A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of a Single Dose of ALXN1210 Administered Subcutaneously Compared to Intravenously in Healthy Subjects

Unique Protocol ID:	ALXN1210-SC-101
NCT Number:	NCT05288829
EudraCT Number:	2016-001617-24
Date of Protocol:	28 July 2016

ALXN1210

ALXN1210-SC-101

A PHASE 1 STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND IMMUNOGENICITY OF A SINGLE DOSE OF ALXN1210 ADMINISTERED SUBCUTANEOUSLY COMPARED TO INTRAVENOUSLY IN HEALTHY SUBJECTS

Sponsor	Alexion Pharmaceuticals, Inc. 100 College Street New Haven, CT 06510 USA
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:	17 May 2016
Date of Amendment 1:	13 Jun 2016
Date of Amendment 2:	28 Jul 2016
IND Number:	118481
EudraCT Number:	2016-001617-24

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ALXN1210. I have read the ALXN1210-SC-101 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 Council for Harmonisation (ICH)/Good Clinical Practices (GCP) and applicable to regulatory requirements.

PPD

Printed Name of Investigator

PPD

Signature of Investigator

02 AUG 2016

Date

CONTRACT RESEARCH ORGANIZATION:

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SPONSOR'S SIGNATURE PAGE

PROTOCOL TITLE: A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of a Single Dose of ALXN1210 Administered Subcutaneously Compared to Intravenously in Healthy Subjects

PROTOCOL NUMBER: ALXN1210-SC-101

PPD

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28-JUL-2016

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
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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:
Alexion Pharmaceuticals, Inc.

Name of Investigational Product:
ALXN1210

Name of Active Ingredient:
ALXN1210

Title of Study: A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of a Single Dose of ALXN1210 Administered Subcutaneously Compared to Intravenously in Healthy Subjects (Protocol ALXN1210-SC-101)
EudraCT Number: 2016-001617-24

Study Center:
This study will be conducted by Richmond Pharmacology Ltd. at the following facility:

Croydon University Hospital (Woodcroft Wing)
530 London Road
Croydon, Surrey
CR7 7YE
United Kingdom

Telephone: PPD

Length of Study:	**Phase of Development:** 1
Estimated date first subject enrolled: September 2016 Estimated date last subject completed: February 2017	

Study Rationale:
The purpose of the study is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of a single dose of ALXN1210 administered subcutaneously (SC) compared to a single dose of ALXN1210 administered intravenously (IV) in healthy subjects. Data from this study will be used to determine the absolute bioavailability of ALXN1210 SC in healthy subjects.

ALXN1210 is a humanized monoclonal antibody (mAb) that inhibits terminal complement. It specifically binds the human complement protein C5 thereby inhibiting its cleavage to C5a and C5b during complement activation. This inhibition not only prevents the release of the proinflammatory mediator C5a, but also inhibits the formation of the cytolytic pore-forming membrane attack complex (MAC) terminal complement complex (C5b-9). The mechanism of action described here 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]).

ALXN1210 has been administered safely to healthy subjects in 200-mg and 400-mg IV doses in a single ascending dose (SAD) study (Study ALXN1210-HV-101; N = 10). Healthy subjects have also been administered multiple 400-mg and 800-mg IV doses on an every 4 week (Q4W) regimen in an ongoing multiple ascending dose (MAD) study (Study ALXN1210-HV-102; N = 12). The starting doses of ALXN1210 IV in the 2 healthy volunteer studies were selected to assess safety and tolerability in healthy volunteers and to have measurable pharmacologic activity (eg, inhibition of complement activation). In addition, administration of multiple doses of ALXN1210 IV to 25 patients with PNH has been safe and tolerated, to date, at single doses up to 2000 mg.

Objectives:
The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of a single dose of ALXN1210 SC compared to ALXN1210 IV in healthy subjects, as assessed by physical examination findings, vital sign measurements, immunogenicity, laboratory analysis, and assessments of adverse events (AEs).
- To determine the absolute bioavailability of ALXN1210 SC.

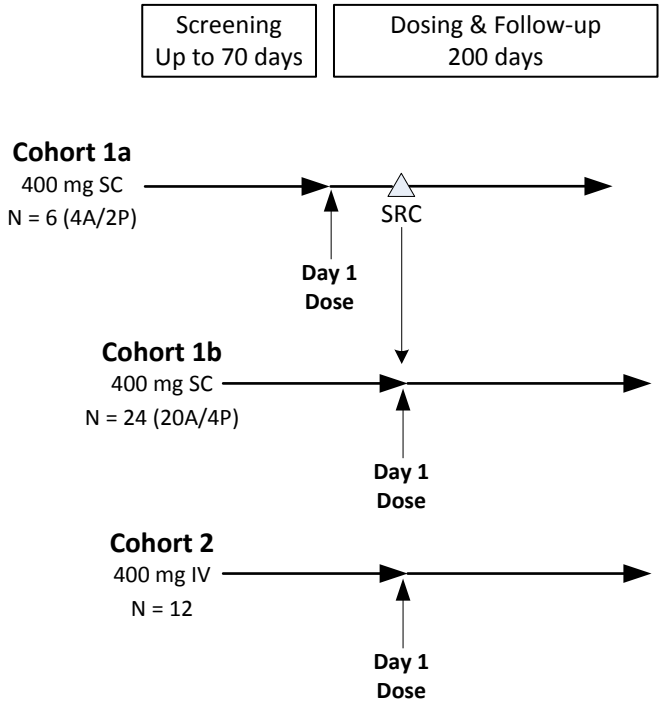
The secondary objective of the study is as follows:

- To evaluate the PD effects of ALXN1210 SC compared to ALXN1210 IV, as assessed by the level of free C5 and chicken red blood cell (cRBC) hemolysis.

Study Design and Methodology:

This is a Phase 1 study designed to evaluate the safety, tolerability, PK, PD, and immunogenicity of a single 400-mg dose of ALXN1210 SC compared to a single 400-mg dose of ALXN1210 IV or placebo SC in 42 healthy subjects. All subjects will be screened for eligibility in the study after providing signed and dated institutional ethics committee-approved written informed consent to participate and before any study-specific screening procedures are performed.

Six subjects will initially be randomly assigned in a 2:1 ratio to Cohort 1a, in a blinded fashion, to receive either a single 400-mg dose of ALXN1210 SC or single dose of placebo SC. The Safety Review Committee (SRC) will evaluate the first 48 hours of post-dose clinical safety data for subjects in Cohort 1a before enrollment into Cohorts 1b or 2 may begin. Thirty-six subjects will then be randomly assigned, in a 2:1 ratio, to either Cohort 1b (N=24) or Cohort 2 (N=12). Within Cohort 1b, the 24 subjects will further be randomly assigned, in a 5:1 ratio and blinded fashion, to receive either a single 400-mg dose of ALXN1210 SC or a single dose of placebo SC, respectively. The 12 subjects in Cohort 2 will receive a single 400-mg dose of ALXN1210 IV in an open-label fashion.



Abbreviations: A = active drug; IV = intravenous; P = placebo; SC = subcutaneous; SRC = Safety Review Committee
Note: The SRC will review the first 48 hours of post-dose safety data from Cohort 1a before enrollment into Cohorts 1b or 2 may begin.

At the sponsor's discretion, up to 8 additional subjects (2 subjects each in Cohorts 1a and 1b and 4 subjects in Cohort 2) may be enrolled into the study if 2 or more subjects discontinue within 3 months for reasons other than drug-related AEs, and after consultation with the SRC. All enrolled subjects will be included in analyses as appropriate. Subjects in Cohorts 1a and 1b will be combined for analyses. Subjects who withdraw from the study subsequent to dosing will be followed for safety assessments through the last scheduled study visit, if possible.

Subjects will participate in the study for up to 39 weeks, including a screening period of up to 70 days, followed by a 200day follow-up period for safety, PK, PD, and immunogenicity assessments after study drug administration.

Number of subjects (planned):
Forty-two subjects are planned for evaluation of the primary and secondary objectives in this study:
6 (4 ALXN1210 SC, 2 placebo SC) subjects in Cohort 1a; 24 (20 ALXN1210 SC, 4 placebo SC) subjects in Cohort 1b, and 12 (ALXN1210 IV) subjects in Cohort 2. See the synopsis section "Study Design and Methodology" regarding addition of subjects who withdraw or are withdrawn from the study after dosing.

Diagnosis and main criteria for inclusion:
All subjects must meet the following inclusion and exclusion criteria. 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.

Inclusion:

1. Healthy subjects, aged 25 through 55 years, inclusive, at the time of dosing.
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 a tetravalent meningococcal conjugate vaccine (MCV4) at least 56 days and not more than 3 years prior to dosing. Documentation must include a positive serum bactericidal antibody (SBA) titer 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, if heterosexually active, must use highly effective or acceptable contraception as defined below, starting at screening and continuing until at least 6 months after study drug administration. Antibiotic prophylaxis is required during this study, which can compromise the efficacy of hormonal contraception. Therefore, it is recommended that subjects using hormonal contraception also use barrier contraception (eg, condom or diaphragm with spermicide) for the duration of antibiotic prophylaxis.

   Highly effective contraceptive methods for females are as follows:
   - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation as follows:
     - Oral
     - Intravaginal
     - Transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation as follows:
     - Oral
     - Injectable
     - Implantable
   - Intrauterine device
   - Intrauterine hormone-releasing system
   - Bilateral tubal occlusion

   Male subjects, if heterosexually active and with a female spouse or partner of childbearing potential or a pregnant or breastfeeding spouse or partner, must agree to use barrier contraception (male condom) for the treatment period and for at least 6 months after study drug administration. 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 after study drug administration. Male subjects must not donate sperm during the screening and treatment periods and for at least 6 months after study drug administration.

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 to) 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 6 months prior to dosing
3. History of any *Neisseria* infection.
4. History of unexplained, recurrent infection, or infection requiring treatment with systemic antibiotics within 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 (TB) infection.
10. History of latent or active TB or exposure to endemic areas within 8 weeks prior to the screening visit.
11. Female subjects who are breastfeeding or are heterosexually active and 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 study drug administration.
12. Positive serum pregnancy test at screening or on Day –1.
13. Serum creatinine greater than the upper limit of normal (ULN) of the reference range of the testing laboratory at screening or on 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 on 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 cell (WBC) count < $3.0 \times 10^3/\mu L$, absolute neutrophil count < $2.0 \times 10^3/\mu L$, and platelet count < 150 or > $400 \times 10^3/\mu L$ at screening or on Day –1. Complete blood count (CBC) clinical laboratory results that are considered clinically relevant and unacceptable by the investigator on 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 an mAb, or participation in a clinical study of an 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 an mAb may be considered for enrollment if they completed that study more than 12 months prior to screening.
20. Prior exposure to ALXN1210.
21. Major surgery or hospitalization within 90 days prior to dosing.
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 (eg, anaphylaxis or 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 on 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 prior to dosing or more than 499 mL of blood within 56 days prior to dosing.
30. History of continuous topical, inhaled, or systemic steroid use > 28 days 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 and 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 28 days 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 dosing.
36. Subjects with any medical history, conditions, or risks that, 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 SC: ALXN1210 SC is formulated at pH 7.4 and each vial contains 100 mg of ALXN1210 in 50 mM sodium phosphate, 25 mM arginine, 5% sucrose, and 0.05% polysorbate 80. ALXN1210 SC is provided as a fully formulated, sterile, preservative-free, 100-mg/mL aqueous solution of ALXN1210 for SC administration and is supplied in 2-mL single-use vials. Each vial of ALXN1210 SC drug product includes a nominal overfill to ensure that 1 mL (100 mg of ALXN1210) can be withdrawn for administration. ALXN1210 SC will be administered SC as four 1-mL injections.

ALXN1210 IV: ALXN1210 IV is formulated at pH 7.0 and each vial contains 150 mg of ALXN1210 in 10 mM sodium phosphate, 150 mM sodium chloride, 0.02% polysorbate 80, and water for injection. ALXN1210 IV is provided as a fully formulated, sterile, preservative-free, 10-mg/mL aqueous solution of ALXN1210 and is supplied in 20-mL single-use vials. ALXN1210 IV will be administered by IV infusion at a maximum rate of 333 mL/hr, excluding interruption for safety or technical reasons.

Reference therapy, dosage, and mode of administration:
Placebo SC: Each dose of placebo SC contains 0.9% sodium chloride for injection, European Pharmacopoeia (Ph Eur) or British Pharmacopeia (BP), to the same volume as specified for Cohorts 1a and 1b.

Planned duration of treatment:
Screening period: up to 70 days
Dosing and observation periods: For Cohorts 1a and 1b, a single 400-mg dose of ALXN1210 SC or placebo SC (administered as four 100-mg SC injections) on Day 1, followed by an observation period of 200 days. For Cohort 2, a single 400-mg dose of ALXN1210 IV on Day 1, followed by an observation period of 200 days. Subjects will be followed for safety, PK, PD, and immunogenicity assessments.

Endpoints:
Safety:
Safety assessments will include physical examination findings, vital sign measurements, immunogenicity (antidrug antibody [ADA]) testing, laboratory evaluations, electrocardiogram (ECG) results, infusion site and injection 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 14 Jun 2010. Laboratory evaluations will include hematology, chemistry, and coagulation panels; CBC with differential; urinalysis; and pregnancy testing for female subjects.

Pharmacokinetics and Pharmacodynamics:

- Serum concentrations of ALXN1210 will be assayed and serum samples for PD assays will be collected from the following sampling time points: pre-dose (within 15 minutes prior to start-of-infusion/injection [SOI]); Day 1 at end of infusion/injection (EOI), 30 minutes post EOI, and the following time points following SOI: 2 h, 4 h, and 8 h; Day 2 (24 h); Day 3 (48 h); Day 5 (96 h); Day 8 (168 h); Day 15 (336 h); Day 22 (504 h); Day 29 (672 h); Day 36 (840 h); Day 43 (1008 h); Day 50 (1176 h); Day 57 (1344 h); Day 71 (1680 h); Day 90 (2136 h); Day 120 (2856 h); Day 150 (3576 h); and Day 200 (4776 h).
- Using noncompartmental analysis methods, the serum concentrations data will be used to derive the following PK parameters: maximum observed serum concentration (C_{max}), time to maximum observed serum concentration (T_{max}), area under the serum concentration versus time curve from time zero to the last quantifiable concentration (AUC_t), AUC from time zero to infinity (AUC_∞), terminal elimination rate constant (λ_z), terminal elimination half-life ($T_{½}$), total clearance (CL or CL/F), and volume of distribution (V_d or V_d/F).

Immunogenicity:

- Serum samples will be collected at the following time points: pre-dose (within 15 minutes prior to SOI), and on Days 15 (336 h), 29 (672 h), 57 (1344 h), 90 (2136 h), 120 (2856 h), 150 (3576 h), and 200 (4776 h) and analyzed for ADA to ALXN1210.

The total anticipated volume of serum collected per subject for clinical laboratory, PK, PD, and immunogenicity assessments will not exceed 500 mL.

Statistical methods:
General:
A total evaluable sample size of 36 subjects, 24 ALXN1210 SC subjects from Cohort 1 and 12 ALXN1210 IV subjects from Cohort 2, will provide >80% power to infer that the lower bound of a 90% confidence interval for the ratio of the bioavailability of ALXN1210 SC to IV is > 0.4 assuming an absolute bioavailability of 0.6 and a coefficient of variation of 0.35. Additionally, 6 subjects will receive placebo SC, 2 in Cohort 1a and 4 in Cohort 1b. Randomization to Cohort 1a will be conducted in a 2:1 ratio, and Cohort 1b in a 5:1 ratio, to receive either ALXN1210 SC or placebo SC. This brings the total planned number of subjects to N=42.

In general, descriptive statistics for continuous variables will include number of nonmissing values, arithmetic mean, standard deviation, median, minimum, and maximum. Descriptive statistics for PK parameters will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (%CV), median, minimum, maximum, geometric mean and geometric %CV. Categorical variables will be summarized using percentages and frequency counts, by cohort and time point.

Safety:
All subjects who received at least 1 dose of 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 post-dose during the study.

Pharmacokinetics/Pharmacodynamics:
Individual PK parameters (including descriptive statistics as follows: number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation [CV], median, minimum, maximum, geometric mean, and geometric CV) will be determined for the ALXN1210-treated subjects.

The PD effects of ALXN1210 SC and IV will be evaluated by assessing changes in serum total and free C5 concentrations, cRBC hemolysis, and other measures of C5 activation over time, using descriptive statistics.

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

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

TABLE OF CONTENTS

LIST OF TABLES

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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
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 zero to infinity
AUC_t	area under the serum concentration versus time curve from time zero to the last quantifiable concentration
BMI	body mass index
BP	British Pharmacopoeia
C5b-9	terminal complement complex
CAP	complement alternative pathway
CBC	complete blood count
CDC	complement-dependent cytotoxicity
CH50	50% hemolytic complement activity (screening test for deficiency of classical complement pathway in which hemolysis of liposomes sensitized by specific antibodies is measured; one CH50 unit is the volume or dilution of serum that lyses 50% of liposomes)
CL	total body clearance of drug from the serum
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
eCRF	electronic case report form
EOI	end of infusion
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous(ly)
mAb	monoclonal antibody
MAD	multiple ascending dose
MCV4	tetravalent meningococcal conjugate vaccine
OP	outpatient
PD	pharmacodynamic(s)

Ph Eur	European Pharmacopoeia
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
Q4W	every 4 week
QTcF	QT interval corrected using the Fridericia's formula
RBC	red blood cell(s)
SAD	single ascending dose
SAE	serious adverse event
SBA	serum bactericidal antibody
SC	subcutaneous(ly)
SOI	start of infusion/injection
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_d	volume of distribution
WBC	white blood cell(s)

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 the 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 inhibits the formation of the cytolytic pore-forming membrane attack complex (MAC) terminal complement complex (C5b-9) while preserving the proximal or early components of complement activation (eg, C3 and C3b) essential for the opsonization of microorganisms and clearance of immune complexes. The mechanism of action provides a rationale for the potential therapeutic use of ALXN1210 in diseases where complement activation is involved (eg, paroxysmal nocturnal hemoglobinuria [PNH], atypical hemolytic uremic syndrome [aHUS]). These disorders of uncontrolled complement activation (PNH and aHUS) are chronic and progressive with severe morbidities and significant premature mortality (Hillmen, 1995; Kavanagh, 2006).

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 200 mg and 400 mg intravenous (IV) doses in a single ascending dose (SAD) study (Study ALXN1210-HV-101, N = 10). Healthy subjects have also been administered multiple 400 mg and 800 mg IV doses on an every 4 week (Q4W) regimen in an ongoing multiple ascending dose (MAD) study (Study ALXN1210-HV-102, N = 12). The starting doses of ALXN1210 IV in these 2 healthy volunteer studies were selected to assess safety in healthy volunteers and 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 pharmacokinetic (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 (area under the serum concentration versus time curve from time zero to the last quantifiable concentration [AUC_t], area under the curve from time zero to infinity [AUC_∞], and maximum observed serum concentration [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 200 mg and 400 mg doses of ALXN1210 IV, all 6 pharmacodynamic (PD) variables (total complement C5 serum concentration, free complement C5 serum concentration, chicken red blood cell [cRBC] hemolysis, classical complement pathway [CCP] activity, complement alternative pathway [CAP] activity, and plasma C5b-9 activity) showed dose-dependent reductions from baseline. The effect of ALXN1210 on these PD variables was immediately evident after end of infusion (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 antidrug antibody (ADA) through Day 150.

In addition, multiple doses of ALXN1210 IV have been administered to patients with PNH.

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 was observed.

ALXN1210 does not exhibit pharmacologic activity or cross-reactivity with any nonhuman animal species (including cynomolgus monkey), prohibiting the design of a predictive nonclinical safety testing strategy. Because ALXN1210 is specific for human C5, nonclinical safety tests (safety pharmacology, general toxicity, and reproductive toxicology) will not be predictive of human on-target toxicity. Moreover, significant immunoreactivity (ADA) to ALXN1210 was observed in a non-GLP PK study in cynomolgus monkeys. In the animals with a positive ADA response, clearance of ALXN1210 was accelerated. This observation suggests that interpretation of results from nonhuman primate toxicology studies performed with ALXN1210 (evaluating only potential off-target effects), might be further confounded by an antibody response, and consequent effects on test article clearance.

To study the potential toxicity of long-term inhibition of C5 and to evaluate the influence of such inhibition on reproductive function, a 26-week repeat-dose toxicity study in mice and Segment I, II, and III reproduction studies in mice were performed using a surrogate murine anti-mouse C5 mAb (BB5.1). Like ALXN1210, the BB5.1 surrogate antibody binds directly to and prevents the cleavage of C5, thereby inhibiting the generation of both C5a and C5b-9 in the mouse. These studies showed no meaningful adverse observations at doses that blocked C5 in a sustained fashion.

In addition to the studies with a surrogate antibody, GLP tissue cross-reactivity studies were performed using a standard set of human and cynomolgus monkey tissues. These studies confirmed the lack of cross-reactivity in a nonhuman primate and demonstrated no unexpected binding to human tissues.

An attempt was made to study the potential local irritation in rabbits of ALXN1210, when administered subcutaneously (SC) with a previous formulation; however, the results were not interpretable due to the development of a severe immune-complex based immunologic response. Such immune responses in animals are not considered predictive of similar potential outcomes in humans. To assess the potential for immunogenicity with ALXN1210, the amino acid substitutions to eculizumab used to make ALXN1210 were modeled in the context of the binding motifs for MHC class II receptors using the Immune Epitope Database Analysis Resource (IEDB, 2016; http://tools.iedb.org/main/). None of the peptide fragments in ALXN1210 that are novel relative to eculizumab were predicted to confer high affinity binding to MHC class II receptors.

5.1.3. General Considerations for This Study

This Phase 1 study will be performed in healthy subjects. Data from this study will be used to evaluate the safety, immunogenicity, PK, and PD investigations obtained in subjects receiving a single dose of ALXN1210 SC compared to results obtained in subjects receiving a single dose of ALXN1210 IV.

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, subjects will receive the MCV4 vaccination at least 56 days prior to dosing with ALXN1210 (if not vaccinated with MCV4 within the last 3 years, or if adequate documentation to verify previous vaccination is unavailable). The serum bactericidal antibody (SBA) titer to the tetravalent vaccine will be established prior to enrollment. Subjects who are not already vaccinated will also receive vaccination for serotype 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. Unless the investigator 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 at Day 56).

Analysis of serum samples to establish actual complement activity will be performed using a CH50 in vitro liposome immunoassay (LIA). The analysis will take place approximately when complement activity is expected to normalize. Results will be used to confirm that complement activity has returned to normal and, once confirmed prophylactic antibiotic treatment can be stopped. All subjects will be closely monitored 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 significant. 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 the following: 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 (Bugelski, 2009; Castells, 2015). The signs and symptoms include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, chills, 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 study drug administration.

6. STUDY OBJECTIVES AND PURPOSE

The purpose of the study is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of a single dose of ALXN1210 administered subcutaneously (SC) compared to a single dose of ALXN1210 administered intravenously (IV) in healthy subjects. Data from this study will be used to determine the absolute bioavailability of ALXN1210 SC in healthy subjects.

6.1. Primary Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of a single dose of ALXN1210 SC compared to ALXN1210 IV in healthy subjects, as assessed by physical examination findings, vital sign measurements, immunogenicity, laboratory analysis, and assessments of AEs.
- To determine the absolute bioavailability of ALXN1210 SC.

6.2. Secondary Objectives

The secondary objective of the study is as follows:

- To evaluate the PD effects of ALXN1210 SC compared to ALXN1210 IV, as assessed by the level of free C5 and chicken red blood cell (cRBC) hemolysis.

7. ENDPOINTS

The safety, immunogenicity, PK, and PD endpoints are described in the sections to follow. The timing of assessments is displayed in the Schedule of Assessments (Section 9).

7.1. Safety Endpoints

Safety endpoints include the following:

- Change from baseline in physical examination findings
- Change from baseline in vital sign measurements
- Incidence of ADA measured via immunogenicity testing
- Change from baseline in electrocardiogram (ECG) parameters
- Change from baseline in laboratory measurements
- Incidence of AEs and serious AEs (SAEs)

7.2. Pharmacokinetic Endpoints

The following PK parameters will be evaluated:

- Maximum observed serum concentration (C_{max})
- Time to maximum observed serum concentration (T_{max})
- Area under the serum concentration versus time curve from time zero to the last quantifiable concentration (AUC_t)
- Area under the serum concentration versus time curve from time zero to infinity (AUC_∞)
- Terminal elimination rate constant (λ_z)
- Terminal elimination half-life ($T_{½}$)
- Total body clearance of drug from the serum (CL)
- Volume of distribution (V_d)

7.3. Pharmacodynamic Endpoints

The following PD effects will be evaluated:

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

8. INVESTIGATIONAL PLAN

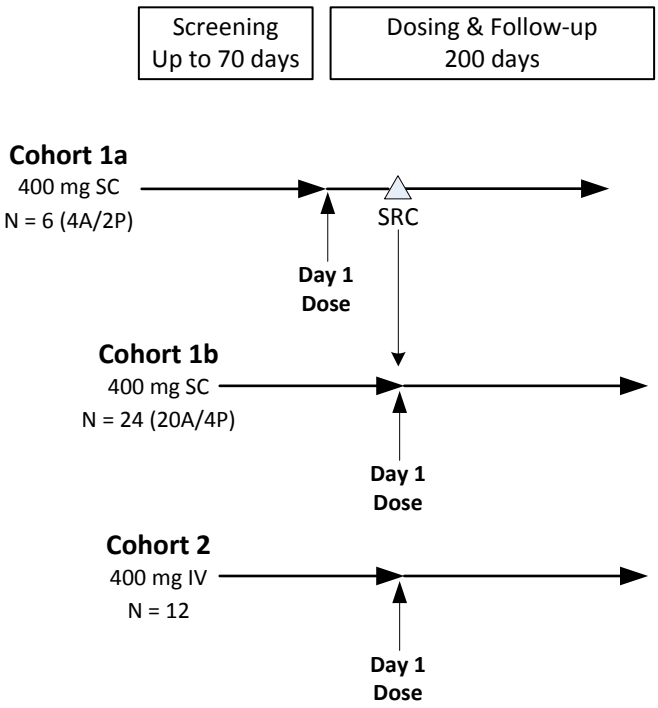
8.1. Overall Study Design

This is a Phase 1 study designed to evaluate the safety, tolerability, PK, PD, and immunogenicity of a single 400 mg dose of ALXN1210 SC compared to a single 400-mg dose of ALXN1210 IV or placebo SC in 42 healthy subjects. All subjects will be screened for eligibility in the study after providing signed and dated institutional ethics committee-approved written informed consent to participate and before any study specific screening procedures are performed.

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.

Six subjects will initially be randomly assigned in a 2:1 ratio to Cohort 1a, in a blinded fashion, to receive either a single 400-mg dose of ALXN1210 SC or single dose of placebo SC (Figure 1). The Safety Review Committee (SRC) will evaluate the first 48 hours of post-dose clinical safety data for subjects in Cohort 1a before enrollment into Cohorts 1b or 2 may begin. Thirty-six subjects will then be randomly assigned, in a 2:1 ratio, to either Cohort 1b (N=24) or Cohort 2 (N=12). Within Cohort 1b, the 24 subjects will further be randomly assigned, in a 5:1 ratio and blinded fashion, to receive either a single 400-mg dose of ALXN1210 SC or a single dose of placebo SC, respectively. The 12 subjects in Cohort 2 will receive a single 400 mg dose of ALXN1210 IV in an open-label fashion.

Figure 1: Study Diagram



Abbreviations: A = active drug; IV = intravenous; P = placebo; SC = subcutaneous; SRC = Safety Review Committee
Note: The SRC will review the first 48 hours of post-dose safety data from Cohort 1a before enrollment into Cohorts 1b or 2 may begin.

At the sponsor's discretion, up to 8 additional subjects (2 subjects each in Cohorts 1a and 1b and 4 subjects in Cohort 2) may be enrolled into the study if 2 or more subjects discontinue within 3 months for reasons other than drug-related AEs, and after consultation with the SRC. All enrolled subjects will be included in analyses as appropriate. Subjects in Cohorts 1a and 1b will be combined for analyses. Subjects who withdraw from the study subsequent to dosing will be followed for safety assessments through the last scheduled study visit, if possible.

Subjects will participate in the study for up to 39 weeks, including a screening period of up to 70 days, followed by a 200-day follow-up period for safety, PK, PD, and immunogenicity assessments after study drug administration.

8.2. Number of Subjects

Forty-two subjects are planned for evaluation of the primary and secondary objectives in this study: 6 (4 ALXN1210 SC, 2 placebo SC) subjects in Cohort 1a; 24 (20 ALXN1210 SC, 4 placebo SC) subjects in Cohort 1b, and 12 (ALXN1210 IV) subjects in Cohort 2. At the sponsor's discretion, up to 8 additional subjects (2 subjects each in Cohorts 1a and 1b and 4 subjects in Cohort 2) may be enrolled into the study if 2 or more subjects discontinue within 3 months for reasons other than drug-related AEs, and after consultation with the SRC.

8.3. Dose Rationale

8.3.1. ALXN1210 IV Dose

The geometric mean (coefficient of variation [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 200-mg and 400-mg doses of ALXN1210 IV 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 the ongoing Study ALXN1210-HV-102, 400-mg and 800-mg (Q4W) doses of ALXN1210 IV are being studied to assess safety, tolerability, PK, PD, and immunogenicity in healthy volunteers.

8.3.2. ALXN1210 SC Dose

A single dose of 400 mg, equivalent to 4 mL, will be administered SC via 4 x 1 mL injections in the abdominal area. Administration of a single 400-mg dose of ALXN1210 SC is expected to have an acceptable safety profile. Single doses of 400 mg of ALXN1210 SC and placebo SC, administered as described in this protocol, are anticipated to provide data from which multiple dose simulations may be generated in order to project the dosing regimens necessary to achieve therapeutic serum concentrations (> 50 μg/mL) in patients.

8.4. Dose Continuation and Suspension/Stopping Rules

Parallel randomization of 36 subjects into Cohort 1b and Cohort 2 will occur based on review by the SRC of the first 48 hours of post-dose clinical safety data from the 6 subjects in Cohort 1a. Enrollment into Cohort 1b and Cohort 2 will proceed as described in Table 3. These rules apply to AEs assessed as related to study drug by the investigator.

Group toxicity rules:

- Toxicity refers to clinically significant drug-related adverse reaction(s).
- ‘Cohort progression’ refers to progression to a consecutive dose/dosing regimen in line with the dose progression rules and minimum data requirements.
- ‘Suspension’ refers to no further IMP being administered at the dose level/dosing regimen concerned and that further cohort progression will be suspended. If a dosing regimen is suspended, an ad hoc SRC meeting will be held. Any resumption at the same dose level/dosing regimen will require a substantial amendment, which has been approved by the competent authority and the IEC.

Table 3: Toxicity Rules

CTCAE Grade	Severity/ Seriousness	Number of Subjects Affected	Action	Effect on cohort progression
I	Mild	N/A	Dose regimen may continue.	Study continues as per clinical study protocol.
II	Moderate	≤ 2 subjects in different SOC		
		2 subjects in same SOC OR 3 subjects in different SOC	Dose regimen may continue.	Cohorts 1b and 2 may commence, if they have not already.
		≥ 3 subjects in same SOC OR ≥ 4 subjects in different SOC	All dose regimens suspended UNLESS the toxicity is either a local tolerability event or and injection/infusion site reaction, in which case only the affected cohort is suspended.	Study continuation (if both cohorts stopped) requires substantial amendment. Continuation of the affected cohort (for local tolerability or injection/infusion site reactions) requires substantial amendment.
III	Severe	1 subject	Dose regimen may continue.	Cohorts 1b and 2 may commence, if they have not already.
		≥ 2 subjects	All dose regimens suspended UNLESS the toxicity is either a local tolerability event or and injection/infusion site reaction, in which case only the affected cohort is suspended.	Study continuation (if both cohorts stopped) requires substantial amendment. Continuation of the affected cohort (for local tolerability or injection/infusion site reactions) requires substantial amendment.
IV	Life-threatening	≥ 1 subject	Study suspended.	Study continuation requires substantial amendment.
V	Fatal			
SAE	Serious	≥ 1 subject	Study suspended.	Study continuation requires substantial amendment.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event; SOC = system organ class.

8.5. Safety Review Committee

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

In order to perform its primary function of ensuring subject safety, the members of the SRC will have access to all safety and clinical data.

The SRC will review the first 48 hours of post-dose clinical safety data for the 6 subjects randomly assigned into Cohort 1a before enrollment into Cohorts 1b or 2 may begin. This will allow for further assessment of safety and tolerability of the SC formulation before exposing additional subjects to ALXN1210 SC. After the SRC has reviewed the safety and clinical data of the last completed subject in Cohort 1a, subjects will be randomly assigned into Cohort 1b in a blinded fashion, to receive either a single 400-mg dose of ALXN1210 SC or a single dose of placebo. In parallel, subjects will be randomly assigned into Cohort 2 to receive a single 400-mg dose of ALXN1210 IV in an open-label fashion.

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 are met that warrant suspension of the study.

The SRC may make recommendations regarding safety issues, study conduct, and modifying (ie, exploring the dose cohort further, suspending dose cohort[s]), 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 warrant termination of the study include, but are not limited to, the following:

- 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. SCHEDULE OF ASSESSMENTS

The timing of study procedures is provided in the Schedule of Assessments (Table 4 and Table 5).

Table 4: Schedule of Assessments: Screening through Visit 1

				Visit 1									
Study Day	**Screening**	**Day –1**		**Day 1**							**Day 2**	**Day 3**	**Day 5**
Assessments[1]	**Day –70 to Day –2**	**Admit Day –1**	**Pre-dose**	**0 h (SOI)**	**EOI**[2]	**15 min post EOI**	**30 min post EOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**24 h**	**48 h**	**96 h**
Status (OP or CRU)	OP	Admit	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU[3]
Informed consent[4]	X												
MCV4 immunization (Day -56)[5]	X												
Meningococcal serogroup B immunization (Day -56 and Day -28)[5]	X												
Serum bactericidal antibody (meningococcal serogroups A, C, W135, and Y)	X												
Medical history & demographics	X												
Physical examination	X	X											X
Height, weight, and BMI	X												
QuantiFERON®-TB test	X												
Chemistry	X	X									X		X
Hematology	X	X									X		X
Coagulation	X	X									X		X
Hepatitis B and C screen	X												
HIV, types I and II screen	X												
Complement activity[6]	X												
CH50[7]		X											
Serum pregnancy test[8]	X	X											
Alcohol breath test	X	X											
Urinalysis and urine chemistry	X	X									X		X
Urine drug screen	X	X											
Vital sign measurements	X	X	X[9]		X		X[9]	X[9]	X[9]	X[9]	X	X	X
ECG	X		X[10]			X					X	X	X
Cardiac telemetry[11]			X	X	(X)	(X)	(X)	(X)					
Randomization				X									
Study drug administration				X									
PK samples			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
Infusion site evaluation[12]			X				X	X	X	X	X	X	
Immunogenicity (ADA)			X										
Review potential safety risks of ALXN1210[13]	X	X											X

				Visit 1									
Study Day	**Screening**	**Day –1**		**Day 1**							**Day 2**	**Day 3**	**Day 5**
Assessments[1]	**Day –70 to Day –2**	**Admit Day –1**	**Pre-dose**	**0 h (SOI)**	**EOI**[2]	**15 min post EOI**	**30 min post EOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**24 h**	**48 h**	**96 h**
Status (OP or CRU)	OP	Admit	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU[3]
Concomitant medications		←Monitor continuously (after ICF is signed at screening)→											
Adverse events[14]		←Monitor continuously (after ICF is signed at screening)→											
Antibiotic prophylactic treatment[15]		←Antibiotic prophylaxis→											

[1] Permissible windows for study assessments are described in the study operations manual.
[2] EOI will be approximately 15 minutes after SOI.
[3] Subject will be discharged from CRU after completing all Day 5 assessments. Subjects will be provided a "Study Participant ID card" with information for Healthcare Provider and participant on symptoms of meningitis infection.
[4] Signed and dated EC-approved ICF must be obtained before any study-specific screening procedures are performed.
[5] 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.
[6] 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.
[7] The sample drawn on Day -1 will be stored for future analysis should the post-dose sample indicate that complement has not normalized.
[8] Serum pregnancy test for all female subjects to confirm a female subject is not pregnant.
[9] On Day 1, vital sign measurements will be assessed pre-dose (within 15 minutes prior to SOI) and at EOI, 30 minutes after EOI, 2 hours after SOI, 4 hours after SOI, and 8 hours after SOI.
[10] On Day 1, triplicate 12-lead ECGs will be performed pre-dose and approximately 15 minutes post-EOI.
[11] Continuous cardiac registration predose through duration of IV infusion (Cohort 2) and until 3 hours post SC injection (Cohorts 1a and 1b).
[12] Infusion or injection site evaluations will be done within 15 minutes of the start of infusion/injection and ± 15 minutes of the other scheduled times on Day 1. Indurations or reactions < 1cm will not be listed as an adverse event unless it persists for more than 24 hr. Pain at site of infusion or injection will be assessed using a Visual Analog Scale (0-10). Pain will not be assessed pre-dose.
[13] The investigator or designee will meet with the subject at each visit to discuss the potential safety risks of ALXN1210, and to address any safety concerns on the part of the subject.
[14] Collection of AEs and SAEs will begin at ICF signing.
[15] Subjects will be administered prophylactic antibiotic treatment, oral penicillin V 500 mg twice daily (equivalent to 1×10^6 units), beginning on the evening of Day -1, until complement activity has normalized, as determined by CH50 assay.

Abbreviations: ADA = antidrug antibody; BMI = body mass index; cRBC = chicken red blood cell; CRU = clinical research unit; ECG = electrocardiogram; EOI = end-of-infusion/injection; HIV = human immunodeficiency virus; ICF = informed consent form; MCV4 = tetravalent meningococcal conjugate vaccine; OP = outpatient; SOI = start-of-infusion/injection; TB = tuberculosis

Table 5: Schedule of Assessments: Visit 2 through Visit 14

	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit	Visit	Visit 12	Visit 13	Visit 14
Procedures	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57**	**Day 71**	**Day 90**	**Day 120**	**Day 150**	**Day 200**
Status (OP or CRU)	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP
Physical Examination		X				X				X	X	X	X
Vital Sign Measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG												X	X
Chemistry	X	X		X		X		X		X	X	X	X
Hematology	X	X		X		X		X		X	X	X	X
Coagulation	X	X		X		X		X		X	X	X	X
Urinalysis and Urine Chemistry		X				X				X	X	X	X
Serum Pregnancy Test												X	X
CH50 Testing						X		X[1]					
Pharmacokinetic Samples	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics Panel (serum C5, cRBC hemolysis)	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity (ADA)		X		X				X		X	X	X	X
Review Potential Safety Risks of ALXN1210[2]	←--- Discuss potential safety risks of ALXN1210 --→												
Concomitant Medications	←--- Monitor continuously (after ICF is signed at screening)--→												
Adverse Events[3]	←--- Monitor continuously (after ICF is signed at screening)--→												
Antibiotic Prophylactic[4]	←--- Antibiotic prophylaxis--→												

[1] Additional samples may be taken after Day 57 as per Section 5.1.4.1.

[2] The investigator or designee will meet with the subject at each visit to discuss the potential safety risks of ALXN1210, and to address any safety concerns on the part of the subject.

[3] Collection of adverse events will begin at ICF signing.

[4] Subjects will be administered prophylactic antibiotic treatment, oral penicillin V 500 mg twice daily (equivalent to 1×10^6 units) until complement activity has normalized, as determined by CH50 assay.

Abbreviations: ADA = antidrug antibody; cRBC = chicken red blood cell; CRU = clinical research unit; ECG = electrocardiogram; ICF = informed consent form; OP = outpatient

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 subjects, aged 25 through 55 years, inclusive, at the time of dosing.
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 titer 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, if heterosexually active, must use highly effective or acceptable contraception as defined below, starting at screening and continuing until at least 6 months after study drug administration. Antibiotic prophylaxis is required during this study, which can compromise the efficacy of hormonal contraception. Therefore, it is recommended that subjects using hormonal contraception also use barrier contraception (eg, condom or diaphragm with spermicide) for the duration of antibiotic prophylaxis.

   Highly effective contraceptive methods for females are as follows:

   - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation as follows:
     - Oral
     - Intravaginal
     - Transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation as follows:
     - Oral
     - Injectable
     - Implantable
   - Intrauterine device

- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

Male subjects, if heterosexually active and with a female spouse or 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 after study drug administration. 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 after study drug administration. Male subjects must not donate sperm during the screening and treatment periods and for at least 6 months after study drug administration.

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 to) 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 6 months prior to dosing
3. History of any *Neisseria* infection.

4. History of unexplained, recurrent infection, or infection requiring treatment with systemic antibiotics within 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 (TB) infection.
10. History of latent or active TB or exposure to endemic areas within 8 weeks prior to the screening visit.
11. Female subjects who are breastfeeding or are heterosexually active and 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 study drug administration.
12. Positive serum pregnancy test at screening or on Day –1.
13. Serum creatinine greater than the upper limit of normal (ULN) of the reference range of the testing laboratory at screening or on 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 on 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 cell (WBC) count < $3.0 \times 10^3/\mu L$, absolute neutrophil count < $2.0 \times 10^3/\mu L$, and platelet count < 150 or > $400 \times 10^3/\mu L$ at screening or on 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 the 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 an mAb, or participation in a clinical study of an 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. Prior exposure to ALXN1210.
21. Major surgery or hospitalization within 90 days prior to dosing.
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 (eg, anaphylaxis or 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 on 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 prior to dosing or more than 499 mL of blood within 56 days prior to dosing.
30. History of continuous topical, inhaled, or systemic steroid use > 28 days 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 and 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 28 days 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 dosing.
36. Subjects with any medical history, conditions, or risks that, 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.

10.3. Subject Withdrawal Criteria

A subject may withdraw from the study at any time at his or 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 (Section 9).

Unless the investigator 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 6.

Table 6: Investigational Product

	Investigational Product		
Product Name	ALXN1210 IV	ALXN1210 SC	Placebo SC
Dosage Form	Sterile solution for infusion	Sterile solution for injection	Sterile solution for injection
Unit Dose	150 mg/vial[1]	100 mg/vial[2]	NA
Route of Administration	Intravenous	Subcutaneous injection	Subcutaneous injection
Physical Description	Sterile, preservative-free solution	Sterile, preservative-free solution	0.9% sodium chloride for injection, Ph Eur or BP, sterile, preservative-free solution
Manufacturer	Alexion Pharmaceuticals, Inc.	Alexion Pharmaceuticals, Inc.	Saline solution marketed in UK

[1] Each vial of ALXN1210 IV drug product includes a nominal overfill to ensure that 15 mL (150 mg of ALXN1210) can be withdrawn for administration.
[2] Each vial of ALXN1210 SC drug product includes a nominal overfill to ensure that 1 mL (100 mg of ALXN1210) can be withdrawn for administration.
Abbreviations: BP = British Pharmacopoeia; IV = intravenous; NA = not applicable; Ph Eur = European Pharmacopoeia; SC = subcutaneous

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 the following:

1. A MCV4 vaccination at least 56 days prior to dosing of ALXN1210 on Day 1 (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, 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.

3. Prophylactic antibiotic treatment, oral penicillin V 500 mg twice daily (equivalent to 1×10^6 units) until complement activity has normalized (as determined by CH50 assay) (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 (dose administration) of study drug. 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 single-dose study:

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, 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 visit. 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 informed consent form (ICF), will take place at specific time points throughout the study as noted in the Schedule 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 ICF until study drug administration) and concomitant medications (any drug or substance taken by the subject after study drug administration until completion of the last study visit) will be recorded on the subject's electronic case report form (eCRF). 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 study drug administration) and concomitant procedures (any therapeutic intervention [eg, surgery/biopsy, physical therapy] performed after

study drug administration until completion of the last study visit) will be recorded on the subject's eCRF.

A concomitant therapy is any drug or substance administered from the time the subject is screened for the study until completion of the last study visit. 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.

A concomitant procedure is any therapeutic intervention (eg, surgery/biopsy, physical therapy) or nonstudy diagnostic assessment (eg, blood gas measurement, bacterial cultures) performed from the time the subject signs the informed consent until the last study visit. Concomitant procedures are not allowed unless medically indicated.

The use of concomitant therapies defined above as well as any AEs related to administration of these therapies or procedures must be documented on the subject's eCRF.

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 (eg, coffee, tea, chocolate) are prohibited for at least 24 hours prior to admission through discharge from the study center, and for 24 hours prior to each follow-up visit.

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

Meals: No outside food or drink is permitted at the study center. 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 study drug administration until discharge from the study center.

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 study center 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 center to ensure compliance with the protocol, and communicate with study centers 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 study center's standard operating procedures.

11.7. Randomization and Blinding

Eligible subjects who meet the inclusion and exclusion criteria will be assigned unique numbers for enrollment and randomization.

This is a partially blinded study such that:

- ***Cohort 1a.*** Dosing (a single 400-mg dose of ALXN1210 SC or placebo SC) is double-blind. Subjects in Cohort 1a will be randomly assigned in a 2:1 ratio (4 ALXN1210 SC, 2 placebo SC; N = 6).
- ***Cohort 1b.*** Dosing (a single 400-mg dose of ALXN1210 SC or placebo SC) is double-blind. Subjects in Cohort 1b will be randomly assigned in an 5:1 ratio (20 ALXN1210 SC, 4 placebo SC; N = 24).
- ***Cohort 2***. Dosing (a single 400-mg dose of ALXN1210 IV) is open-label (N = 12).

During Cohort 2 dosing, both subjects and onsite medical/nursing staff will know the drug/dose being administered.

During Cohorts 1a and 1b dosing, subjects and onsite medical/nursing staff at the study center will be blinded to study drug assignment. The pharmacy staff preparing the SC injections will not be blinded, nor will the study drug administrator(s), while all other study center staff involved in the safety evaluations will remain blinded to study drug assignment. Sponsor staff will be unblinded as needed (eg, to monitor that the SC injections are being prepared appropriately, to determine reportability of SAEs), and will refrain from sharing any information on study drug assignment with the study center staff.

In the event of an emergency, an envelope for each subject containing his or her study drug assignment will be available from the pharmacy staff preparing the investigational products. There is no antidote to reverse the effects of ALXN1210; therefore, unblinding would not be helpful in the planning of subject treatment for a given event.

Unblinding should only be considered for the safety of the subject. If unblinding is deemed necessary by the investigator, the investigator can unblind the subject's treatment allocation using the envelope available from the pharmacy staff. The investigator must note the date, time, and reason for unblinding. The investigator should inform the medical monitor that the subject was unblinded; however, the investigator is not required to reveal to the medical monitor the subject's treatment allocation. When an AE is serious, unexpected, and related, the blind will be broken by the sponsor only for that specific subject. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, investigator, etc) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to health authorities, IEC, or

persons performing ongoing safety evaluations during the study. The investigator will receive only blinded information unless unblinded information is judged necessary for safety reasons.

12. STUDY DRUG MATERIALS AND MANAGEMENT

12.1. Study Drugs

12.1.1. ALXN1210 SC

Each vial of ALXN1210 SC contains 100 mg of ALXN1210 (100 mg/mL) in 50 mM sodium phosphate, 25 mM arginine, 5% sucrose, and 0.05% polysorbate 80. ALXN1210 SC is formulated at pH 7.4 and is provided as a fully-formulated, sterile, preservative-free, 100-mg/mL aqueous solution of ALXN1210 supplied in 2-mL single-use vials. Each vial of ALXN1210 SC includes a nominal overfill to ensure that 1 mL (100 mg of ALXN1210) can be withdrawn for administration.

ALXN1210 SC 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 ALXN1210 IB and in the pharmacy manual.

12.1.2. Placebo SC

Each dose of placebo SC contains 0.9% sodium chloride injection, Ph Eur or BP, to the same volume as specified for Cohorts 1a and 1b.

Placebo SC will be provided by the study center and is suitable for human use and manufactured under current Good Manufacturing Practices.

Further details are provided in the pharmacy manual.

12.1.3. ALXN1210 IV

Each vial of ALXN1210 IV contains 150 mg of ALXN1210 in 10 mM sodium phosphate, 150 mM sodium chloride, 0.02% polysorbate 80, and water for injection. ALXN1210 IV is formulated at pH 7.0 and is provided as a fully-formulated, sterile, preservative-free, 10-mg/mL aqueous solution of ALXN1210, supplied in 20-mL single-use vials. ALXN1210 IV will be diluted in 0.9% sodium chloride injection, Ph Eur or BP, and administered by IV infusion at a maximum rate of 333 mL/hr, excluding interruption for safety or technical reasons.

ALXN1210 IV 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 ALXN1210 IB 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 and placebo SC doses must be performed in accordance with study center-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.

12.4.1. Preparation of ALXN1210 SC and Placebo SC

ALXN1210 SC and placebo SC will be prepared in a blinded fashion in a syringe for SC administration. There will be no dilution of ALXN1210 SC or placebo SC. ALXN1210 SC and placebo SC will be placed directly into the syringe.

The pharmacy staff preparing the SC injections for Cohort 1a and Cohort 1b will be unblinded, as will the study drug administrator(s). All other staff involved will be blinded (Section 11.7).

Please refer to the pharmacy manual for additional dose preparation instructions and the SOM for additional information regarding blinding and study drug administration.

12.4.2. Preparation of ALXN1210 IV

ALXN1210 IV is designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; Ph Eur or BP) for IV infusion at a maximum rate of 333 mL/hr, excluding interruption for safety or technical reasons.

The pharmacy staff preparing the infusions for Cohort 2 will be unblinded to study drug assignment; the subjects and all other study center staff involved in the study will also be unblinded (Section 11.7).

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

12.4.3. In-Use Shelf Life

ALXN1210 IV will be diluted with 0.9% sodium chloride injection, Ph Eur or BP, before administration (dosing solution). The in-use shelf life of the dosing solution is 4 hours at room temperature 15°C to 25°C (59°F to 77°F).The expiration date and time of the dosing solution is calculated from breach of the first vial. The dose must be administered within the expiration date and time.

Each 1-mL syringe of ALXN1210 SC or placebo SC that is drawn up (4 syringes per subject) should be administered within 1 hour once drawn up from vial to syringe.

12.5. Administration

12.5.1. Administration of ALXN1210 SC and Placebo SC

All doses of ALXN1210 SC or placebo SC will be administered by four 100-mg SC injections of 1 mL each (Table 7) in the abdominal area. All four 1-mL injections should be administered over a 15-minute period, and there should be at least 15 minutes between the end of injection in one subject and the start of injection in the next subject.

Table 7: Dosing Reference Chart for ALXN1210 SC and Placebo SC Preparation

Cohort	Study drug and dose	Number of 1-mL syringes prepared	Total volume administered
1a	1 dose of 400 mg ALXN1210 SC or placebo SC	4	4 mL
1b	1 dose of 400 mg ALXN1210 SC or placebo SC	4	4 mL

For further information regarding the preparation and administration of study drug, please see the pharmacy manual. Please refer to the SOM for additional information regarding blinding and study drug administration.

12.5.2. Administration of ALXN1210 IV

All doses of ALXN1210 IV will be administered by IV infusion, using IV sets with in-line filters, at a maximum rate of 333 mL/hr, excluding interruption for safety or technical reason. There should be at least 15 minutes between the end of infusion in one subject and the start of infusion in the next subject. For further information regarding the preparation and administration of study drug, please see the pharmacy manual.

Table 8: Dosing Reference Chart for ALXN1210 IV Preparation

Cohort	Study drug and dose	ALXN1210 volume per dose (mL)	Diluent volume per dose (mL)	Infusion volume (mL)	Maximum infusion rate (mL/h)	Minimum infusion duration[1] minutes (hour)
2	1 dose of 400 mg ALXN1210 IV	40	40	80	333	15 (0.25)

[1] Infusion duration is approximate.

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

12.6. Management of Potential Adverse Events During Study Drug Administration

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 their 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/injection in one subject and the start of infusion/injection in the next subject. No

more than 6 subjects will be dosed per day. Any reactions will be treated and taken into account in the dose continuation/escalation and toxicity rules (see Table 3). 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 that results 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.

Similar reactions could potentially occur with SC injections of mAbs.

12.7. Study Drug Accountability

The study center must maintain accurate records demonstrating dates and amount of study drug received from Alexion, to whom study drug was dispensed (a 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 study center, the investigator must obtain prior approval by Alexion. The investigator must notify Alexion, in writing, of the method, date, and location of the 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 AND PHARMACODYNAMIC ASSESSMENTS

13.1. Serum Sample Collection

The total anticipated volume of serum collected per subject for clinical laboratory, PK, PD, and immunogenicity assessments will not exceed 500 mL per subject. Please refer to the laboratory manual for specific details regarding serum volumes.

After study drug administration, serum samples for the determination of serum ALXN1210 concentrations and for analyses of total and free C5 concentrations, cRBC hemolysis, and potentially other measures of C5 activation will be collected at the following time points, with the actual serum sampling dates and times being recorded and used in the PK and PD calculations:

- Serum concentrations of ALXN1210 will be assayed from the following sampling time points: pre-dose (within 15 minutes prior to start-of-infusion/injection [SOI]); Day 1 at end of infusion/injection (EOI), 30 minutes post EOI, and the following time points following SOI: 2 h, 4 h, and 8 h; Day 2 (24 h); Day 3 (48 h); Day 5 (96 h); Day 8 (168 h); Day 15 (336 h); Day 22 (504 h); Day 29 (672 h); Day 36 (840 h); Day 43 (1008 h); Day 50 (1176 h); Day 57 (1344 h); Day 71 (1680 h); Day 90 (2136 h); Day 120 (2856 h); Day 150 (3576 h); and Day 200 (4776 h).

Please refer to the SOM for the time windows for collection, and to the laboratory manual for details on sample collection, including the serum 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. All subjects providing PD samples will be included in the PD analysis population.

13.3. Sample Analysis

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

14. IMMUNOGENICITY ASSESSMENTS

14.1. Serum Sample Collection

Serum samples will be collected at the following time points: pre-dose (within 15 minutes prior to SOI), and on Days 15 (336 h), 29 (672 h), 57 (1344 h), 90 (2136 h), 120 (2856 h), 150 (3576 h), and 200 (4776 h) and analyzed for ADA to ALXN1210.

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 the time windows for collection, and to the laboratory manual for details on sample collection, including the serum volume requirements.

14.2. Criteria for Evaluation

All subjects who provide a pre-dose and a post-dose sample for ADA will be included in the immunogenicity analysis population.

14.3. Sample Analysis

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

15. ASSESSMENT OF SAFETY

Safety assessments will include TB testing, physical examination findings, vital sign measurements, immunogenicity (ADA) testing, laboratory evaluations, ECGs, infusion site and injection site evaluations (eg, bleeding, bruising, erythema, swelling, induration, and pain), and monitoring of AEs. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 (CTCAE v4.03), published 14 Jun 2010. Laboratory evaluations will include hematology, chemistry, and coagulation panels; CBC with differential; urinalysis; and serum pregnancy test for female subjects.

15.1. Safety Parameters

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

15.1.1. Demographic/Medical History

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

15.1.2. Vital Sign Measurements

Vital sign measurements will be taken after the subject has been resting in the supine or semirecumbent position for at least 5 minutes and will include temperature (°C; oral), respiratory rate, supine blood pressure, and pulse. The timing of vital sign measurements is described in the Schedule 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.

15.1.3. Weight, Height, and BMI

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

15.1.4. Physical Examination

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

15.1.5. 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 Schedule of Assessments (Section 9). In addition, continuous cardiac registration will be performed at each dose administration from pre-dose to end of IV infusion in Cohort 2 and from pre-dose to 3 hours post end of SC injection in Cohorts 1a and 1b.

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

15.1.6. Laboratory Assessments

Blood samples for analysis of hematology, clinical chemistry, coagulation, and virus serology, and urine samples for urinalysis, urine chemistry, and drug and alcohol screens will be collected as described in the Schedule 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 manual.

15.1.6.1. Hematology

Blood samples will be analyzed for the following hematology parameters: platelet, red blood cell (RBC) count, 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 Schedule of Assessments (Section 9).

15.1.6.2. 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 Schedule of Assessments (Section 9).

15.1.6.3. 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 Schedule of Assessments (Section 9).

15.1.6.4. 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 Schedule of Assessments (Section 9).

15.1.6.5. 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 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.

15.1.6.6. 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). An alcohol breath test will be performed. If positive prior to dosing, dosing will not proceed.

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

15.1.6.7. Pregnancy Testing

Pregnancy testing (beta human chorionic gonadotropin) will be performed in all female subjects (Section 16.8). The timing of pregnancy testing is described in Schedule of Assessments (Section 9).

15.1.6.8. Tuberculosis

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

15.1.6.9. 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.

Serum samples will be collected at baseline and during follow-up for measurement of CH50 activity using an in vitro LIA to confirm normalization of complement activity. If a normal CH50 result is obtained from a subject's first CH50 sample collected during follow-up, antibiotic prophylaxis can be stopped and the second scheduled CH50 sample is not required. If the first and second CH50 samples are not normal, the baseline sample may be analyzed, and further CH50 samples will be taken until complement activity has been restored (see Schedule of Assessments in Section 9).

15.1.6.10. Serum Bactericidal Antibody

An SBA titer against meningococcal serogroups A, C, W135, and Y will be performed at screening (see Schedule of Assessments in Section 9). Titer measurements will be used to exclude subjects without an immune response from being dosed.

15.1.6.11. Injection or Infusion Site Evaluation

Subcutaneous injection or IV infusion site evaluations will be performed as described in Section 9. Pain at the site of SC injection or IV infusion will be assessed using a Visual Analog Scale (0-10). Pain will not be assessed pre-dose. Indurations or reactions ≤ 1 cm in size will not be listed as an AE unless they persist for more than 24 hours.

15.1.6.12. Immunogenicity Evaluation

Serum samples will be analyzed for ADA. The timing of ADA serum sample collection is described in the Schedule of Assessments (Section 9).

16. ADVERSE EVENT MANAGEMENT

The investigator is responsible for detecting, assessing, documenting, and reporting all AEs. All AEs will be recorded from the signing of ICF 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.

16.1. 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, that 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 the following:

- 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 gallbladder)
- Pre-existing diseases or conditions, present at 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)

16.2. 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 department visit of 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 that 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 department 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.

16.3. Severity Assessment

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

16.4. 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 study 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 the event; the event corresponds with the known pharmaceutical profile; improvement on discontinuation; reappearance on rechallenge.

16.5. 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.

16.6. Recording Adverse Events

All observed or volunteered AEs, regardless of dose cohort or causal relationship, must be reported as described in Section 16.4 (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 gallbladder).

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.

16.7. 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 center 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 E-mail or fax using the same contact information.

Additional follow-up information, if required or available, should be entered into the eCRF and sent to sponsor within 24 hours of the investigator or study center 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

16.8. 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 methods 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.

16.9. Reporting Requirements

This protocol will use the current IB as the reference safety document. The expectedness and reporting criteria of an SAE will be determined by Alexion, based on the Reference Safety Document.

16.9.1. 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 that 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, IRBs or IECs, and the investigator.

16.9.2. 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 on the eCRF, and are submitted to the sponsor at regular monthly intervals, or more frequently during the course of the investigation.

17. 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 on the eCRF. This information will be provided to the respective study centers by means of electronic or manual queries.

The investigator or designee will prepare and maintain adequate and accurate source documents (eg, 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.

18. STATISTICS

18.1. Statistical Analysis Plan Summary

A formal statistical analysis plan (SAP) 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.

18.2. 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 and cRBC hemolysis data. The PD population will be used for PD summaries.

The immunogenicity analysis population will consist of all subjects who have a pre-dose and post-dose ADA sample collected.

18.3. Sample Size and Power

A total evaluable sample size of 36 subjects, 24 ALXN1210 SC subjects from Cohort 1 and 12 ALXN1210 IV subjects from Cohort 2, will provide > 80% power to infer that the lower bound of a 90% confidence interval for the ratio of the bioavailability of ALXN1210 SC to IV is > 0.4 assuming an absolute bioavailability of 0.6 and a coefficient of variation of 0.35. Additionally, 6 subjects will receive placebo SC, 2 in Cohort 1a and 4 in Cohort 1b. Randomization to Cohort 1a will be conducted in a 2:1 ratio, and Cohort 1b in a 5:1 ratio, to receive either ALXN1210 SC or placebo SC. This brings the total planned number of subjects to N=42.

18.4. Descriptive Statistics

In general, descriptive statistics for continuous variables will include number of nonmissing values, arithmetic mean, standard deviation, median, minimum, and maximum. Descriptive statistics for PK parameters will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (%CV), median, minimum, maximum, geometric mean and geometric %CV. Categorical variables will be summarized using percentages and frequency counts, by cohort and time point.

18.5. 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 cohort. Demographics and baseline characteristics will be summarized for all subjects by each cohort and overall.

18.6. Safety Analysis

Safety analyses will be performed on the safety population, and will be reported by each cohort. 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 cohort and overall, by relationship to study drug. Treatment-emergent AEs will also be summarized by cohort and overall by severity. 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 sign measurements and laboratory assessments (eg, chemistry, CBC with differential, and urinalysis) will be summarized by each cohort. Laboratory parameter values will be graded according to the CTCAE. Shift tables by cohort will be produced for these laboratory parameters. These tables will summarize the number of subjects with each baseline grade relative to the reference ranges and changes to the worst highest grade assessed post-dose 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 cohort.

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 cohort:

- 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.

18.7. 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 methods using Phoenix WinNonlin 6.3 or higher.

The following PK parameters will be derived: maximum observed serum concentration (C_{max}), time to maximum observed serum concentration (T_{max}), area under the serum concentration versus time curve from time zero to the last quantifiable concentration (AUC_t) area under the curve from time zero to infinity (AUC_∞), terminal elimination rate constant (λ_z), terminal elimination half-life ($T_{½}$), total clearance (CL or CL/F), and volume of distribution (V_d or V_d/F).

The geometric means ratio (ALXN1210 SC/ALXN1210 IV) and its 90% CI will be computed for C_{max}, AUC_t, and AUC_∞, and will be tabulated. The CI will be computed using the between-subject variance. Assessments of concentration over time will be presented.

Further details will be provided in the Statistical Analysis Plan (SAP).

18.8. Pharmacodynamic and Immunogenicity Analyses

The PD effects of ALXN1210 SC and IV 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 performed on samples collected as described in the Schedule of Assessments (Section 9).

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

18.9. Interim Analysis

An interim analysis may be performed as needed.

19. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

19.1. Study Monitoring

Before a study center can enter a subject into the study, a representative of Alexion (sponsor) will visit the investigational study center to do the following:

- 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 and/or designee will have regular contact with the study center, to do 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 on the eCRF, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data on the eCRF 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; and
- Confirm that AEs and SAEs have been properly documented on the eCRF, and confirm that 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.

19.2. Audits and Inspections

Authorized representatives of the sponsor or designee, a regulatory authority, or an IRB/IEC may visit the study center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported, according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council for Harmonisation (ICH), and any applicable regulatory requirements. The investigator is expected to contact the sponsor immediately if contacted by a regulatory agency about an inspection.

19.3. Institutional Review Board/Independent Ethics Committee

The investigator must obtain IRB/IEC approval for the clinical study (see Section 21.1). 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.

19.4. Safety Review Committee

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

19.5. Regulatory Agency

As required by the Medicines and Healthcare products Regulatory Agency (MHRA), 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.

20. 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 19.2 for more details regarding the audit process.

21. ETHICS

21.1. 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 screening 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 all protocol amendments prior to implementation at the study center. 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.

21.2. 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.

21.3. 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.

21.4. 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 (MHRA).

22. DATA HANDLING AND RECORDKEEPING

22.1. Inspection of Records

The sponsor or designee will be allowed to conduct study center 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. See also Section 20 regarding audits.

22.2. Retention of Records

The study center will maintain adequate study records according to local regulatory requirements after completion or termination of the 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 study center 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 documentation relating to the study, the investigator must permit access to such records.

23. 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.

24. LIST OF REFERENCES

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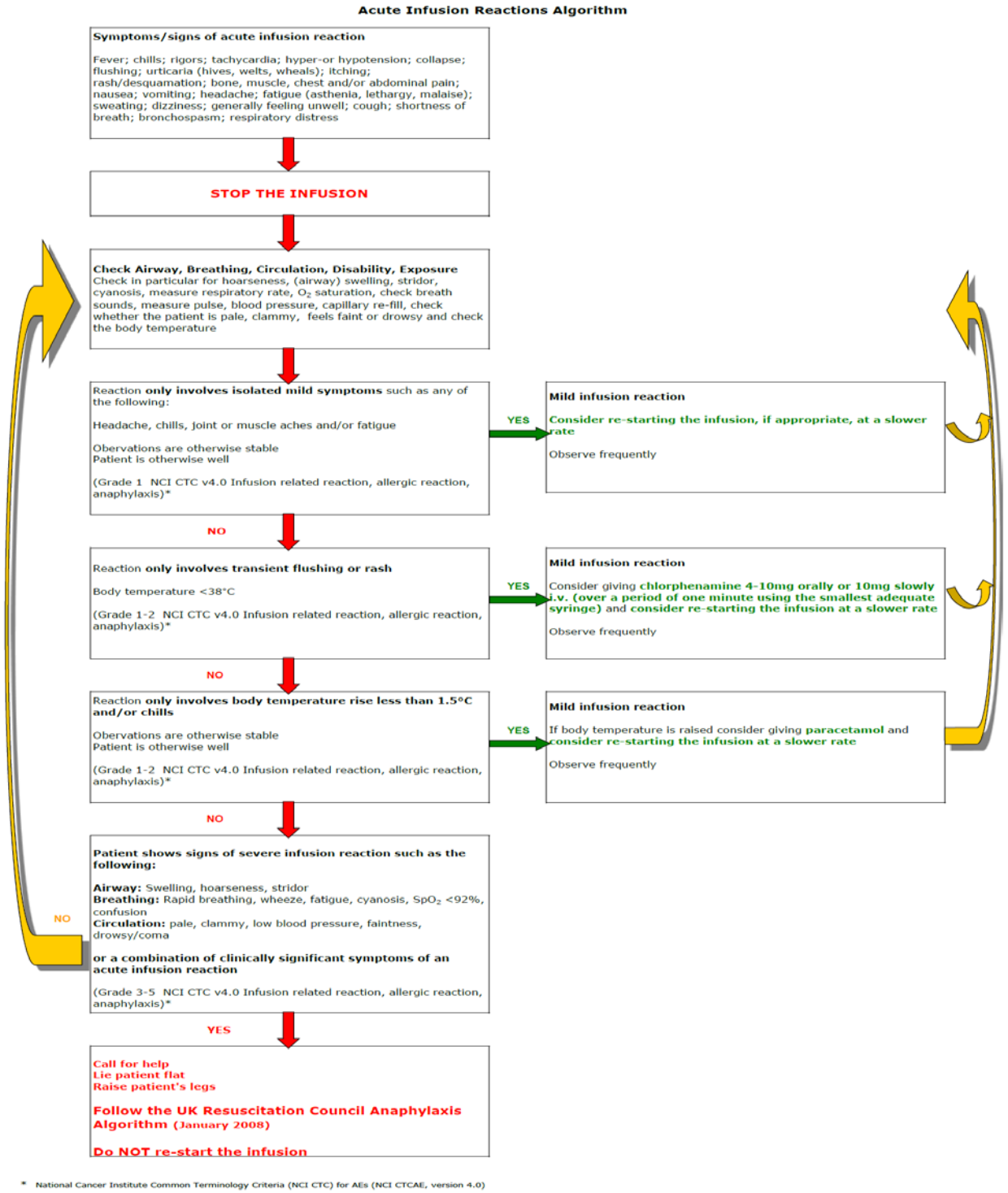
25. APPENDICES

Appendix 1 Acute Infusion Reactions

Appendix 2 United Kingdom Resuscitation Council Anaphylaxis Algorithm

APPENDIX 1. ACUTE INFUSION REACTIONS ALGORITHM



* National Cancer Institute Common Terminology Criteria (NCI CTC) for AEs (NCI CTCAE, version 4.0)

APPENDIX 2. UNITED KINGDOM RESUSCITATION COUNCIL ANAPHYLAXIS ALGORITHM