterial infection) within 14 days prior to the first dosing.
36. Subjects with any medical history, conditions, or risks which, in the opinion of the investigator, may interfere with the subject's full participation in the study or compliance with the protocol, or may pose any additional risk for the subject or confound the assessment of the subject or outcome of the study.

Investigational product, dosage and mode of administration:
ALXN1210 is formulated at pH 7.0 and each vial contains 150 mg of ALXN1210, in 10 mM sodium phosphate, 150 mM NaCl, 0.02% polysorbate 80, and water for IV administration. ALXN1210 is presented as a sterile, preservative-free 10 mg/mL solution for IV administration and is supplied in 20-mL single-use vials.

ALXN1210 will be administered by IV infusion at a fixed rate of 686 mg/hr, excluding interruption for safety or technical reason.

Duration of treatment:
Screening period: up to 70 days
Dosing and observation periods: For Cohorts 1 and 2, single dose of ALXN1210 on Day 1, followed by an observation period of 119 days (Cohort 1) or 139 days (Cohort 2). For Cohort 3, a total of 5 doses of ALXN1210 on Days 1, 29, 57, 85, and 113, followed by an observation period of 185 days. Subjects will be followed for safety, PK, PD, and immunogenicity assessments.

Reference therapy, dosage and mode of administration:
None

Criteria for evaluation:
Safety evaluation:
Safety assessments will include physical examination findings, vital signs measurements, immunogenicity (anti-drug antibody [ADA]) testing, laboratory evaluations, electrocardiogram (ECG) results, infusion site evaluations, and monitoring of AEs. Adverse events will be graded according to criteria from the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03, published June 14, 2010. Laboratory evaluations include hematology, chemistry, and coagulation panels, CBC with differential, urinalysis, and pregnancy testing for female subjects. The potential risks of ALXN1210, specifically the risk of infection, will be reviewed with the subjects at screening and on a regular basis throughout the course of the study, after dosing. Subjects will meet with the investigator or designee to discuss the potential safety risks of ALXN1210 and address any safety concerns on the part of the subject at the time points shown in the Schedule of Assessments. During the second, third, and fourth dosing periods of Cohort 3, the subjects will be contacted by telephone to assess selected safety information.

Pharmacokinetics:

Table 1s: Collection Time Points for Serum Concentrations of ALXN1210

Collection Time Points for Cohort 1	
(Days 1-120)	On Day 1 before dosing (within 15 min prior to the start of infusion [SOI]); end-of-infusion (EOI), 30 min after the EOI, and at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), Day 5 (96 hr), Day 8 (168 hr), Day 15 (336 hr), Day 22 (504 hr), Day 29 (672 hr), Day 36 (840 hr), Day 43 (1008 hr), Day 50 (1176 hr), Day 57 (1344 hr), Day 71 (1680 hr), Day 90 (2136 hr), and Day 120 (2856 hr)

Collection Time Points for Cohort 2	
(Days 1-140)	On Day 1 before dosing (within 15 min prior to the start of infusion [SOI]); end-of-infusion (EOI), 30 min after the EOI, and at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), Day 5 (96 hr), Day 8 (168 hr), Day 15 (336 hr), Day 22 (504 hr), Day 29 (672 hr), Day 36 (840 hr), Day 43 (1008 hr), Day 50 (1176 hr), Day 57 (1344 hr), Day 71 (1680 hr), Day 90 (2136 hr), Day 120 (2856 hr), and Day 140 (3336 hr)
Collection Time Points for Cohort 3	
Period 1 (Days 1-28)	On Day 1 before dosing (within 15 min prior to the SOI), EOI, 30 min after the EOI, at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), Day 5 (96 hr); Day 8 (168 hr), Day 15 (336 hr), and Day 22 (504 hr)
Period 2 (Days 29-56)	Before dosing on Day 29 (within 15 min prior to the SOI), EOI on Day 29, 30 min after the EOI, at the following time points: Day 29 (4 hr and 8 hr), Day 30 (24 hr), Day 31 (48 hr), Day 33 (96 hr), and Day 43 (336 hr)
Period 3 (Days 57-84)	Before dosing on Day 57 (within 15 min prior to the SOI), EOI on Day 57, 30 min after the EOI, at the following time points: Day 57 (4 hr and 8 hr), Day 58 (24 hr), Day 59 (48 hr), Day 61 (96 hr), and Day 71 (336 hr)
Period 4 (Days 85-112)	Before dosing on Day 85 (within 15 min prior to the SOI), EOI on Day 85, 30 min after the EOI, at the following time points: Day 85 (4 hr and 8 hr), Day 86 (24 hr), Day 87 (48 hr), Day 89 (96 hr), and Day 99 (336 hr)
Period 5 and Follow-up (Days 113-298)	Before dosing on Day 113 (within 15 min prior to SOI), EOI and 30 min after the EOI on Day 113, at the following time points: Day 113 (4 hr and 8 hr), Day 114 (24 hr), Day 115 (48 hr), Day 117 (96 hr), Day 120 (168 hr), Day 127 (336 hr), Day 134 (504 hr), Day 141 (672 hr), Day 148, Day 155, Day 162, Day 169, Day 183, Day 197, Day 225, Day 253, and Day 298

Using noncompartmental PK methods, the serum concentrations 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 observed minimum serum concentrations (C_{min}) just prior to Periods 2 to 5 (and 28 days after Period 5 dose) for Cohort 3, area under the serum concentration versus time curve from time 0 to the last quantifiable concentration (AUC_t) after each dose, area under the curve from time 0 (dosing) to the end of the dosing interval (AUC_τ), apparent terminal-phase elimination rate constant (λ_z), terminal elimination half-life ($t_{½}$), total clearance (CL), volume of distribution (V_{ss}), assessment of steady-state, and accumulation at steady state. The relationship between ALXN1210 exposure and PD markers may be assessed, and dose proportionality in PK parameters may be assessed.

Pharmacodynamics:

Blood samples for the analyses of total and free C5 levels and cRBC hemolysis will be collected at the time points listed in the following tables. Additional biomarker assays may be conducted as an exploratory analysis on collected samples.

Table 2s: Collection Time Points for Serum C5 Levels and cRBC Hemolysis

Collection Time Points for Cohort 1	
(Days -1-120)	On Day -1, on Day 1 before dosing (within 15 min prior to the SOI), EOI, 30 min after the EOI, and at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), and Day 5 (96 hr), Day 8 (168 hr), Day 15 (336 hr), Day 22 (504 hr), Day 29 (672 hr), Day 36 (840 hr), Day 43 (1008 hr), Day 50 (1176 hr), Day 57 (1344 hr), Day 71 (1680 hr), Day 90 (2136 hr), and Day 120 (2856 hr)
Collection Time Points for Cohort 2	
(Days -1-140)	On Day -1, on Day 1 before dosing (within 15 min prior to the SOI), EOI, 30 min after the EOI, and at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), and Day 5 (96 hr), Day 8 (168 hr), Day 15 (336 hr), Day 22 (504 hr), Day 29 (672 hr), Day 36 (840 hr), Day 43 (1008 hr), Day 50 (1176 hr), Day 57 (1344 hr), Day 71 (1680 hr), Day 90 (2136 hr), Day 120 (2856 hr), and Day 140 (3336 hr)
Collection Time Points for Cohort 3	
Period 1 (Days -1-28)	On Day -1, on Day 1 before dosing (within 15 min prior to the SOI), EOI, 30 min after the EOI, at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), Day 5 (96 hr), Day 8 (168 hr), Day 15 (336 hr), and Day 22 (504 hr)
Period 2 (Days 29-56)	Before dosing on Day 29 (within 15 min prior to the SOI), EOI on Day 29, 30 min after the EOI, at the following time points: Day 29 (4 hr and 8 hr), Day 30 (24 hr), Day 31 (48 hr), Day 33 (96 hr), and Day 43 (336 hr)

Period 3 (Days 57-84)	Before dosing on Day 57 (within 15 min prior to the SOI), EOI on Day 57, 30 min after the EOI, at the following time points: Day 57 (4 hr and 8 hr), Day 58 (24 hr), Day 59 (48 hr), Day 61 (96 hr), and Day 71 (336 hr)
Period 4 (Days 85-112)	Before dosing on Day 85 (within 15 min prior to the SOI), EOI on Day 85, 30 min after the EOI, at the following time points: Day 85 (4 hr and 8 hr), Day 86 (24 hr), Day 87 (48 hr), Day 89 (96 hr), and Day 99 (336 hr)
Period 5 and Follow-up (Days 113-298)	Before dosing on Day 113 (within 15 min prior to SOI), EOI and 30 min after the EOI on Day 113, at the following time points: Day 113 (4 hr and 8 hr), Day 114 (24 hr), Day 115 (48 hr), Day 117 (96 hr), Day 120 (168 hr), Day 127 (336 hr), Day 134 (504 hr), Day 141 (672 hr), Day 148, Day 155, Day 162, Day 169, Day 183, Day 197, Day 225, Day 253, and Day 298

Immunogenicity:

Table 3s: Collection Time Points for Serum Samples for Analyses of Antidrug Antibodies to ALXN1210

Collection Time Points for Cohort 1	
(Days 1-120)	Pre-dose on Day 1, and on Day 15, Day 29, Day 57, Day 90, and Day 120
Collection Time Points for Cohort 2	
(Days -1-140)	Pre-dose on Day 1, and on Day 15, Day 29, Day 57, Day 90, Day 120, and Day 140
Collection Time Points for Cohort 3	
Periods 1 to 5 (Days 1-298)	Pre-dose on Day 1; on Day 8, Day 15, and Day 22 after Dose 1; on Day 29 prior to Dose 2 and on Day 43 after Dose 2; on Day 57 prior to Dose 3 and on Day 71 after Dose 3; on Day 85 prior to Dose 4 and on Day 99 after Dose 4; on Day 113 prior to Dose 5 and on Day 120, Day 141, Day 169, Day 197, Day 225, Day 253, and Day 298 following Dose 5

Please refer to the Study Operation Manual (SOM) for time windows for collection, and to the laboratory manual for details on sample collection including blood volume requirements.

No more than 470 mL of blood will be taken within each 16-week period in accordance with the guidance of NHS Blood and Transplant (http://www.blood.co.uk/about-blood/how-the-body-replaces-blood/).

Statistical methods:

The sample size of 4 subjects in each of the single-dose cohorts (Cohorts 1 and 2) and 6 to 8 subjects in the 800 mg multiple-dose cohort will allow for the characterization of the central tendency of PK parameters as they relate to ALXN1210 and to gain initial knowledge of PK/PD relationships in Japanese subjects. To ensure future modeling and simulations are accurate, it is preferred to estimate the PK parameters with a maximum imprecision of < 25% following the IV administration of ALXN1210. Six subjects in Cohort 3 will provide 23.3% maximum imprecision for the estimation of area under the serum concentration versus time curve from time 0 extrapolated to infinity (AUC_{∞}), in terms of the relative distance of the lower 90% confidence limit from the observed PK parameter that will be obtained with 80% assurance and assuming the within-subject SD of the log-transformed AUC_{∞} is as much as 0.19.

All continuous variables will be summarized by cohort and time point with descriptive statistics (the number of nonmissing values, mean, SD, median, minimum, and maximum). All categorical variables will be summarized by cohort and time point with frequency counts and percentages.

All subjects dosed with study drug will be included in the safety analysis. Safety data will be assessed using descriptive statistics. No inferential statistical analyses are planned on the safety parameters of this study. Safety analysis will include an analysis of all AEs, laboratory values, ECGs, and vital sign measurements.

Shift tables will be produced for selected laboratory parameters. These tables will summarize the number of subjects with each baseline grade relative to the normal ranges and changes to the worst highest grade assessed postdose during the study.

Individual PK parameters (including descriptive statistics: geometric mean, geometric coefficient of variation [CV], arithmetic mean, SD, arithmetic CV, median, minimum, and maximum) will be determined for the ALXN1210-treated subjects. The PK data may be assessed for dose proportionality. The PK data may be explored for time linearity.

The PD effects of ALXN1210 will be evaluated by assessing serum total and free C5 concentrations and cRBC hemolysis over time, using descriptive statistics, and the ALXN1210 concentration required for complete terminal complement inhibition based on PD effects evaluated. An exploratory analysis of ALXN1210 concentrations and PD responses assessed at similar time points may be performed.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Terms

Abbreviation or Term	Explanation
λ_z	apparent terminal-phase elimination rate constant
%CV	percent coefficient of variance
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
aHUS	atypical hemolytic uremic syndrome
AUC_∞	area under the serum concentration versus time curve from 0 extrapolated to infinity
AUC_t	area under the serum concentration versus time curve from time 0 to the last quantifiable concentration
AUC_τ	area under the serum concentration versus time curve from time 0 (dosing) to the end of the dosing interval
BMI	body mass index
BP	British Pharmacopoeia
C5b-9	terminal complement complex
CAP	complement alternative pathway
CDC	complement-dependent cytotoxicity
CL	total clearance
C_{max}	maximum observed serum concentration
cRBC	chicken red blood cell
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
EOI	end of infusion
ET	Early Termination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBcAg	hepatitis B core antigen
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
mAb	monoclonal antibody
MAC	membrane attack complex
MAD	multiple ascending dose
MCV4	meningococcal conjugate vaccine
MSD	multiple set dose
OP	outpatient

PD	pharmacodynamic(s)
Ph. Eur.	European Pharmacopoeia
PNH	paroxysmal nocturnal hemoglobinuria
PK	pharmacokinetic(s)
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SOI	start of infusion
SOM	study operations manual
SRC	Safety Review Committee
$t_{½}$	terminal elimination half-life
TB	tuberculosis
t_{max}	time to maximum observed serum concentration
ULN	upper limit of normal
V_{ss}	volume of distribution
WBC	white blood cell

5. INTRODUCTION

ALXN1210 is a humanized monoclonal antibody (mAb) that is structurally related to eculizumab (Soliris®) and is being developed by Alexion Pharmaceuticals, Inc. (Alexion). It specifically 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 (MAC) 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 provides a rationale for the potential therapeutic use of ALXN1210 in diseases where complement activation is involved (eg, paroxysmal nocturnal hemoglobinuria [PNH] or atypical hemolytic uremic syndrome [aHUS]). These disorders of uncontrolled complement activation are chronic and progressive, with severe morbidities and significant premature mortality.

5.1. 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 Investigator's Brochure (IB).

5.1.1. Clinical Studies

ALXN1210 has been administered safely to healthy subjects in single intravenous (IV) doses of 200 mg and 400 mg in a single ascending dose (SAD) study (Study ALXN1210-HV-101, N = 14) and in multiple IV doses of 400 mg and 800 mg on an every 4 week (Q4W) regimen in an ongoing multiple ascending dose (MAD) study (Study ALXN1210-HV-102, N = 16). The starting doses of ALXN1210 in these two studies were selected to assess safety in healthy volunteers but also to have measurable pharmacologic activity (eg, inhibition of complement activation) based on the therapeutic exposure required with eculizumab. No safety concerns have been identified in either of the Phase 1 studies, both of which were randomized, blinded, and placebo controlled. In the completed Study ALXN1210-HV-101 (SAD), no serious adverse drug reactions, treatment discontinuations, or deaths were reported.

Conclusions from Study ALXN1210-HV-101 are 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_∞, and C_{max}) increased in a slightly less than dose proportional manner over the studied range of 200 to 400 mg based on the protocol-specified statistical analysis.
- Following single IV infusion (200- and 400-mg) dose administrations of ALXN1210, all 6 PD variables showed dose-dependent reductions from Baseline. The effect of ALXN1210 on these PD variables was immediately evident after EOI. 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 longer following a 400-mg dose than a 200-mg dose.
- All subjects were negative for ADA through Day 150.

5.1.2. Nonclinical Studies

The binding characteristics, potency, and effector functions of ALXN1210 have been studied in vitro and compared with its parent molecule, eculizumab. ALXN1210 does not bind with strong affinity to any FcγR subclass or to C1q, and has shown only a modest increased binding capacity to FcγRIIa, relative to eculizumab. Based on the structure of the antibody (IgG4 FcR portion) and the soluble target, ALXN1210 is unlikely to be capable of initiating antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) in vivo. In Study ALXN1210-HV-101, no indication of CDC or ADCC has been observed.

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

5.1.3. General Considerations for This Study

The planned Phase 1 study will be performed in healthy Japanese subjects. Data from this study will be used to determine whether results of safety, immunogenicity, PK, and PD investigations obtained in non-Japanese subjects may be extrapolated to Japanese subjects.

5.1.4. Potential Risks

5.1.4.1. Infections (*Neisseria meningitidis* and Other Encapsulated Organisms)

A risk associated with complete terminal complement inhibition, such as that anticipated with ALXN1210, is infection with encapsulated organisms, particularly *N meningitidis*. Clinically, this risk is mitigated in patients receiving complement inhibitors such as eculizumab by vaccinating all patients against *N meningitidis* with a tetravalent meningococcal conjugate vaccine (MCV4) before dosing. In the current setting, ie, normal healthy subjects with an induced transient state of complement deficiency, an additional conservative step of treating subjects with prophylactic antibiotics is planned, in addition to MCV4 vaccination at least 56 days prior to dosing with ALXN1210 (if not vaccinated with MCV4 within the last 3 years, or if subjects have been previously vaccinated but there is not adequate documentation to verify prior vaccination). The serum bactericidal antibody (SBA) titer to the tetravalent vaccine will be established. Subjects who are not already vaccinated will also receive vaccination for serogroup B meningococcal infections at least 56 days prior to Day 1 dosing with a booster administered at least 28 days prior to dosing on Day 1.

In addition to vaccination against *N meningitidis* with MCV4 and the serogroup B vaccine, all subjects will be treated with prophylactic antibiotics (oral penicillin V 500 mg twice daily) for the duration of reduced complement activity, ie, until complement activity is predicted to be restored to normal based on an exposure-response analysis of data from clinical study ALXN1210-HV-101 and emerging data from the ALXN1210 program. Unless the PI and sponsor agree to an alternative regimen, all subjects will take prophylactic antibiotics (oral penicillin V 500 mg twice daily) until complement activity has normalized (anticipated by

Day 50 for Cohort 1, Day 140 for Cohort 2, and Day 298 for Cohort 3). Analysis of blood samples to establish actual complement activity based on an in vitro liposome immunoassay (LIA) will be used as confirmation. The analysis will take place approximately 2 to 5 weeks prior to the anticipated end of antibiotic prophylaxis. All subjects will be monitored closely for signs of infection throughout the study.

5.1.4.2. 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 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). 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. In addition, readministration of some mAbs has been associated with serum sickness-like reactions, manifesting 1 to 14 days after drug administration.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of single and multiple doses of ALXN1210 following IV administration to healthy Japanese subjects.

6.2. Secondary Objectives

Secondary objectives are as follows:

- To investigate the immunogenicity of ALXN1210 in healthy Japanese subjects.
- To characterize the PK of single and multiple doses of ALXN1210 in healthy Japanese subjects.
- To evaluate the PD effects of ALXN1210 as assessed by total and free C5 concentrations and chicken red blood cell (cRBC) hemolysis in healthy Japanese subjects.

7. ENDPOINTS

Safety, immunogenicity, PK, and PD endpoints are described in the sections to follow. Timing of assessments is displayed in the Schedules of Assessments.

7.1. Safety Endpoints

Safety endpoints include the following:

- Change from baseline in physical examination assessments
- Change from baseline in vital signs
- Incidence of antidrug antibody (ADA) measured via immunogenicity testing
- Change from baseline in electrocardiogram (ECG) parameters
- Change from baseline in laboratory measurements
- Incidence of AEs and SAEs

7.2. Pharmacokinetic Endpoints

The following PK parameters will be evaluated:

- C_{max}
- Time to maximum observed serum concentration (t_{max})
- Observed minimum serum concentrations (C_{min}) just prior to Doses 2 to 5, and 28 days after the 5th dose
- Area under the serum concentration versus time curve from time 0 to the last quantifiable concentration (AUC_t) after each dose
- AUC from time 0 (dosing) to the end of the dosing interval (AUC_τ)
- Apparent terminal-phase elimination rate constant (λ_z)
- $t_{½}$
- Total body clearance of drug from the serum (CL)
- Volume of distribution at steady state (V_{ss})
- Assessment of steady state
- Accumulation at steady state

7.3. Pharmacodynamic Endpoints

Pharmacodynamic effects will be evaluated as follows:

- Change in serum total and free C5 concentration over time
- Change in cRBC hemolysis over time

- ALXN1210 concentration required for terminal complement inhibition based on PD effects evaluated

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design

This is a Phase 1, open-label, single ascending and multiple set dose study designed to evaluate the safety, tolerability, immunogenicity, PK, and PD of ALXN1210 in healthy Japanese subjects.

All subjects are to be screened for eligibility in the study after providing written informed consent to participate. Subjects who fail to meet eligibility criteria may not be rescreened for participation in the study, unless the condition that led to eligibility failure is transient, self-limited, and easily treatable, and is expected to be resolved at the time of dosing, as agreed by the investigator and medical monitor.

A total of 3 cohorts and up to 16 subjects are planned for evaluation. The cohorts will be enrolled sequentially and all subjects will receive IV ALXN1210:

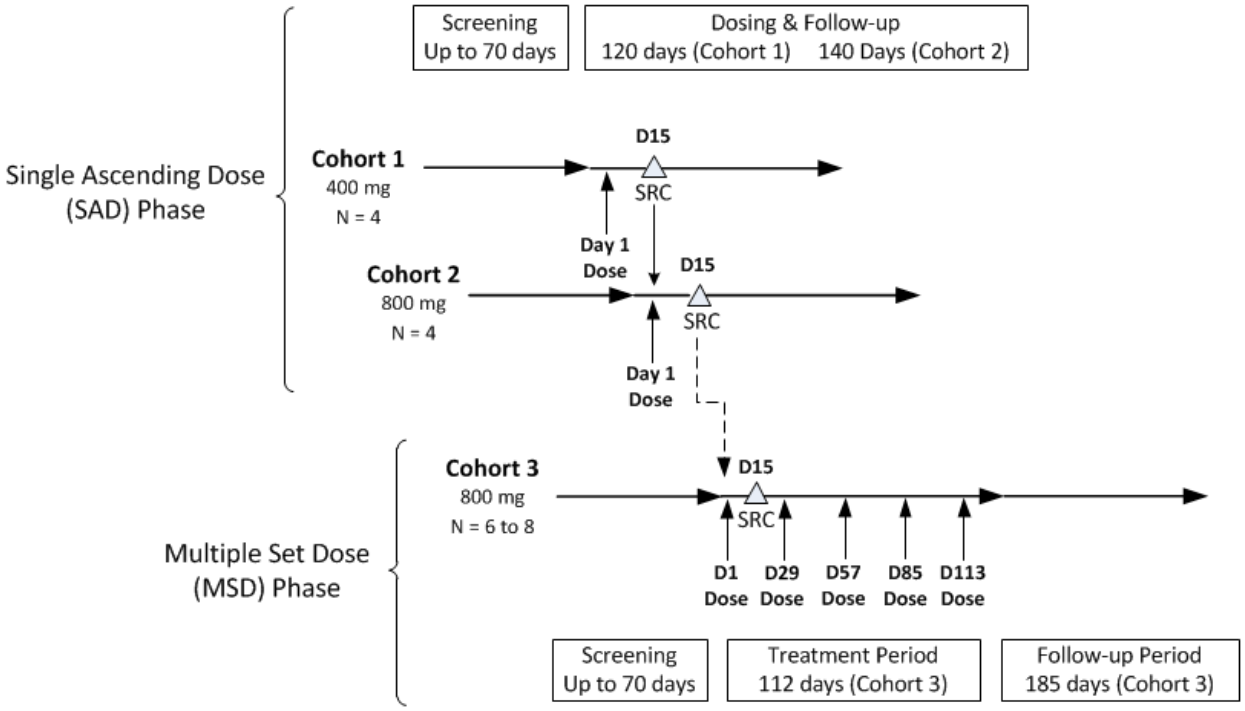
- Cohort 1, 400 mg single dose (N = 4)
- Cohort 2, 800 mg single dose (N = 4)
- Cohort 3, 800 mg Q4W for a total of 5 doses (N = 6 to 8)

A Safety Review Committee (SRC) will conduct a review of the available clinical and safety data after the last subject in the 400 mg cohort (Cohort 1) has completed Day 15 to determine if dose escalation to 800 mg may proceed (Cohort 2). The SRC will conduct a review of all available clinical and safety data after the last subject in the 800 mg cohort (Cohort 2) has completed Day 15 to determine if dosing in Cohort 3 may begin. Dose escalation to the multiple repeated dose phase will proceed as scheduled and the study will continue as long as no prespecified toxicity events occur (see Table 3). Dose continuation within Cohort 3 after Period 2 will proceed following review of the available safety and tolerability data by the PI in accordance with the protocol's toxicity rules. Minimum data requirements do not apply for the PI review; however, it is expected to include available data up to 14 days after each dose.

Up to 2 subjects per cohort may be added if 2 or more subjects discontinue before Day 15 (first dose only for Cohort 3) for reasons other than drug-related AEs, and after consultation with the SRC. All enrolled subjects will be included in analyses as appropriate. Subjects who have been dosed and who withdraw from the study will be followed for safety assessments through the last study visit, if possible.

Subjects in Cohorts 1 and 2 will participate in the study for up to 27 or 30 weeks, respectively, including a screening period of up to 70 days, followed by a 120-day (Cohort 1) or 140-day (Cohort 2) dosing and observation period for safety, immunogenicity, PK, and PD assessments after study drug administration. Subjects in Cohort 3 will participate in the study for approximately 52 weeks, including a screening period of up to 70 days, a treatment period of 112 days, and a 185-day observation period for safety, immunogenicity, PK, and PD assessments after the fifth dose of study drug.

Figure 1: Study Diagram



8.2. Number of Subjects

Up to 16 subjects are planned for evaluation of the primary and secondary objectives, and a maximum of 22 subjects could be enrolled and dosed. See the synopsis section "Methodology" regarding addition of subjects who withdraw or are withdrawn from the study after dosing. The total number of subjects dosed (including potential added subjects) will remain within a maximum of 6 subjects each in Cohorts 1 and 2 and 10 subjects in Cohort 3, for a maximum of 22 subjects in this study.

8.3. Dose Rationale

The geometric mean (CV%) ALXN1210 half-life in Study ALXN1210-HV-101 ranged from 30.8 (10.2%) to 32.4 (16.2%) days over the studied doses. Following single IV infusion (200- and 400-mg) dose administrations of ALXN1210 to healthy volunteers, all studied PD variables showed dose-dependent changes from baseline that recovered back to baseline. The effect of ALXN1210 on these PD variables was immediately evident after EOI. At the EOI, the mean free C5 serum concentrations and cRBC hemolysis activity were inhibited by > 99% and > 97%, respectively. In ongoing Study ALXN1210-HV-102, ALXN1210 IV doses of 400 every 4 weeks and 800 mg every 4 weeks are being studied to assess PK, PD, and tolerability in healthy volunteers. The PK, PD, and tolerability data from the non-Japanese studies (Study ALXN1210-HV-101 and Study ALXN1210-HV-102) will be compared with the data from the current study to assess PK, PD, and tolerability bridging between Japanese and non-Japanese healthy volunteers. In the current study, dose escalation (400 mg to 800 mg single dose) and dose progression (800 mg single dose to 800 mg multiple dose) will be decided upon SRC review of the safety and tolerability data from the preceding cohort.

8.4. Criteria for Dose Continuation and Dose Escalation

For the purpose of this protocol, progression rules are based on toxicity (ie, clinically significant AEs which are assessed as at least possibly related to the investigational medicinal product). For the purpose of this protocol, the term "dose escalation" is defined as progression to the next cohort.

For the purpose of this protocol, the term "suspension" is defined as no further study drug will be administered at the dose level and that further dose escalation/continuation will be suspended. If a dose level is suspended, an ad hoc SRC meeting will be held.

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; v4.03, published June 14, 2010) will be used to grade AEs (see Section 17.3).

Abnormal laboratory and other tests should always be repeated before grading in order to ensure consistency and to exclude technical errors. If applicable, diurnal variations in laboratory parameters and other measurements as well as baseline status should be taken into account when assessing whether abnormal laboratory values constitute a drug-related AE and when grading AEs.

8.4.1. Dose Escalation, Dose Continuation, and Suspension/Stopping Rules

To determine if escalation to the next cohort should occur, the SRC will review the available safety data after Day 15 of the last subject in Cohort 1. Study assessments through Day 15 must be completed for a minimum of 3 subjects to determine if it is appropriate to escalate to Cohort 2. Dose escalation will occur based on the recommendation of the SRC (Section 8.5). The same process will be followed for escalation from Cohort 2 to Cohort 3. Study assessments through Day 15 of each dose must be completed for a minimum of 3 subjects to determine if it is appropriate to begin dosing in Cohort 3. Dose escalation will occur based on the recommendation of the SRC.

Dose continuation in Cohort 3 will occur based on review by the SRC of data from at least 4 subjects through Day 15 post first dose.

Dose escalation and dose continuation will proceed as described in Table 3 and will be limited by whether these toxicity rules are met.

Table 3: Toxicity Rules

CTCAE Grade	Severity/ Seriousness	Reversibility	Number of Subjects Affected	Action	Effect on Dose Progression/ Escalation
1	Mild	N/A	N/A	Next dose determined by SRC	N/A
2	Moderate	Showing signs of reversibility; i.e. event which shows signs of improvement in the judgment of investigator	≤ 2 subjects in different SOC*		
			≤ 2 subjects in same SOC OR 3 subjects in different SOC*	Dose level may continue OR be extended AND Dose escalation on hold until results of continuation or extension are available	Following continuation or extension, dose escalation may proceed as per clinical study protocol
			≥ 3 subjects in same SOC OR ≥ 4 subjects in different SOC*	Dose level suspended	Dose continuation, extension, or escalation requires substantial amendment
		Showing no signs of reversibility	≥ 2 subjects*		
3	Severe	Showing signs of reversibility; i.e. event which shows signs of improvement in the judgment of investigator	1 subject*	Dose level may continue OR be extended AND Dose escalation on hold until results of continuation or extension are available	Following continuation or expansion, dose escalation may proceed as per the clinical study protocol
			≥ 2 subjects*	Dose level suspended	Dose continuation, extension, or escalation requires substantial amendment
		Showing no signs of reversibility	≥ 1 subject*		
4	Life-threatening	N/A	≥ 1 subject	Study suspended	Study continuation requires substantial amendment
5	Fatal				
N/A	Serious	N/A	≥ 1 subject	Study suspended	Study continuation requires substantial amendment

Abbreviations: N/A = not applicable; SOC = system organ class; SRC = Safety Review Committee.
* Within 2 weeks from each dose

8.4.2. Individual Subject Dose Continuation and Suspension/Stopping Rules

Individual dose continuation rules are presented in Table 4. These rules apply to study drug-related AEs and SAEs in individual subjects enrolled.

Table 4: Individual Progression Rules

AE Grade	Severity	Action
1	Mild	No action required.
2	Moderate	Study drug administration may continue at the same dose if the SRC considers it safe for the subject.
3	Severe	Study drug administration will be discontinued.
4	Life-threatening	Study drug administration will be discontinued.
5	Fatal	
Serious	N/A	

Abbreviation: N/A = not applicable

8.5. Safety Review Committee

The SRC is composed of the medical monitor, biostatistician, pharmacovigilance representative, clinical pharmacologist, and principal investigator. The membership, schedule of meetings, data required for each safety review, and requirements for documenting meeting discussions and outcome will be outlined in a charter to which the SRC adhere.

Since its primary function will be to ensure subject safety, the members of the SRC will have access to all safety data.

The SRC will review the available clinical and safety data at the following points in the study to determine whether dose escalation or continuation may proceed:

- After the last subject (minimum of 3) in the 400 mg cohort (Cohort 1) has completed Day 15 to determine if dose escalation to 800 mg may proceed (Cohort 2).
- After the last subject (minimum of 3) in the 800 mg cohort (Cohort 2) has completed Day 15 to determine if repeat dosing with 800 mg may begin (Cohort 3).
- After at least 4 subjects in the 800 mg multiple dose cohort (Cohort 3) have completed Day 15 to determine if dosing in Cohort 3 may continue. Dose escalation or continuation will proceed as scheduled and the study will continue as long as no prespecified toxicity events occur.

The SRC will convene to review safety data if unexpected safety concerns arise. The SRC will conduct a review of the clinical and safety data of individual subjects if prespecified criteria as described in Table 3 and Table 4 are met that warrant the suspension of dosing or the study.

The SRC may make recommendations regarding safety issues, study conduct, and modifying (ie, exploring the dose cohort further, suspending dose cohort(s), exploring lower dosing regimens), or stopping the study.

8.6. Criteria for Study Termination

The investigator, Competent Authority, or sponsor 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 subjects enrolled in the study
- Decision on the part of the sponsor 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 subject's last visit.

9. SCHEDULES OF ASSESSMENTS

The timing of overall study procedures is provided in the Schedules of Assessments as follows:

- Cohorts 1 and 2 (Table 5)
- Cohort 3
  - Screening and Doses 1 through 4 (Table 7)
  - Dose 5 and follow up (Table 8)
  - Follow up/ET for subjects who discontinue during Doses 1 through 4 (Table 9)

The timing of PK, PD, immunogenicity, infusion site evaluation, vital signs and ECG collection procedures is provided for:

- Cohorts 1 and 2 (Table 6)
- Cohort 3 (Table 10)

Table 5: Schedule of Assessments: Cohorts 1 and 2 (Refer to Table 6 for Pharmacokinetics, Pharmacodynamics, Immunogenicity, Infusion Site Evaluation, Vital Signs, and ECG Collection Time Points Required on Day 1)

		Treatment Period					Follow-up Period											
Study Day	**Screening**	**–1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**71**	**90**	**120**	**140 (C2)[16]**
Status (OP, PC, or CRU)	**OP**	**CRU Day -1**	**CRU Day 1**	**CRU Day 2**	**CRU Day 3**	**CRU Day 5**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**
Assessments[1]																		
Informed consent[2]	X																	
MCV4 immunization (Day -56)[3]	X																	
Meningococcal serogroup B immunization (Day -56 and Day -28)[3]	X																	
Serum bactericidal antibody (meningococcus Group A, C, W135, and Y)[3]	X																	
Medical history and demographics	X																	
QuantiFERON TB test	X																	
Hepatitis B and C screen	X																	
HIV, types 1 and 2 screen	X																	
Complement activity[4]	X																	
CH50[5]		X									X (C1)		X (C1)		X (C2)	X (C2)	X (C2)	X (C2)
Alcohol breath test	X	X																
Urine drug screen	X	X																
Height, weight, BMI[6]	X	X																
Pregnancy test[7]	X	X															X	X
Admittance to CRU		X																
Physical examination	X	X				X		X		X		X		X		X	X	X
Vital signs[8]	X	X	X	X	X	X		X		X		X		X		X	X	X
ECG (triplicate)[9]	X		X	X	X	X		X				X		X		X	X	X
Cardiac telemetry[9]			X															
Chemistry[10]	X	X	X	X		X		X		X		X		X		X	X	X
Hematology[10]	X	X	X	X		X		X		X		X		X		X	X	X
Coagulation[10]	X	X	X	X		X		X		X		X		X		X	X	X
Urinalysis and urine chemistry[10]	X	X		X		X		X		X		X		X		X	X	X
Study drug administration			X															

Table 5: Schedule of Assessments: Cohorts 1 and 2 (Refer to Table 6 for Pharmacokinetics, Pharmacodynamics, Immunogenicity, Infusion Site Evaluation, Vital Signs, and ECG Collection Time Points Required on Day 1) (Continued)

		Treatment Period					Follow-up Period											
Study Day	**Screening**	**–1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**71**	**90**	**120**	**140 (C2)[16]**
Status (OP, PC, or CRU)	**OP**	**CRU Day -1**	**CRU Day 1**	**CRU Day 2**	**CRU Day 3**	**CRU Day 5**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**
Assessments[1]																		
PK samples[8]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD panel (serum C5, cRBC hemolysis)[8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity (ADA)[8]			X					X		X				X		X	X	X
Infusion site evaluation[8,11]			X	X	X	X		X			X	X	X	X		X		
Concomitant medications		←----Monitored continuously----→																
Adverse events[12]		←----Monitored continuously----→																
Antibiotic prophylaxis[13]		←----Daily until CH50 normalizes ----→																
Discharge from CRU[14]						X												
Discuss safety risks with subject[15]	X		X			X	X	X	X	X			X	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; BMI = body mass index; C1 = Cohort 1; C2 = Cohort 2; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; ICF = informed consent form; MCV4 = meningococcal conjugate vaccine; OP = outpatient; PC = phone call; PD = pharmacodynamic; PK = pharmacokinetic; TB = tuberculosis.

1 Permissible windows for study assessments are described in the Study Operations Manual (SOM).

2 Signed and dated EC-approved ICF must be obtained before any study-specific screening procedures are performed.

3 For subjects who do not have adequate documentation of prior MCV4 immunization or serogroup B vaccination, MCV4 immunization will be performed at least 56 days prior to first dose on Day 1, and vaccination for serogroup B meningococcal infections will be administered at least 28 days prior to Day 1 dosing with a booster administered at least 28 days prior to dosing on Day 1.

4 Complement activity, confirmed by a suitable assay such as complement alternative pathway (CAP) ELISA/C5 (hemolysis) inhibition, will be performed at screening to confirm subjects do not have a complement deficiency.

5 The sample drawn on Day -1 will be stored for future analysis should the post-dose sample indicate that complement has not normalized. The post-dose sample will be taken on Day 36 (Cohort 1) or Day 71 (Cohort 2); if complement has not normalized, additional samples will be obtained on Day 50 for Cohort 1 and Days 90, 120 and 140 for Cohort 2. Interim CH50 samples may be taken at the discretion of the investigator to allow for samples taken between Days 120 and 140. Once a normal CH50 result is obtained, antibiotic prophylaxis can be stopped and additional CH50 samples are not required; if the Day 140 CH50 sample is not normal, the baseline sample will be analyzed and the investigator will contact the subject regarding whether antibiotic prophylaxis must be further extended.

6 Height at Screening only.

7 Serum pregnancy test at Screening and urine pregnancy test at other visits as indicated for all female subjects. Positive urine pregnancy results should be confirmed by serum test.

8 See Table 6 for pharmacokinetics, pharmacodynamics, immunogenicity, infusion site evaluation, vital signs, and ECG collection time points required on each dosing day.

9 Continuous cardiac registration predose through the duration of infusion.

Table 5: Schedule of Assessments: Cohorts 1 and 2 (Refer to Table 6 for Pharmacokinetics, Pharmacodynamics, Immunogenicity, Infusion Site Evaluation, Vital Signs, and ECG Collection Time Points Required on Day 1) (Continued)

[10] Clinical safety laboratory measurements on Day 1 will be collected 4 hours post dose. Follicle-stimulating hormones and estradiol levels will be measured at screening to confirm postmenopausal status, as described in Section 16.1.6.2.
[11] Induration or reaction < 1 cm will not be listed as an AE unless it persists for more than 24 hours. Pain at site of infusion will be assessed using a visual assessment scale (0-10).
[12] Collection of AEs and SAEs will begin after the ICF is signed.
[13] Subjects will receive oral penicillin V 500 mg twice daily (equivalent to 1,600,000 units) for the duration of the reduced complement activity, depending on their dose cohort assignment as described in Section 11.2.1. The first dose of antibiotic will be administered on Day -1 in the evening, prior to Day 1 (first dose) of ALXN1210. A suitable system (such as text messaging) will be used for daily monitoring of subjects' compliance with the antibiotic prophylaxis regimen.
[14] Subjects will be discharged from the CRU after completing all assessments on Day 5.
[15] Subjects will be provided a safety card with information for the healthcare provider and participant on symptoms of meningitis infection as well as contact information. This information will be reviewed with the subjects on a regular basis throughout the study (as indicated), and on the day of discharge.
[16] Day 140 assessments are for Cohort 2 subjects only. Cohort 1 subjects will not undergo Day 140 assessments.

Table 6: Cohort 1 and 2: Pharmacokinetics, Pharmacodynamics, Immunogenicity, Infusion Site Evaluation, Vital Signs, and ECG Collection Time Points

	Pre dose	EOI	Post EOI	Post SOI										
Collection Time Relative to Dose	**pre**	**EOI**	**30 min**	**15 min**	**30 min**	**60 min**	**1.5 hr**	**2 hr**	**4 hr**	**8 hr**	**18 hr**	**24 hr**	**30 hr**	**36 hr**	**48 hr**
Study Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**3**
Assessments[1]															
ECG (triplicate)	X							X				X			
Infusion site evaluation		X						X	X	X		X			X
Vital signs[2]	X	X		X	X (C2)	X	X	X	X	X		X			X
PK samples	X	X	X						X	X		X			X
PD panel (serum C5, cRBC hemolysis)	X	X	X						X	X		X			X
Immunogenicity (ADA)	X														

Abbreviations: ADA = antidrug antibody; C2 = Cohort 2; ECG = electrocardiogram; EOI = end of infusion; PD = pharmacodynamic; PK = pharmacokinetic; SOI = start of infusion.

[1] Permissible windows for study assessments are described in the Study Operations Manual (SOM).

[2] 30-min post-SOI vitals for Cohort 2 only.

Table 7: Schedule of Assessments: Cohort 3; Screening, Doses 1 to 4 (Refer to Table 8 for Period 5 and Follow-up)

	Screening	Period 1								Periods 2, 3, and 4							
Doses 1 and 2 Study Day		**–1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**28**	**29**	**30**	**31**	**33**	**36**	**43**	**50**
Dose 3 Study Day										**56**	**57**	**58**	**59**	**61**	**64**	**71**	**78**
Dose 4 Study Day										**84**	**85**	**86**	**87**	**89**	**92**	**99**	**106**
Day relative to start of dosing period		**-1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**-1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**
Status (OP, PC, or CRU)	**OP**	**CRU Day -1**	**CRU Day 1**	**CRU Day 2**	**CRU Day 3**	**CRU Day 5**	**OP**	**OP**	**OP**	**CRU Day -1**	**CRU Day 1**	**CRU Day 2**	**CRU Day 3**	**OP**	**PC**	**OP**	**PC**
Assessments[1]																	
Informed consent[2]	X																
MCV4 immunization (Day -56)[3]	X																
Meningococcal serogroup B immunization (Day -5 and Day -28)[3]	X																
Serum bactericidal antibody (meningococcus Group A, C, W135, and Y)[3]	X																
Medical history and demographics	X																
QuantiFERON TB test	X																
Hepatitis B and C screen	X																
HIV, types 1 and 2 screen	X																
Complement activity[4]	X																
CH50[5]		X															
Alcohol breath test	X	X															
Urine drug screen	X	X															
Height, weight, BMI[6]	X	X															
Pregnancy test[7]	X	X								X							
Admittance to CRU		X								X							
Physical examination	X	X				X		X		X				X		X	
Vital signs[8]	X	X	X	X	X	X		X		X	X	X	X	X		X	
ECG (triplicate)[9]	X		X	X	X	X		X			X	X		X		X	
Cardiac telemetry[9]			X								X						
Chemistry[10]	X	X	X	X		X		X		X		X		X		X	
Hematology[10]	X	X	X	X		X		X		X		X		X		X	

Table 7: Schedule of Assessments: Cohort 3; Screening, Doses 1 to 4 (Refer to Table 8 for Period 5 and Follow-up) (Continued)

	Screening	Period 1								Periods 2, 3, and 4							
Doses 1 and 2 Study Day		**–1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**28**	**29**	**30**	**31**	**33**	**36**	**43**	**50**
Dose 3 Study Day										**56**	**57**	**58**	**59**	**61**	**64**	**71**	**78**
Dose 4 Study Day										**84**	**85**	**86**	**87**	**89**	**92**	**99**	**106**
Day relative to start of dosing period		**-1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**	**-1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**
Status (OP, PC, or CRU)	**OP**	**CRU Day -1**	**CRU Day 1**	**CRU Day 2**	**CRU Day 3**	**CRU Day 5**	**OP**	**OP**	**OP**	**CRU Day -1**	**CRU Day 1**	**CRU Day 2**	**CRU Day 3**	**OP**	**PC**	**OP**	**PC**
Assessments[1]																	
Coagulation[10]	X	X	X	X		X		X		X		X		X		X	
Urinalysis and urine chemistry[10]	X	X		X		X		X		X		X		X		X	
Study drug administration[11]			X								X						
PK samples[8]			X	X	X	X	X	X	X		X	X	X	X		X	
PD panel (serum C5, cRBC hemolysis)[8]		X	X	X	X	X	X	X	X		X	X	X	X		X	
Immunogenicity (ADA)[8]			X				X	X	X		X					X	
Infusion site evaluation[8,12]			X	X	X	X		X			X	X	X	X		X	
Concomitant medications		X	←----Monitored continuously----→														
Adverse events[13]		X	←----Monitored continuously----→														
Antibiotic prophylaxis[14]		X	←----Daily----→														
Discharge from CRU[15]						X							X				
Discuss safety risks with subject[16]	X		X			X	X	X	X	X			X	X	X	X	X

Abbreviations: ADA = antidrug antibody; BMI = body mass index; CRU = clinical research unit; ECG = electrocardiogram; HIV = human immunodeficiency virus; ICF = informed consent form; MCV4 = meningococcal conjugate vaccine; OP = outpatient; PC = phone call; PD = pharmacodynamic; PK = pharmacokinetic; TB = tuberculosis.

[1] Permissible windows for study assessments are described in the Study Operations Manual (SOM).

[2] Signed and dated EC-approved ICF must be obtained before any study-specific screening procedures are performed.

[3] For subjects who do not have adequate documentation of prior MCV4 immunization or serogroup B vaccination, MCV4 immunization will be performed at least 56 days prior to first dose on Day 1, and vaccination for serogroup B meningococcal infections will be administered at least 56 days prior to Day 1 dosing with a booster administered at least 28 days prior to dosing on Day 1.

[4] Complement activity, confirmed by a suitable assay such as complement alternative pathway (CAP) ELISA/C5 (hemolysis) inhibition, will be performed at screening to confirm subjects do not have a complement deficiency.

[5] The CH50 sample drawn on Day -1 will be stored for future analysis should all the post-dose samples indicate that complement has not normalized.

Table 7: Schedule of Assessments: Cohort 3; Screening, Doses 1 to 4 (Refer to Table 8 for Period 5 and Follow-up) (Continued)

[6] Height at Screening only.
[7] Serum pregnancy test at Screening and urine pregnancy test as indicated for all female subjects. Positive urine pregnancy results should be confirmed by serum test.
[8] See Table 9 for pharmacokinetics, pharmacodynamics, immunogenicity, infusion site evaluation, vital signs, and ECG collection time points required on each dosing day.
[9] Continuous cardiac registration predose through the duration of infusion.
[10] Clinical safety laboratory measurements on Day 1 Period 1 will be collected 4 hours post dose. Follicle-stimulating hormones and estradiol levels will be measured at screening to confirm postmenopausal status, as described in Section 16.1.6.2.
[11] Subjects who discontinue from the study before Dose 5 will be followed for 185 days after the last dose and instructed to return for follow-up visits (see Table 9). Subjects who discontinue the study after Dose 5 will be instructed to return for study visits through Day 298.
[12] Induration or reaction < 1 cm will not be listed as an AE unless it persists for more than 24 hours. Pain at site of infusion will be assessed using a visual assessment scale (0-10).
[13] Collection of AEs and SAEs will begin after the ICF is signed.
[14] Subjects will receive oral penicillin V 500 mg twice daily (equivalent to 1,600,000 units) for the duration of the reduced complement activity, depending on their dose cohort assignment as described in Section 11.2.1. The first dose of antibiotic will be administered on Day -1 in the evening, prior to the Day 1 (first dose) of ALXN1210. A suitable system (such as text messaging) will be used for daily monitoring of subjects' compliance with the antibiotic prophylaxis regimen.
[15] For Dose 1 and 5, subjects will be discharged from the CRU after completing all assessments on Day 5. For Doses 2 to 4, subjects will be discharged from the CRU on Day 3 after completing all assessments through 48 hours.
[16] Subjects will be provided a safety card with information for the healthcare provider and participant on symptoms of meningitis infection as well as contact information. This information will be reviewed with the subjects on a regular basis throughout the study (as indicated), and on the day of discharge.

Table 8: Schedule of Assessments: Cohort 3; Period 5 and Follow-up

	Period 5								Follow-Up Post Period 5									
Dose 5 Study Day	**112**	**113**	**114**	**115**	**117**	**120**	**127**	**134**	**141**	**148**	**155**	**162**	**169**	**183**	**197**	**225**	**253**	**298**
Day relative to dosing	**-1**	**1**	**2**	**3**	**5**	**8**	**15**	**22**										
Status (OP or CRU)	**CRU Day -1**	**CRU Day 1**	**CRU Day 2**	**CRU Day 3**	**CRU Day 5**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**
Assessments[1]																		
Pregnancy test[2]	X															X	X	X
Physical examination	X				X		X		X				X			X	X	X
Vital signs[3]	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
ECG (triplicate)[3]		X	X	X	X		X										X	X
Cardiac telemetry[4]		X																
Chemistry[5]	X	X	X		X		X		X				X			X	X	X
Hematology[5]	X	X	X		X		X		X				X			X	X	X
Coagulation[5]	X	X	X		X		X		X				X			X	X	X
Urinalysis and urine chemistry[5]	X		X		X		X		X				X			X	X	X
CH50 assay[6]															X	X	X	X
Study drug administration[7]		X																
PK samples[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD panel (serum C5, cRBC hemolysis)[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity (ADA)[3]		X				X			X				X		X	X	X	X
Infusion site evaluation[3,8]		X	X	X	X		X											
Concomitant medications	X	←----Monitored continuously----→																
Adverse events	X	←----Monitored continuously----→																
Antibiotic prophylaxis[9]	X	←----Daily until CH50 normalizes ----→																
Discharge from CRU[10]		X			X													
Discuss safety risks with subject[11]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; CRU = clinical research unit; ECG = electrocardiogram; ICF = informed consent form; OP = outpatient; PD = pharmacodynamic; PK = pharmacokinetic.

[1] Permissible windows for study assessments are described in the Study Operations Manual (SOM).

[2] Urine pregnancy test for all female subjects as indicated. Positive urine pregnancy results should be confirmed by serum test

[3] See Table 10 for pharmacokinetics, pharmacodynamics, immunogenicity, infusion site evaluation, vital signs, and ECG collection time points required on each dosing day.

Table 8: Schedule of Assessments: Cohort 3; Period 5 and Follow-up (Continued)

[4] Continuous cardiac registration pre-dose through the duration of infusion.
[5] Clinical safety laboratory measurements on Day 113 of Period 5 will be collected 4 hours post dose.
[6] CH50 sample will be taken on Days 197, 225, 253, and 298. Interim CH50 samples may be taken at the discretion of the PI to allow for samples taken between Days 197, 225, 253, and 298. Once a normal CH50 result is obtained, antibiotic prophylaxis can be stopped and additional CH50 samples are not required; if the Day 298 CH50 sample is not normal, the baseline sample will be analyzed and the investigator will contact the subject regarding whether antibiotic prophylaxis must be further extended.
[7] Subjects who discontinue from the study before Dose 5 will be followed for 185 days after the last dose and instructed to return for follow-up visits (see Table 9). Subjects who discontinue the study after Dose 5 will be instructed to return for study visits through Day 298.
[8] Indurations or reactions < 1 cm will not be listed as an AE unless it persists for more than 24 hours. Pain at site of infusion will be assessed using a visual assessment scale (0-10).
[9] Subjects will receive oral penicillin V 500 mg twice daily (equivalent to 1,600,000 units) for the duration of the reduced complement activity, depending on their dose cohort assignment as described in Section 11.2.1. Subjects will receive the first dose on Day -1 in the evening. A suitable system (such as text messaging) will be used for daily monitoring of subjects' compliance with the antibiotic prophylaxis regimen.
[10] For Dose 5, subjects will be discharged from the CRU after completing all assessments on Day 5.
[11] Subjects will be provided a safety card with information for healthcare provider and participant on symptoms of meningitis infection and contact information. This information will be reviewed with the subjects on a regular basis throughout the study (as indicated), and on the day of discharge.

Table 9: Cohort 3: Follow-Up and Early Termination Procedures for Subjects Who Discontinue During Periods 1 to 4

Days Relative to Last Dose	28	35	42	49	56	70	84	112	140	168	185	ET
Dose 1 Study Day	29	36	43	50	57	71	85	113	141	169	186	
Dose 2 Study Day	57	64	71	78	85	99	113	141	169	197	214	
Dose 3 Study Day	85	92	99	106	113	127	141	169	197	225	242	
Dose 4 Study Day	113	120	127	134	141	155	169	197	225	253	270	
Status (OP or CRU)	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP
Assessments[1]												
Pregnancy test[2]										X	X	X
Physical examination	X				X			X		X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
ECG (triplicate)										X	X	X
Chemistry	X				X			X		X	X	X
Hematology	X				X			X		X	X	X
Coagulation	X				X			X		X	X	X
Urinalysis and urine chemistry	X				X			X		X	X	X
CH50[3]								X		X	X	
PK samples	X	X	X	X	X	X	X	X	X	X	X	X
PD panel (serum C5, cRBC hemolysis)	X	X	X	X	X	X	X	X	X			X
Immunogenicity (ADA)	X				X		X	X	X	X	X	X
Concomitant medications	←----Monitored continuously----→											X
Adverse events	←----Monitored continuously----→											X
Antibiotic prophylaxis[4]	←----Daily until CH50 normalizes ----→											
Discuss safety risks with subject[5]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; CRU = clinical research unit; ECG = electrocardiogram; ET= Early Termination; ICF = informed consent form; OP = outpatient; PD = pharmacodynamic.

[1] Permissible windows for study assessments are described in the SOM.

[2] Urine pregnancy test for all female subjects. Positive urine pregnancy results should be confirmed by serum test.

[3] CH50 samples will be taken 112, 168, and 185 days relative to last dose. Once a normal CH50 result is obtained, antibiotic prophylaxis can be stopped and additional CH50 samples are not required; if the CH50 sample 185 days after last dose is not normal, the baseline sample will be analyzed and the investigator will contact the subject regarding whether antibiotic prophylaxis must be further extended.

[4] Subjects will receive oral penicillin V 500 mg twice daily (equivalent to 1,600,000 units) for the duration of the reduced complement activity, depending on their dose cohort assignment as described in Section 11.2.1. The first dose of antibiotic will be administered on Day -1 in the evening, prior to the Day 1 (first dose) of ALXN1210. A suitable system (such as text messaging) will be used for daily monitoring of subjects' compliance with the antibiotic prophylaxis regimen.

[5] Subjects will be provided a safety card with information for healthcare provider and participant on symptoms of meningitis infection and contact information. This information will be reviewed with the subjects on a regular basis throughout the study (as indicated).

Table 10: Cohort 3: Pharmacokinetics, Pharmacodynamics, Immunogenicity, Infusion Site Evaluation, Vital Signs, and ECG Collection Time Points Required on Each Dosing Day

Collection Time Relative to Dose	Pre dose	EOI	Post EOI	Post SOI											
	pre	EOI	30 min	15 min	30 min	60 min	1.5 hr	2 hr	4 hr	8 hr	18 hr	24 hr	30 hr	36 hr	48 hr
Dose 1 Study Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**3**
Dose 2 Study Day	**29**	**29**	**29**	**29**	**29**	**29**	**29**	**29**	**29**	**29**	**29**	**30**	**30**	**30**	**31**
Dose 3 Study Day	**57**	**57**	**57**	**57**	**57**	**57**	**57**	**57**	**57**	**57**	**57**	**58**	**58**	**58**	**59**
Dose 4 Study Day	**85**	**85**	**85**	**85**	**85**	**85**	**85**	**85**	**85**	**85**	**85**	**86**	**86**	**86**	**87**
Dose 5 Study Day	**113**	**113**	**113**	**113**	**113**	**113**	**113**	**113**	**113**	**113**	**113**	**114**	**114**	**114**	**115**
Assessments[1]															
ECG (triplicate)	X							X				X			
Infusion site evaluation		X						X	X	X		X			X
Vital signs	X	X		X	X	X	X	X	X	X		X			X
PK samples	X	X	X						X	X		X			X
PD panel (serum C5, cRBC hemolysis)	X	X	X						X	X		X			X
Immunogenicity (ADA)	X														

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; EOI = end of infusion; PD = pharmacodynamic; PK = pharmacokinetic; SOI = start of infusion.
[1] Permissible windows for study assessments are described in the SOM.

10. SELECTION AND WITHDRAWAL OF SUBJECTS

10.1. Subject Inclusion Criteria

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

1. Healthy Japanese males or females aged 25 through 55 years, inclusive (subjects must have lived outside of Japan for ≤ 10 years and be first generation Japanese, defined as born in Japan and having 4 biologic grandparents who are ethnic Japanese).
2. Body mass index (BMI) from 18 through 29.9 kg/m^2, inclusive, and weight between 50 and 100 kg, inclusive.
3. QT interval (corrected using the Fridericia's formula; QTcF) ≤ 450 msec for males and ≤ 470 msec for females at screening and prior to dosing on Day 1.
4. Willing and able to give written informed consent and comply with the study visit schedule.
5. Documented vaccination with MCV4 at least 56 days and not more than 3 years prior to dosing. Documentation must include a positive SBA to confirm an immune response before study drug administration.
6. Vaccination with serogroup B meningococcal vaccine at least 56 days prior to dosing on Day 1, with a booster administered at least 28 days prior to dosing on Day 1, with at least 28 days between the first and second injections.
7. Female subjects of childbearing potential must use highly effective contraception as defined below, starting at screening and continuing until at least 6 months (Cohort 1) or 8 months (Cohorts 2 and 3) after the last dose of ALXN1210.

   Highly effective contraceptive methods for females are as follows*:

   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - Oral
     - Intravaginal
     - Transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation:
     - Oral
     - Injectable
     - Implantable
   - Intrauterine device
   - Intrauterine hormone-releasing system
   - Bilateral tubal occlusion

* It is recommended that heterosexually active female subjects of childbearing age who take oral contraceptives and penicillin V, or any other antibiotics with the potential to reduce the effectiveness of hormonal contraception, should use a barrier method (eg, condom or diaphragm and spermicide) in addition to the oral contraceptive medication.

Male subjects 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 6 months (Cohort 1) or 8 months (Cohorts 2 and 3) after the last dose of ALXN1210. Barrier contraception is required even with documented medical assessment of surgical success of a vasectomy. Female spouses or partners of male subjects who are of childbearing potential must use highly effective contraception as defined above, or acceptable contraception as defined below, starting at screening and continuing until at least 6 months (Cohort 1) or 8 months (Cohorts 2 and 3) after the last dose of ALXN1210. Male subjects must not donate sperm during the screening and treatment periods and for at least 6 months (Cohort 1) or 8 months (Cohorts 2 and 3) after the last dose of ALXN1210.

Acceptable contraceptive methods are as follows:

- Simultaneous use of male condom and, for the female partner, occlusive cap (diaphragm or cervical/vault caps) with intravaginally applied spermicide

10.2. Subject Exclusion Criteria

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

1. Subjects who are in intimate and prolonged contact with (defined as living under the same roof or providing personal care) people younger than 2 years of age or older than 65 years of age, or who are either immunocompromised or have one of the following underlying medical conditions: anatomic or functional asplenia (including sickle cell disease); congenital complement, properdin, factor D, or primary antibody deficiencies; acquired complement deficiencies (eg, those receiving eculizumab); or human immunodeficiency virus (HIV)
2. Subjects who are one of the following:
   - Professionals who are exposed to environments of greater risk for meningococcal disease
   - Research, industrial, and clinical laboratory personnel who are routinely exposed to *N meningitidis*
   - Military personnel during recruit training (military personnel may be at increased risk of meningococcal infection when accommodated in close quarters)
   - Daycare center workers
   - Those living on a college or university campus

- Those who plan to travel during the course of the study to or have travelled to endemic areas for meningococcal meningitis (eg, India, Sub-Saharan Africa, pilgrimage to Saudi Arabia for Hajj) within the past 6 months

3. History of any *Neisseria* infection
4. History of unexplained, recurrent infection; or infection requiring treatment with systemic antibiotics within the last 90 days prior to dosing.
5. HIV infection (evidenced by HIV-1 or HIV-2 antibody titer).
6. Acute or chronic hepatitis B virus (HBV) infection. Hepatitis B surface antigen (HBsAg) testing is required for all subjects prior to enrollment. Subjects with positive HBsAg will not be enrolled.

   For subjects with negative HBsAg, the following testing algorithm will be required:

   - If hepatitis B core antibody (HBcAb) is negative, the subject is eligible to enroll.
   - If HBcAb is positive, the hepatitis B surface antibody (HBsAb) will be tested.
     - If both HBcAb and HBsAb are positive, the subject is eligible to enroll.
     - If HBcAb is positive and HBsAb is negative, the subject will not be enrolled.
7. Acute or chronic hepatitis C virus (HCV) infection (evidenced by antibody titer).
8. Active systemic viral or fungal infection within 14 days prior to dosing.
9. Positive or indeterminate QuantiFERON®-TB test indicating possible tuberculosis infection.
10. History of latent or active tuberculosis or exposure to endemic areas within 8 weeks prior to the screening visit.
11. Female subjects who are breastfeeding or are unwilling to practice contraception and are not postmenopausal. Postmenopausal is defined as amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle-stimulating hormone level ≥ 40 mIU/mL and estradiol concentration ≤ 110 pmol/L within the 6 months prior to drug administration.
12. Positive serum pregnancy test at screening or Day –1.
13. Serum creatinine greater than the upper limit of normal (ULN) of the reference range of the testing laboratory at screening or Day –1.
14. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > ULN of the reference range of the testing laboratory at screening or > 1.5 × ULN of the reference range of the testing laboratory at Day –1.
15. Any of the following hematology results: hemoglobin < 130 g/L for males and < 115 g/L for females; hematocrit < 0.37 L/L for males and < 0.33 L/L for females; white blood cells (WBC) < $3.0 \times 10^3/\mu L$; absolute neutrophils < $2.0 \times 10^3/\mu L$; and platelets < 150 or > $400 \times 10^3/\mu L$ at screening or Day –1. Complete blood count (CBC) clinical laboratory results that are considered clinically relevant and unacceptable by the investigator at Day –1.

16. History of complement deficiency or complement activity below normal reference range as evaluated by CAP ELISA at screening.
17. History of malignancy 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. Participation in a clinical study within 30 days before initiation of dosing on Day 1 or use of any experimental small-molecule therapy within 30 days prior to dosing on Day 1.
19. Participation in more than one clinical study of a mAb, or participation in a clinical study of a mAb within the 12 months prior to screening, during which the subject was exposed to the active study drug. Subjects who have participated in only one study of a mAb may be considered for enrollment if they completed that study more than 12 months prior to screening.
20. Major surgery or hospitalization within 90 days prior to dosing.
21. Contraindication to receiving MCV4 and/or serogroup B vaccine, including severe allergic reaction to a previous dose of MCV4 and/or serogroup B vaccine; severe allergy to any vaccine component; or previous diagnosis of Guillain-Barré syndrome.
22. History of allergy to excipients of ALXN1210 (eg, polysorbate 80).
23. Documented history of allergy to penicillin or cephalosporin.
24. History of significant allergic reaction (anaphylaxis, angioedema) to any product (food, pharmaceutical, etc.).
25. Currently smokes > 10 cigarettes daily (former smokers may be permitted to enroll at the investigator's discretion).
26. History of illicit drug abuse, history of significant alcohol abuse within 1 year prior to the screening visit, or regular use of alcohol within 6 months prior to the screening visit (more than 14 units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]).
27. Positive urine drug toxicology screen at screening or Day –1.
28. Alcohol consumption within 48 hours prior to study drug administration or positive alcohol breath test on Day –1.
29. Donation of plasma within 7 days prior to dosing. Donation or loss (excluding volume drawn at screening) of more than 50 mL of blood within 30 days of dosing or more than 499 mL of blood within 56 days of dosing.
30. History of continuous topical/inhaled or systemic steroid use > 1 month or history of any inhaled or topical immunosuppressive therapy within 90 days prior to study drug administration.
31. Use of prescription medications (excluding oral contraceptives) within 14 days prior to study drug administration.
32. Regular use of nonprescription, over-the-counter medications, including herbal remedies/supplements, within 14 days prior to study drug administration. Multivitamins,

acetaminophen ≤ 2 g per day, and topical skin products without significant systemic absorption are allowed.

33. Clinical diagnosis of any autoimmune or rheumatologic disease (eg, systemic lupus erythematosus, rheumatoid arthritis).
34. Immunization with a live-attenuated vaccine 1 month prior to dosing or planned vaccination during the course of the study (except for the vaccination planned by the study protocol). Immunization with inactivated or recombinant influenza vaccine is permitted.
35. Presence of fever (confirmed body temperature > 37.6°C) (eg, a fever associated with a symptomatic viral or bacterial infection) within 14 days prior to the first dosing.
36. Subjects with any medical history, conditions or risks, which in the opinion of the investigator, may interfere with the subject's full participation in the study, or compliance with the protocol, or pose any additional risk for the subject, or confounds the assessment of the subject or outcome of the study.

10.3. Subject Withdrawal Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. Subjects who discontinue dosing will be instructed to return for follow-up visits as described in the schedule of assessments.

Unless the PI and sponsor agree to an alternative regimen, all subjects will take prophylactic antibiotics (oral penicillin V 500 mg twice daily) until complement activity has normalized (as determined by CH50 assay).

11. TREATMENT OF SUBJECTS

11.1. Description of Study Drug

The investigational product is described in Table 11.

Table 11: Investigational Product

	Investigational Product
Product Name	ALXN1210
Dosage Form	Sterile solution for intravenous administration
Unit Dose	150 mg/vial
Route of Administration	Intravenous
Physical Description	Sterile, preservative-free solution
Manufacturer	Alexion Pharmaceuticals, Inc.

BP= British Pharmacopoeia; Ph. Eur. = European Pharmacopoeia.

11.2. Infection

11.2.1. Vaccine and Antibiotic Prophylaxis

To mitigate the risk of infection associated with terminal complement inhibition, subjects in this study will be administered:

1. MCV4 vaccination at least 56 days prior to dosing with ALXN1210 (if not vaccinated with MCV4 within the last 3 years, or if subjects have been previously vaccinated but there is not adequate documentation to verify prior vaccination).
2. Two injections of the serogroup B meningococcal vaccine. The first injection must be administered at least 56 days prior to dosing on Day 1, and the booster must be administered at least 28 days prior to dosing on Day 1, with at least 28 days between the first and second injections.
3. Prophylactic antibiotic treatment, oral penicillin V 500 mg twice daily (equivalent to 1,600,000 units) for the duration of the reduced complement activity, ie, until complement activity is predicted to be restored to normal based on the expected drug concentration, and based on the in vitro hemolytic activity assay analysis for the cohort at 2 to 5 weeks prior to the planned termination of the antibiotic prophylaxis (see Section 5.1.4.1).

The first dose of antibiotic will be administered orally on Day –1 in the evening, prior to the Day 1 (first dose) of ALXN1210. For the outpatient portion of the study, subjects will be instructed to take the antibiotic approximately at the same times (twice daily) on each scheduled day. A suitable system (such as text messaging) will be used for daily monitoring of subjects' compliance with the antibiotic prophylaxis regimen.

The following observations support the administration of antibiotic prophylaxis in this multiple-dose study of ALXN1210:

1. Penicillin is the drug of choice in eradication of *N meningitidis* in carriers.
2. Complement-deficient patients who received monthly injections with benzathine penicillin G as prophylaxis for recurrent meningococcal disease during a 2- to 4-year period experienced significantly fewer episodes of Neisseria infection than deficient individuals not receiving prophylaxis (Figueroa 1991).
3. High levels of resistance to penicillin caused by plasmid-encoded β-lactamases are rarely encountered in meningococcal strains (Yazdankhah 2004).
4. Antibiotic prophylaxis with orally administered penicillin V 500 mg twice daily has been provided in the treatment of PNH and aHUS patients with eculizumab by some physicians (Kelly 2011; Leeds Teaching Hospitals NHS Trust and Kings College Hospital NHS Foundation Trust 2013).
5. Uncertainty around the effectiveness of vaccines in immunocompromised patients has prompted several countries, such as France, to recommend continuous antibiotic prophylaxis for the duration of eculizumab treatment in PNH and aHUS patients (Zuber 2012).

11.2.2. Risk of Infection Reminders

Risk of infection will be explained and discussed with subjects during the informed consent process, occurring at the screening session (see the Informed Consent Form [ICF], Part 2, Risk of Side Effects). In order to increase the risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the subjects during the course of the study, additional discussion and explanation of the potential risks, signs, and symptoms, as described in the ICF, will take place at specific time points throughout the study as noted in the Schedules of Assessments (Section 9). Subjects will also be provided a safety card to carry with them at all times.

11.3. Prior and Concomitant Medications and Procedures

Prior medications (any drug or substance taken by the subject within 14 days prior to the time the subject signs the informed consent until the first dose of study drug) and concomitant medications (any drug or substance taken by the subject after the first dose of study drug until completion of the last study visit) will be recorded on the subject's case report form. Prior procedures (any therapeutic intervention [eg, surgery/biopsy, physical therapy] performed within 14 days prior to the time the subject signs the informed consent until the first dose of study drug) and concomitant procedures (any therapeutic intervention [eg, surgery/biopsy, physical therapy] performed after the first dose of study drug until completion of the last study visit) will be recorded on the subject's case report form.

For the duration of the study, subjects will be instructed not to start taking any new medications, including nonprescription drugs and herbal preparations, unless they have received permission from the investigator. The occasional use of over-the-counter antipyretics or analgesics (eg, acetaminophen) may be allowed during the study, at the discretion of the investigator.

Concomitant procedures are not allowed unless medically indicated.

The use of concomitant therapies defined above must be recorded. Adverse events related to administration of these therapies or procedures must be documented.

11.4. Permitted Medications

Subjects are permitted to take multivitamins, acetaminophen ≤ 2 g per day, and topical skin products without significant systemic absorption. Subjects are also permitted to receive a booster vaccine, if required.

11.5. Restrictions

Caffeine: Xanthine-containing products (coffee, tea, chocolate) are prohibited for at least 24 hours prior to admission through discharge from the clinical unit, and for 24 hours prior to each follow-up visit.

Alcohol: Alcohol use is prohibited 48 hours prior to admission until discharge from the clinical unit, and for 24 hours prior to each follow-up visit.

Meals: No outside food or drink is permitted at the clinical site. All meals and snacks will be provided. Subjects will receive standard meals and snacks at regimented times during confinement.

Poppy seeds: Subjects are required to abstain from food containing poppy seeds within 24 hours prior to admission.

Tobacco: Subjects will be required to abstain from smoking from at least 2 hours prior to start of infusion (SOI) until discharge from the clinical unit.

11.6. Treatment Compliance

Subjects will be administered study drug in a controlled setting under the supervision of the investigator, thereby ensuring compliance with study drug administration. Study coordinators at the investigative site will ensure that all subjects are adequately informed on the specific study drug dosing regimen required for compliance with the study protocol.

Alexion or its designee will periodically monitor the study site 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.

11.7. Randomization and Blinding

This is an open-label study (subjects and on-site medical/nursing staff and pharmacy staff are aware of study drug/dose assignment). Eligible subjects who meet the inclusion/exclusion criteria will be sequentially enrolled and assigned to receive ALXN1210. Once a subject identification number has been assigned to 1 subject, it may not be assigned to another subject.

12. STUDY DRUG MATERIALS AND MANAGEMENT

12.1. Study Drug

Each vial of study drug contains 150 mg of ALXN1210 in 10 mM sodium phosphate, 150 mM sodium chloride, 0.02% polysorbate 80, and Water for Injection. ALXN1210 is formulated at pH 7.0 and is presented as a sterile, preservative-free 10-mg/mL solution for IV administration, supplied in 20-mL single-use vials, and will be diluted in 0.9% Sodium Chloride Injection European Pharmacopoeia (Ph. Eur.) or British Pharmacopoeia (BP) and administered by IV infusion at a fixed rate of 686 mg/h, excluding interruption for safety or technical reasons. 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.

12.2. 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 local regulatory requirements.

12.3. 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.

12.4. Study Drug Preparation

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

The handling and preparation of materials used to prepare and administer the investigational product must be carried out using aseptic techniques for sterile products.

For each subject, doses will be prepared as required for the dose cohort as indicated in Table 12.

12.4.1. ALXN1210 Dose Preparation

ALXN1210 will be diluted with 0.9% Sodium Chloride Injection Ph. Eur. or BP and administered by IV infusion at a fixed rate of 686 mg/h, excluding interruption for safety or technical reasons.

Table 12: Dosing Reference Chart for ALXN1210 Dose Preparation

Cohort	ALXN1210 Dose (mg)	ALXN1210 Volume per Dose (mL)	Diluent Volume per Dose (mL)	Infusion Volume (mL)
1	1 dose of 400 mg	40	40	80
2	1 dose of 800 mg	80	80	160
3	5 doses of 800 mg each	80	80	160

Please refer to the pharmacy manual for additional dose preparation instructions.

12.4.2. In-Use Shelf Life

ALXN1210 will be diluted with 0.9% Sodium Chloride Injection Ph. Eur. or BP 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) and for 24 hours at 2°C to 8°C (36°F to 46°F). The expiration date and time of the dosing solution is calculated from the time dose preparation is complete. The dose must be administered within the expiration date and time.

12.5. Administration

All doses of ALXN1210 will be administered by IV infusion, using IV sets with in-line filters, at a fixed rate of 686 mg/h (equivalent to 137 mL/h), excluding interruption for safety or technical reason. Infusion volume and duration is summarized in Table 13. Infusion of a subject must be completed before starting the infusion of the next subject in the same cohort. For further information regarding the preparation and administration of study drug, please see the Pharmacy Manual.

Table 13: Infusion Volume and Duration

Cohort	ALXN1210 Dose (mg)	Infusion Volume (mL)	Infusion Duration (Minutes)*	Infusion Rate (mg/h)	Infusion Rate (mL/h)	Concentration of Dosing Solution (mg/mL)
1	1 dose of 400 mg	80	50	686	137	5.0
2	1 dose of 800 mg	160	90	686	137	5.0
3	5 doses of 800 mg each	160	90	686	137	5.0

*Infusion durations are approximate.

For safety reasons, subjects will remain supine or semi-reclined for the time of drug administration and until at least 2 hours after end of infusion (EOI). Failure of subjects to comply with this requirement does not constitute a deviation from the protocol if it is medically necessary, procedurally required, or to go to the bathroom. When appropriate, subjects will be accompanied by a staff member during ambulation.

Time of dosing (t = 0) will be defined as ALXN1210 SOI. All procedures will be performed in relation to SOI or EOI as described in the Schedules of Assessments (Section 9).

12.6. Management of Potential Drug Infusion Reactions

Some subjects 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.

Subjects will be closely monitored during and after study drug administration for any symptoms of anaphylaxis and other hypersensitivity reactions, including circulatory and/or respiratory changes or arrest, or urticaria, arthralgias, myalgias or other signs of related reactions. Adequate treatment will be immediately available. Infusion-associated AEs may occur, and depending on its type and severity, discontinuation of infusion may be required. Subjects will be informed of early symptoms and signs of hypersensitivity reactions including hives, swollen face, eyelids, lips, or tongue, or trouble with breathing. An acute infusion reaction algorithm will be used to manage infusion related reactions (see Appendix 1: Acute Infusion Reactions Algorithm). In this study regular assessments to monitor infusion reactions and infusion site reactions will be done.

To ensure that reactions can be dealt with promptly there will be at least 15 minutes between the end of infusion in one subject and the start of infusion in the next subject; no more than 4 subjects will be dosed per day. Any reactions will be treated and taken into account in the dose continuation/escalation and toxicity rules. If anaphylactic reactions occur, the current "UK Treatment Guideline for Anaphylactic Reactions" of the UK Resuscitation Council will be followed (see Appendix 2: United Kingdom Resuscitation Council Anaphylaxis Algorithm).

Subjects who experience a severe reaction during administration of study drug resulting in discontinuation of study drug should undergo all scheduled safety, immunogenicity, PK, and PD evaluations required by the protocol. Subjects will therefore be instructed to attend all scheduled visits and undergo all procedures per protocol.

12.7. Study Drug Accountability

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

Unless otherwise notified, all vials both used and unused, must be saved for study drug accountability. 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.

12.8. Study Drug Handling and Disposal

If any study drug supplies are to be destroyed at the site, the investigator must obtain prior approval by Alexion. The investigator must notify Alexion, in writing, of the method, date, and location of destruction.

At the completion of the study, in order to satisfy regulatory requirements regarding drug accountability, all remaining investigational product inventory will be reconciled and retained or destroyed according to applicable United Kingdom regulations and the policies and procedures applicable to the study center.

For handling instructions, please refer to the Pharmacy Manual.

13. PHARMACOKINETIC ASSESSMENTS

13.1. Blood Sample Collection

No more than 470 mL of blood will be taken within each 16-week period. This allows for regeneration of RBCs and is in accordance with the guidance of NHS Blood and Transplant (http://www.blood.co.uk/about-blood/how-the-body-replaces-blood/). Please refer to the laboratory manual for specific details regarding blood volumes.

After study drug administration, blood samples for the determination of serum ALXN1210 concentrations will be collected at the time points indicated in the Schedules of Assessments (Section 9), with the actual blood sampling dates and times being recorded and used in the 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 subject will not exceed the currently planned number of time points.

Serum concentrations will be collected at the time points indicated in Table 14.

Table 14: Collection Time Points for Serum Concentrations of ALXN1210

Collection Time Points for Cohort 1	
(Days 1-120)	On Day 1 before dosing (within 15 min prior to the start of infusion [SOI]); end-of-infusion (EOI), 30 min after the EOI, and at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), Day 5 (96 hr), Day 8 (168 hr), Day 15 (336 hr), Day 22 (504 hr), Day 29 (672 hr), Day 36 (840 hr), Day 43 (1008 hr), Day 50 (1176 hr), Day 57 (1344 hr), Day 71 (1680 hr), Day 90 (2136 hr), and Day 120 (2856 hr)
Collection Time Points for Cohort 2	
(Days 1-140)	On Day 1 before dosing (within 15 min prior to the start of infusion [SOI]); end-of-infusion (EOI), 30 min after the EOI, and at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), Day 5 (96 hr), Day 8 (168 hr), Day 15 (336 hr), Day 22 (504 hr), Day 29 (672 hr), Day 36 (840 hr), Day 43 (1008 hr), Day 50 (1176 hr), Day 57 (1344 hr), Day 71 (1680 hr), Day 90 (2136 hr), Day 120 (2856 hr), and Day 140 (3336 hr)
Collection Time Points for Cohort 3	
Period 1 (Days 1-28)	On Day 1 before dosing (within 15 min prior to the SOI), EOI, 30 min after the EOI, at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), Day 5 (96 hr); Day 8 (168 hr), Day 15 (336 hr), and Day 22 (504 hr)
Period 2 (Days 29-56)	Before dosing on Day 29 (within 15 min prior to the SOI), EOI on Day 29, 30 min after the EOI, at the following time points: Day 29 (4 hr and 8 hr), Day 30 (24 hr), Day 31 (48 hr), Day 33 (96 hr), and Day 43 (336 hr)
Period 3 (Days 57-84)	Before dosing on Day 57 (within 15 min prior to the SOI), EOI on Day 57, 30 min after the EOI, at the following time points: Day 57 (4 hr and 8 hr), Day 58 (24 hr), Day 59 (48 hr), Day 61 (96 hr), and Day 71 (336 hr)
Period 4 (Days 85-112)	Before dosing on Day 85 (within 15 min prior to the SOI), EOI on Day 85, 30 min after the EOI, at the following time points: Day 85 (4 hr and 8 hr), Day 86 (24 hr), Day 87 (48 hr), Day 89 (96 hr), and Day 99 (336 hr)
Period 5 and Follow-up (Days 113-298)	Before dosing on Day 113 (within 15 min prior to SOI), EOI and 30 min after the EOI on Day 113, at the following time points: Day 113 (4 hr and 8 hr), Day 114 (24 hr), Day 115 (48 hr), Day 117 (96 hr), Day 120 (168 hr), Day 127 (336 hr), Day 134 (504 hr), Day 141 (672 hr), Day 148, Day 155, Day 162, Day 169, Day 183, Day 197, Day 225, Day 253, Day 298

Please refer to the SOM for time windows for collection, and to the laboratory manual for details on sample collection including blood volume requirements.

13.2. Criteria for Evaluation

All subjects providing an adequate number of serum PK samples to characterize a concentration-time profile will be included in the PK analysis population.

13.3. Sample Analysis

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

14. PHARMACODYNAMIC ASSESSMENTS

14.1. Blood Sample Collection

Blood samples for analyses of total and free C5 concentrations, cRBC hemolysis, and potentially other measures of C5 activation will be collected at the time points indicated in Table 15.

Table 15: Collection Time Points for Serum C5 Levels and cRBC Hemolysis

Collection Time Points for Cohort 1	
(Days -1-120)	On Day -1, on Day 1 before dosing (within 15 min prior to the SOI), EOI, 30 min after the EOI, and at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), and Day 5 (96 hr), Day 8 (168 hr), Day 15 (336 hr), Day 22 (504 hr), Day 29 (672 hr), Day 36 (840 hr), Day 43 (1008 hr), Day 50 (1176 hr), Day 57 (1344 hr), Day 71 (1680 hr), Day 90 (2136 hr), and Day 120 (2856 hr)
Collection Time Points for Cohort 2	
(Days -1-140)	On Day -1, on Day 1 before dosing (within 15 min prior to the SOI), EOI, 30 min after the EOI, and at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), and Day 5 (96 hr), Day 8 (168 hr), Day 15 (336 hr), Day 22 (504 hr), Day 29 (672 hr), Day 36 (840 hr), Day 43 (1008 hr), Day 50 (1176 hr), Day 57 (1344 hr), Day 71 (1680 hr), Day 90 (2136 hr), Day 120 (2856 hr), and Day 140 (3336 hr)
Collection Time Points for Cohort 3	
Period 1 (Days -1-28)	On Day -1, on Day 1 before dosing (within 15 min prior to the SOI), EOI, 30 min after the EOI, at the following time points (relative to SOI on Day 1): 4 hr, 8 hr, Day 2 (24 hr), Day 3 (48 hr), Day 5 (96 hr), Day 8 (168 hr), Day 15 (336 hr), and Day 22 (504 hr)
Period 2 (Days 29-56)	Before dosing on Day 29 (within 15 min prior to the SOI), EOI on Day 29, 30 min after the EOI, at the following time points: Day 29 (4 hr and 8 hr), Day 30 (24 hr), Day 31 (48 hr), Day 33 (96 hr), and Day 43 (336 hr)
Period 3 (Days 57-84)	Before dosing on Day 57 (within 15 min prior to the SOI), EOI on Day 57, 30 min after the EOI, at the following time points: Day 57 (4 hr and 8 hr), Day 58 (24 hr), Day 59 (48 hr), Day 61 (96 hr), and Day 71 (336 hr)
Period 4 (Days 85-112)	Before dosing on Day 85 (within 15 min prior to the SOI), EOI on Day 85, 30 min after the EOI, at the following time points: Day 85 (4 hr and 8 hr), Day 86 (24 hr), Day 87 (48 hr), Day 89 (96 hr), and Day 99 (336 hr)
Period 5 and Follow-up (Days 113-298)	Before dosing on Day 113 (within 15 min prior to SOI), EOI and 30 min after the EOI on Day 113, at the following time points: Day 113 (4 hr and 8 hr), Day 114 (24 hr), Day 115 (48 hr), Day 117 (96 hr), Day 120 (168 hr), Day 127 (336 hr), Day 134 (504 hr), Day 141 (672 hr), Day 148, Day 155, Day 162, Day 169, Day 183, Day 197, Day 225, Day 253, and Day 298

Please refer to the SOM for time windows for collection, and to the laboratory manual for details on sample collection including blood volume requirements.

14.2. Criteria for Evaluation

All subjects providing PD samples will be included in the PD analysis population.

14.3. Sample Analysis

Detailed instructions on the procedure for collecting, processing, storing, and shipping of blood samples for PD analysis will be provided in the laboratory manual. All sample analysis will be performed by Alexion or designee.

15. IMMUNOGENICITY ASSESSMENTS

15.1. Blood Sample Collection

Samples for ADA will be collected at the time points indicated in Table 16.

Table 16: Collection Time Points for Serum Samples for Immunogenicity Analyses of Antidrug Antibodies to ALXN1210

Collection Time Points for Cohort 1	
(Days 1-120)	Pre-dose on Day 1, and on Day 15, Day 29, Day 57, Day 90, and Day 120
Collection Time Points for Cohort 2	
(Days 1-140)	Pre-dose on Day 1, and on Day 15, Day 29, Day 57, Day 90, Day 120, and Day 140
Collection Time Points for Cohort 3	
Periods 1 to 5 (Days 1-298)	Predose on Day 1; on Day 8, Day 15, and Day 22 after Dose 1; on Day 29 prior to Dose 2 and on Day 43 after Dose 2; on Day 57 prior to Dose 3 and on Day 71 after Dose 3; on Day 85 prior to Dose 4 and on Day 99 after Dose 4; on Day 113 prior to Dose 5 and on Day 120, Day 141, Day 169, Day 197, Day 225, Day 253, and Day 298 following Dose 5

Further characterization of antibody response may be conducted as appropriate based on PK/PD and safety data of ALXN1210.

Please refer to the SOM for time windows for collection, and to the laboratory manual for details on sample collection including blood volume requirements.

15.2. Criteria for Evaluation

All subjects providing a predose and a postdose sample for ADA will be included in the immunogenicity analysis population.

15.3. Sample Analysis

The immunogenicity assay will evaluate ADA to ALXN1210. Detailed instructions on the procedure for collecting, processing, storing, and shipping blood samples for immunogenicity analysis will be provided in the laboratory manual. All sample analyses will be performed by Alexion or designee.

16. ASSESSMENT OF SAFETY

Safety assessments will include physical examination findings, vital signs measurements, immunogenicity (antidrug antibody [ADA]) testing, laboratory evaluations, ECGs, infusion site evaluations (eg, bleeding, bruising, erythema, swelling, induration, and pain), and monitoring of AEs. Adverse events will be graded according to CTCAE v4.03, published June 14, 2010. Laboratory evaluations will include hematology, chemistry, and coagulation panels, CBC with differential, urinalysis, and a serum pregnancy test for female subjects. The potential risks of ALXN1210, specifically the risk of infection, will be reviewed with the subjects at screening and on a regular basis throughout the course of the study, after dosing. Subjects will meet with the investigator or designee to discuss the potential safety risks of ALXN1210 and address any safety concerns on the part of the subject at the time points shown in the Schedule of Assessments. During the second, third, and fourth dosing periods of Cohort 3, the subjects will be contacted by telephone to assess selected safety information.

16.1. Safety Parameters

Clinical and laboratory assessments will be performed to assess safety of ALXN1210. The timing of the assessments is described in the Schedules of Assessments (Section 9). Any abnormal result should be followed until resolution or stabilization.

16.1.1. Demographic/Medical History

A review of demographic parameters, including age, gender, race, and ethnicity will be performed as described in the Schedules of Assessments (Section 9). A complete medical history will be taken and documented.

16.1.2. Vital Signs

Vital signs will be taken after the subject has been resting in the supine or semi-recumbent position for at least 5 minutes and will include temperature (°C; oral), respiratory rate, supine blood pressure, and pulse. The timing of vital sign assessments is described in the Schedules of Assessments (Section 9). 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.

16.1.3. Weight and Height

Weight, height, and BMI will be recorded as described in the Schedules of Assessments (Section 9).

16.1.4. Physical Examination

Each examination will include the following assessments: general appearance; skin; head, ear, eye, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limbs; central nervous system; and musculoskeletal.

16.1.5. Electrocardiogram

A triplicate 12-lead ECG will be obtained after the subject has been resting for at least 5 minutes. The timing of ECGs is described in the Schedules of Assessments (Section 9). In addition, continuous cardiac registration will be performed at each dose administration from predose through the duration of infusion.

Heart rate, PR, QRS, RR, and QT will be measured and corrected QTcF intervals will be calculated.

16.1.6. Laboratory Assessments

Blood samples for analysis of hematology, clinical chemistry, coagulation, urinalysis/urine chemistry, virus serology, and drug/alcohol screening parameters will be collected as described in the Schedules of Assessments (Section 9). Clinical laboratory evaluations will be performed by a local laboratory. Abnormal results should be followed up, as appropriate. Handling and shipping clinical laboratory samples will be outlined in the Laboratory Study Manual.

16.1.6.1. Hematology

Blood will be analyzed for the following hematology parameters: platelet, RBC, and WBC counts; automated differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils); hemoglobin; hematocrit; and RBC indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration).

The timing of hematology assessments is described in the Schedules of Assessments (Section 9).

16.1.6.2. Blood Chemistry

Blood samples will be analyzed for the following clinical chemistry parameters: blood urea nitrogen; creatinine; glucose; sodium; phosphorus; potassium; chloride; total carbon dioxide; total calcium; magnesium; AST; ALT; gamma-glutamyltransferase; alkaline phosphatase; lactate dehydrogenase; total, direct, and indirect bilirubin; uric acid; albumin; and total protein. 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 screening for postmenopausal female subjects to confirm their postmenopausal status.

The timing of chemistry assessments is described in the Schedules of Assessments (Section 9).

16.1.6.3. Coagulation

Blood samples will be analyzed for prothrombin time, international normalized ratio, and partial thromboplastin time.

The timing of coagulation assessments is described in the Schedules of Assessments (Section 9).

16.1.6.4. Urinalysis and Urine Chemistry

Urinalysis will include specific gravity, pH, glucose, protein, blood, and ketones. A microscopic examination of urine samples will be performed only on abnormal findings.

Urine samples will also be sent to the pathology laboratory to measure protein and creatinine in order to calculate the urine protein:creatinine ratio.

The timing of urinalysis and urine chemistry assessments is described in the Schedules of Assessments (Section 9).

16.1.6.5. Virus Serology

Blood samples collected at screening will be analyzed for HIV-1, HIV-2, HBsAg, and HCV antibody titers.

Hepatitis B surface antigen testing is required for all subjects prior to enrollment. Subjects with positive HBsAg will not be enrolled.

For subjects with negative HBsAg, the following testing algorithm will be required:

1. If hepatitis B core antibody (HBcAb) is negative, the subject is eligible to enroll.
2. If HBcAb is positive, the hepatitis B surface antibody (HBsAb) will be tested.
    a. If both HBcAb and HBsAb are positive, the subject is eligible to enroll.
    b. If HBcAb is positive and HBsAb is negative, the subject will not be enrolled.

16.1.6.6. Drug and Alcohol Screen

A urine sample for drug screen will be analyzed for the following compounds: amphetamines; barbiturates; benzodiazepines; cocaine; methadone; opiates; phencyclidine; methamphetamine; 3,4-methylenedioxy-methamphetamine and tetrahydrocannabinol (cannabinoids). Alcohol breath tests will be performed. If positive prior to dosing, dosing will not proceed.

Timing of urine drug and alcohol breath tests are described in the Schedules of Assessments (Section 9).

16.1.6.7. Pregnancy Testing

Pregnancy testing (beta human chorionic gonadotrophin) will be performed in all female subjects (Section 17.8). The timing of pregnancy testing is described in Schedules of Assessments (Section 9).

16.1.6.8. Tuberculosis

Blood samples for a QuantiFERON®-TB test will be collected as described in the Schedules of Assessments (Section 9).

16.1.6.9. Complement Activity

A suitable assay for determining complement activity, such as CAP ELISA/C5 (hemolysis) inhibition, will be performed at screening to confirm subjects do not have a complement deficiency. Subjects found to be complement deficient will be excluded from participating in the study.

Blood samples will be collected at baseline and during follow-up for measurement of CH50 activity using an in vitro liposome immunoassay to confirm normalization of complement activity. If a normal CH50 result is obtained from a subject's CH50 sample collected during

follow-up, antibiotic prophylaxis can be stopped and the additional scheduled CH50 samples are not required. If the last CH50 sample is not normal, the baseline sample may be analyzed (see Schedules of Assessments in Section 9) and the investigator will contact the subject regarding whether antibiotic prophylaxis must be further extended.

16.1.6.10. Serum Bactericidal Antibody

An SBA titer against meningococcus Group A, C, W135, and Y will be performed at screening. Titer measurements will be used to exclude subjects without an immune response from being dosed.

17. 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 data capture system. Adverse events reported by the subject 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.

17.1. 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)

17.2. Definition of a Serious Adverse Event

Any AE that fulfills any 1 of the criteria listed below must be recorded as an SAE.

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

1. Results in death
2. Is life threatening[a]
3. Requires hospitalization or prolongation of hospitalization[b]. 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
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect
6. Is an important medical event[c]

[a] The term "life threatening" in the definition of "serious" refers to an event in which the subject 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 subject or may require intervention to

prevent 1 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.

17.3. Severity Assessment

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

17.4. Causality Assessment

An investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the data capture system and on any additional forms, as appropriate. The definitions for the 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 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.

17.5. 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 data capture system and on any additional forms, as appropriate.

If a subject 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 subject 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.

17.6. Recording Adverse Events

All observed or volunteered AEs, regardless of dose cohort or causal relationship, must be reported as described in Section 17.4 (Causality Assessment).

For all AEs, the investigator must do the following:

1. Determine the AE outcome
2. Determine if the event meets criteria for an SAE
3. Assess AE severity
4. 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 on the data capture system 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 data capture system 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 data capture system.

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

17.7. Reporting of 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 the study drug.

The investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via E-mail or fax to the contact information provided below:

E-mail: PPD

Fax: PPD

When further information becomes available, the SAE should be updated with the new information and reported immediately via the same contact information.

Additional follow-up information, if required or available, should be entered into the case report form and sent to sponsor within 24 hours of the investigator or study site staff becoming aware of this additional information via the reporting process outlined above. These reporting timelines need to be followed for all initial SAE cases and follow-up versions of the initial cases.

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

17.8. Exposure During Pregnancy and Lactation

Pregnancy data will be collected during this study for all subjects.

For all Alexion products, both in development or postapproval, exposure during pregnancy must be recorded and followed. 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.

If a female subject participating in this study or a male subject'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/Breast Feeding Form" to Alexion or designee via the same method as SAE reporting. Female subjects who become pregnant will be discontinued from dosing, but will continue to be followed for safety where feasible. Male subjects may continue in

the study if an accidental pregnancy of their female partner occurs despite adequate contraception.

The female subject should be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth or congenital abnormality), even if the subject discontinues study drug or discontinues from the study. When the outcome of the pregnancy becomes known, the 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.

17.9. 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.

17.9.1. Sponsor

The sponsor or legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria. The sponsor will inform the investigator of any safety issues that may arise during the course of the study. Any safety issue which may alter the current benefit-risk assessment of the study drug will be reported by the sponsor (or delegate) on an expedited basis to Health Authorities, Ethics Committees, and the investigator.

17.9.2. Investigator

The investigator must fulfill all local regulatory requirements for investigators conducting clinical studies. It is the investigator's responsibility to notify the IRB or 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 case report form, and are retrieved by or submitted to the sponsor at regular monthly intervals, or more frequently during the course of the investigation.

18. DATA COLLECTION

All clinical raw data will be recorded promptly, accurately, and legibly, either electronically or on paper. A detailed list of the type (electronic or paper) and location for all source data will be included in the Trial Master File. All raw data will be preserved in order to maintain data integrity. The investigator or designee will assume the responsibility of ensuring the completeness, accuracy, and timeliness of the clinical data.

At each scheduled monitoring visit, the investigator or designee will cooperate with the sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data.

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

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

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. STATISTICS

19.1. Statistical Analysis Plan Summary

A formal statistical analysis plan will be developed and finalized before database lock.

Statistical analyses will be performed by Richmond Pharmacology Ltd. Pharmacokinetic parameters will be calculated by Nuventra Pharma Sciences using Phoenix® WinNonlin® 6.3 or higher (Certara, Inc, Princeton, NJ). Tables, figures, and listings will be produced using an automated system (Certara L.P.).

Any deviations from the planned analyses will be described in the final integrated clinical study report.

19.2. Analysis Populations

The safety population will consist of all subjects who receive at least 1 dose of study drug. Subjects in this population will be used for the safety analysis.

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

The PD population will consist of all subjects who have sufficient total and free C5 concentration data, cRBC hemolysis data, or other data measuring C5 activation to enable the evaluation of the PD effects. The PD population will be used for PD summaries.

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

19.3. Sample Size and Power

The sample size of 4 subjects in each of the single-dose cohorts (Cohorts 1 and 2) and 6 to 8 subjects in the 800 mg multiple-dose cohort will allow for the characterization of the central tendency of PK parameters as they relate to ALXN1210 and to gain initial knowledge of PK/PD relationships in Japanese subjects. To ensure future modeling and simulations are accurate, it is preferred to estimate the PK parameters with a maximum imprecision of < 25% following the IV administration of ALXN1210. Six subjects in Cohort 3 will provide 23.3% maximum imprecision (Table 17) for the estimation of area under the serum concentration versus time curve from time 0 extrapolated to infinity (AUC_∞), in terms of the relative distance of the lower 90% confidence limit from the observed PK parameter that will be obtained with 80% assurance and assuming the within-subject SD of the log-transformed AUC_∞ is as much as 0.19.

Table 17: Estimation of the Maximum Imprecision in the Estimate of PK Parameters for Selected Sample Sizes

Number of Subjects on Active	Maximum Imprecision (%)
4	33.6
6	23.3
8	18.9

19.4. Descriptive Statistics

All continuous variables will be summarized by cohort and time point with descriptive statistics (the number of nonmissing values, mean, SD, median, minimum, and maximum). All categorical variables will be summarized by cohort and time point with frequency counts and percentages. Treatment group refers to all dose cohorts of ALXN1210.

19.5. Demographics, Baseline Characteristics, and Subject Disposition

All subjects will be included in the summary of subject disposition, which will summarize the frequency and percentage of subjects screened and treated who completed or discontinued from the study, along with reason for discontinuation, by treatment group. Demographics and baseline characteristics will be summarized for all subjects by each treatment dose and overall.

19.6. Safety Analysis

Safety analyses will be performed on the safety population, and will be reported by each treatment dose. Safety analyses will include an analysis of 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 the safety parameters of this study. The incidence of treatment-emergent AEs and SAEs will be summarized by system organ class and preferred term for each treatment dose and overall, by severity, and by relationship to study drug. Serious AEs and AEs resulting in withdrawal from the study will be listed. Subjects having multiple AEs within a category (eg, overall, system organ class, preferred term) will be counted once in that category. For severity tables, a subject's most severe event within a category will be counted.

Changes from baseline in vital signs and laboratory assessments (chemistry, CBC with differential, and urinalysis) will be summarized by each treatment dose. Laboratory parameter values will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; v4.03, published June 14, 2010). Shift tables by treatment group will be produced for these laboratory parameters. These tables will summarize the number of subjects with each baseline grade relative to the normal ranges and changes to the worst highest grade assessed postdose during the study.

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 each treatment dose.

An outlier analysis will be performed that will summarize the frequency and percentage of subjects who meet any of the following outlier criteria at each visit by treatment group:

- QT, QTcF interval > 450 msec
- QT, QTcF interval > 480 msec
- QT, QTcF interval > 500 msec
- QT, QTcF interval increases from baseline > 30 msec
- QT, QTcF interval increases from baseline > 60 msec

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

19.7. Pharmacokinetic Analysis

The individual serum concentration data for ALXN1210-treated subjects, with actual sampling dates and times, will be used to derive the PK parameters by noncompartmental analyses using Phoenix WinNonlin 6.3 or higher.

The following PK parameters will be derived: maximum observed serum concentration (C_{max}) after each dose, time to maximum observed serum concentration (t_{max}), the observed minimum serum concentrations (C_{min}) just prior to Periods 2 to 5 (and 28 days after Period 5 dose) for Cohort 3, area under the serum concentration versus time curve from time 0 to the last quantifiable concentration (AUC_t) after each dose, area under the curve from time 0 (dosing) to the end of the dosing interval (AUC_τ), apparent terminal-phase elimination rate constant (λ_z), terminal elimination half-life ($t_{½}$), total clearance (CL), volume of distribution (V_{ss}), assessment of steady-state, and accumulation at steady state. Assessment of dose proportionality and time linearity in PK parameters may be conducted.

19.8. Pharmacodynamic and Immunogenicity Analyses

The PD effects of ALXN1210 administered intravenously will be evaluated by assessing changes in serum total and free C5 concentrations, cRBC hemolysis, and other measures of C5 activation over time. Analyses will be initially performed on samples collected as described in the Schedules of Assessments (Section 9).

An exploratory PK/PD analysis may be performed.

Immunogenicity, as measured by ADA, will be summarized in tabular form by treatment dose and by-subject listings.

19.9. Interim Analysis

Interim analyses may be performed as needed.

20. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

20.1. Study Monitoring

Before an investigational site can enter a subject 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 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 case report form, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the case report form with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (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 case report form, and confirm any SAEs have been forwarded to the sponsor or designee, and those SAEs that met 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.

20.2. 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 Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact the sponsor or designee immediately if contacted by a regulatory agency about an inspection.

20.3. Institutional Review Board/Independent Ethics Committee

The investigator must obtain IRB/IEC approval for the clinical study. Initial, subsequent, and ongoing IRB/IEC approvals, and all materials approved by the IRB/IEC for this study, including the subject consent form and recruitment materials, must be maintained by the investigator and made available for inspection.

20.4. Safety Review Committee

Since its primary function will be to ensure subject safety, the members of the SRC will have access to all safety data. For additional details regarding the SRC, please see Section 8.5.

20.5. Regulatory Agency

As required by the United Kingdom regulatory agency, a Clinical Trial Application will be submitted before the beginning of the study and a Notice of Acceptance Letter must be received prior to screening.

21. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor or designee may conduct a quality assurance audit. Please see Section 20.2 for more details regarding the audit process.

22. ETHICS

22.1. 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 designee prior to enrolling subjects.

The investigator is responsible for informing the IRB/IEC of any amendment to the protocol, in accordance with local regulatory requirements. The IRB/IEC must review and approve any protocol amendments prior to implementation at the study site. The IRB/IEC will review the protocol at least annually or as local regulations require. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study.

The investigator is also responsible for informing the IRB/IEC of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The sponsor or 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.

22.2. 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 Alexion's policy on bioethics.

22.3. Written Informed Consent

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

The subject's signed and dated ICF must be obtained before conducting any study procedures, and documented in the subject's study record.

The investigator must maintain the original of all signed ICF versions. A copy of the signed ICF(s) must be given to the subject.

22.4. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the study drug, and this new event is likely to affect the safety of subjects, the sponsor and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard. The sponsor will work with the investigator to ensure the IRB/IEC is notified. The sponsor will also inform the Medicines and Healthcare Products Regulatory Agency.

23. DATA HANDLING AND RECORDKEEPING

23.1. Inspection of Records

The sponsor or 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, subject charts, and study source documents, and other records relative to study conduct.

23.2. Retention of Records

The clinical site will maintain adequate study records according to local regulatory requirements after completion or termination of study or for a minimum period of 5 years. After that period, the sponsor will be contacted to determine whether the study records will be forwarded to the sponsor, destroyed, or kept at the clinical site or another facility for a longer period of time, at the sponsor's expense. If it becomes necessary for the sponsor or designee or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

24. 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.

25. LIST OF REFERENCES

1. Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, Michaud P, Papo T, Ugo V, Teyssandier I, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N.Engl.J.Med. 2002 Feb 14;346(7):469-75.

2. Li J, Yang C, Xia Y, Bertino A, Glaspy J, Roberts M, Kuter DJ. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood 2001 Dec 1;98(12):3241-8.

3. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, Brown SG, Camargo CA, Jr., Cydulka R, Galli SJ, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J.Allergy Clin.Immunol. 2006 Feb;117(2):391-7.

4. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. Clin.Microbiol.Rev. 1991 Jul;4(3):359-95.

5. Yazdankhah SP, Caugant DA. Neisseria meningitidis: an overview of the carriage state. J.Med.Microbiol. 2004 Sep;53(Pt 9):821-32.

6. Kelly RJ, Hill A, Arnold LM, Brooksbank GL, Richards SJ, Cullen M, Mitchell LD, Cohen DR, Gregory WM, Hillmen P. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood 2011 Jun 23;117(25):6786-92.

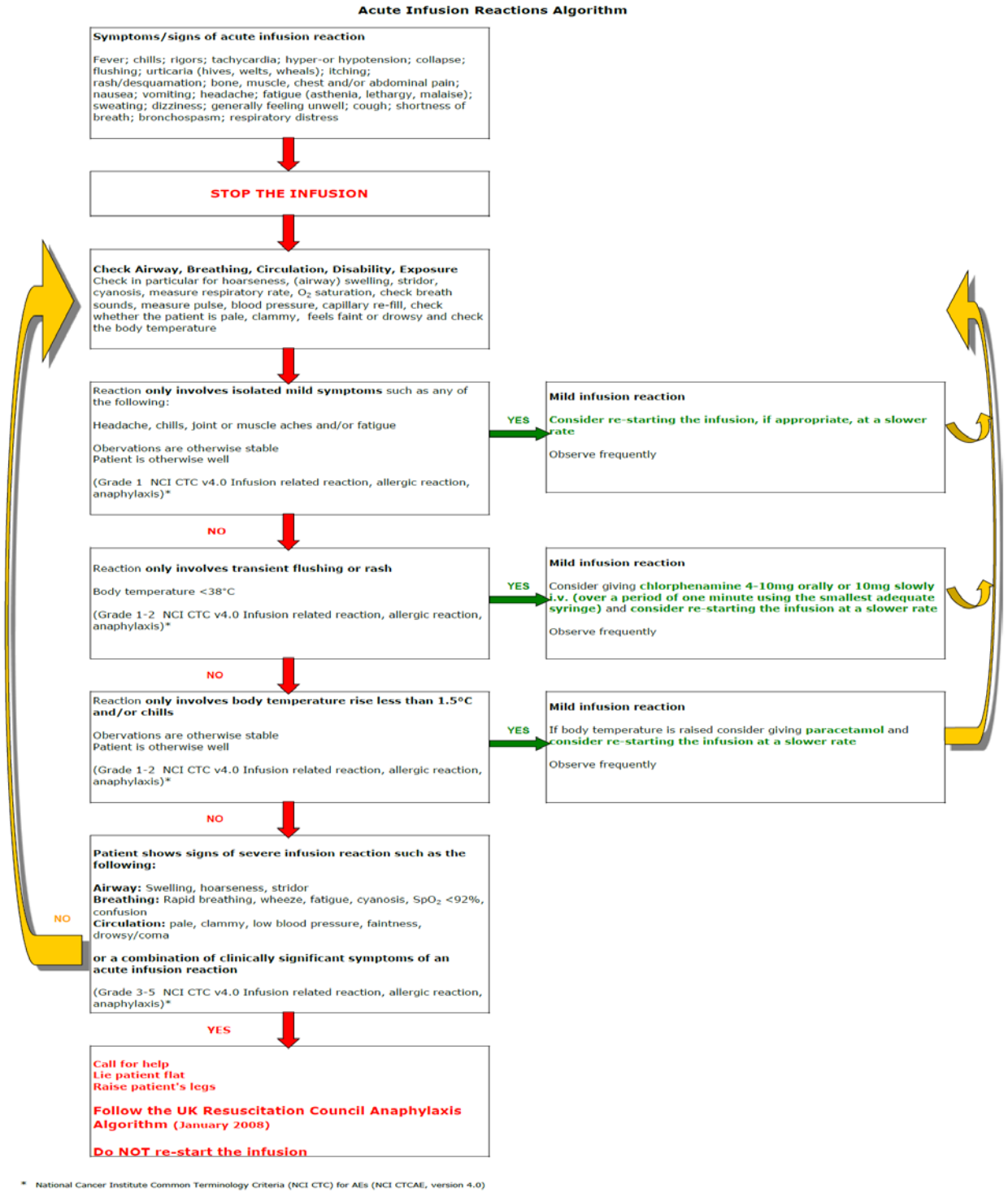
7. Leeds Teaching Hospitals NHS Trust, Kings College Hospital NHS Foundation Trust. National Specialised Commissioning Team (NSCT) Service Specification Paroxysmal Nocturnal Haemoglobinuria (PNH). 2013.

8. Zuber J, Fakhouri F, Roumenina LT, Loirat C, Fremeaux-Bacchi V. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. Nat.Rev.Nephrol. 2012 Nov;8(11):643-57.

26. APPENDICES

26.1. Appendix 1

Acute Infusion Reactions Algorithm



26.2. Appendix 2

United Kingdom Resuscitation Council Anaphylaxis Algorithm