TITLE PAGE

Protocol Title:

A Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study of Subcutaneous and Intravenous ALXN1820 in Healthy Participants

Protocol Number: ALXN1820-HV-101

Amendment Number: 1 (Global)

Compound: ALXN1820

Study Phase: Phase 1

Short Title:

Safety, Pharmacokinetic, and Pharmacodynamic Study of ALXN1820 in Healthy Adult Participants

Sponsor Name: Alexion Pharmaceuticals, Inc.

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Regulatory Agency Identifying Number(s):

NCT: 04631562
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Approval Date: 06 Jul 2021

Sponsor Signatory:

[redacted]

12-Jul-2021 | 08:16:45 EDT

Date

Medical Monitor Name and Contact Information will be provided separately.

INVESTIGATOR'S AGREEMENT

I have read the study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 1 (06 Jul 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The main rationale for this amendment is a change in dose escalation rules to make Cohort 10 independent of data from Cohort 9.

Other changes implemented through this protocol amendment constitute removing monthly pregnancy testing for spouses/partners of male participants, revising exclusion criterion to allow for other vaccines during the study, revision of guidance for injection/infusion-associated reactions, and addition of COVID-19 risk assessment.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Table 2	It was clarified that dose in Cohort 7 will be determined based on the safety data up to Cohort 6 and interim PK/PD modeling with data up to Cohort 5. Dose in Cohort 10 will be determined based on safety data up to cohort 8 and interim PK/PD modeling with data up to Cohort 5.	Updated to accurately reflect the decision for the dose in Cohorts 7 and 10.
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 4.3 Justification for Dose, and Section 6.6 Dose Modification	Dependency on data from Cohort 9 for dose escalation to Cohort 10 was removed.	Updated to accurately reflect that Cohort 9 is flexible and not required for dose escalation to Cohort 10.
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 6.6 Dose Modification	"Optional" was added in relation to Cohort 7, and language around number of total cohorts was updated to reflect that.	Wording added to clarify that Cohort 7 is optional.
Section 1.1 Synopsis, Section 4.1 Overall Design	Language amended regarding timing of dosing of participants to at least 48 hours after dosing of the sentinel pair.	To clarify timing of dosing within cohorts.
Section 1.1 Synopsis, Section 4.1 Overall Design	Text stating the number of sites was replaced by the number of cohorts in the study and that all participants within each cohort will be recruited at a single site.	To reflect the option to open additional sites and clarify that all participants within a cohort will be enrolled from a single site.
Section 1.3 Schedule of Activities, Tables 4 - 11	The following text has been added as a new footnote to accompany the row titled Immunogenicity (ALXN1820 ADA): "In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event"	To allow collection of additional serum samples for assessment of potential ADA.
Section 1.3 Schedule of Activities, Table 4, Table 6, and Table 9, Section 8.2.3.2	The timing of the 24-hour Holter ECG was amended from "at Screening" to "up to 3 months prior to Day 1".	To allow for flexibility of timing for the 24-hour Holter ECG.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, Table 6, and Table 9, Section 8.2.3.2	The option to use cardiac telemetry has been added for continuous monitoring from 1 hour pre dose to 2 hours post first dose of study drug.	To allow the option for use of cardiac telemetry should ECG not be available.
Section 5.1 Inclusion Criteria	Inclusion criterion 4 was revised to extend the upper range of BMI from 30 to 32 kg/m^2	To allow a broader range of potentially eligible participants without altering safety consideration for all participants.
Section 5.1 Inclusion Criteria	Inclusion criterion 9 was revised to detail the vaccination schedule for serogroup B meningococcal vaccination naïve participants and participants vaccinated more than 2 years and 6 months prior to dosing.	To clarify the inclusion criteria regarding serogroup B meningococcal vaccination.
Section 5.2 Exclusion Criteria	Language specifying that immunization with inactivated or recombinant influenza vaccine is permitted was removed.	Due to the COVID-19 pandemic, language for the exclusion criterion was revised to allow for other vaccines in addition to influenza vaccines. Only live-attenuated vaccines are excluded.
Section 5.3 Lifestyle Considerations, Table 17	Reference to the study plan for standard unit times for standard meals was removed.	Corrected as the standard unit times for standard meals are not in the study plan.
Section 8 Study Assessments and Procedures	Clarification a participant's procedures that are obtained prior to signing of the ICF may be utilized if consistent with site SOP	Updated to align with practices at study site.
Section 8.2.6 Pregnancy	Monthly pregnancy tests for female spouses/partners of male participants was removed.	Study assessments cannot be performed on female spouses/partners of male participants as they do not sign an ICF.
Section 9.5 Safety Review Committee (SRC)	Added Investigators from participating sites to the SRC membership, and the following sentence: "In the event a significant safety issue is identified, an ad hoc SRC meeting will be convened within 24 hours following its identification."	Clarified membership of the SRC, as well as trigger and timing for ad hoc SRC meetings.
Section 10.3.3 Recording and Follow-Up of AE and/or SAE	"Alexion" was added in the text in place of [X].	For clarification
Section 10.4.2.2 Male Participants	Time frame for following contraception guidance was updated from "up to 5 months after last dose" to "at least 5 months after last dose".	Updated to ensure contraception guidance is followed for a minimum of 5 months after last dose.
Section 10.6 Appendix 6: Management of Potential Adverse Events During Study Drug Administration	Updated to provide clarification on identification and treatment of infusion/injection-associated reactions.	Updated to accurately reflect current practices.
Section 10.7 Appendix 7: COVID-19 Risk Assessment	Updated to provide guidance to study sites during COVID-19 pandemic.	Updated to accurately reflect current practices.
Section 10.9 Protocol Amendment History	Table of document history was added.	To accurately reflect the document history

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Updated amendment number and date and incorporated minor editorial changes.	Updated to reflect current amendment and sign-off date, and other minor changes.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study of Subcutaneous and Intravenous ALXN1820 in Healthy Participants

Short Title: Safety, Pharmacokinetic and Pharmacodynamic Study of ALXN1820 in Healthy Adult Participants

Rationale: ALXN1820 (anti-properdin/anti-serum albumin bispecific VHH antibody) is a novel properdin blocking agent being developed for the treatment of diseases involving dysregulated complement activity. The ALXN1820 molecule is bispecific, comprising a VHH antibody domain that binds and blocks properdin, connected via a linker to a VHH domain that binds serum albumin, thereby conferring an extended circulatory half-life to the molecule. ALXN1820 formulation is designed for subcutaneous (SC) administration. The purpose of this first-in-human (FIH) study in healthy adult participants is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of single ascending doses (SAD) and multiple ascending doses (MAD) of ALXN1820 administered SC (ALXN1820 SC) and a single dose of ALXN1820 administered intravenously (ALXN1820 IV). The study will be conducted in healthy adult participants and will also include a multiple SC dose cohort in healthy participants of Japanese descent. Data from this study are anticipated to help design future studies in patients with complement-mediated diseases.

Objectives and Endpoints

Table 1: Mapping Objectives to Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of ALXN1820 SC and ALXN1820 IV	Safety assessed by incidence of TEAEs and SAEs, physical examination, vital sign measurements, clinical laboratory, and electrocardiogram results
Secondary	
To assess the single- and multiple-dose PK of ALXN1820 SC and single-dose PK of ALXN1820 IV	Serum ALXN1820 single- and multiple-dose PK profiles and PK parameters
To explore the PD effects of ALXN1820 SC and ALXN1820 IV	Change in serum concentrations of total and free properdin over time Change in CAP activity using the Wieslab AP assay
To assess the immunogenicity of ALXN1820 SC and ALXN1820 IV	Incidence of anti-drug antibodies (ADAs) to ALXN1820
To estimate the absolute bioavailability of ALXN1820 SC	ALXN1820 PK parameters (AUC) SC versus IV will be compared
To compare safety, tolerability, PK, PD, and immunogenicity of ALXN1820 SC between Japanese and non-Japanese healthy participants	Quantitative assessment of safety, PK, PD parameters, and immunogenicity (ADA) between healthy non-Japanese participants and participants of Japanese descent

Abbreviations: ADA = antidrug antibody; AP = alternative pathway; AUC = area under the concentration-time curve; CAP = complement alternative pathway; IV = intravenous; PD = pharmacodynamics(s); PK = pharmacokinetic(s); SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event.

Overall Design

This is a Phase 1, randomized, double-blind, placebo-controlled study of single and multiple ascending doses of ALXN1820 SC and IV to be conducted in approximately 80 healthy adult participants (60 on ALXN1820, 20 on placebo) in up to 10 Cohorts. Eight participants will be randomly assigned in a 3:1 ratio to each cohort to receive either single or multiple doses of ALXN1820 SC (n = 6 per cohort), a single dose of ALXN1820 IV (n = 6 per cohort), or a single or multiple doses of placebo (n = 2 per cohort) (Table 2). The single dose portion of the study consists of up to 7 cohorts (Cohorts 1 to 7). Dosing in these cohorts will precede sequentially from 12.5 mg SC to a potential maximum dose of ≤ 2250 mg SC, including a single IV dose of 450 mg (Cohort 5). The multiple dose portion of the study consists of 2 cohorts with doses of 150 mg once weekly (QW) × 5 weeks in healthy participants (Cohort 8) and healthy participants of Japanese ethnicity (Cohort 9) and a higher dose (to be determined) administered as multiple doses QW × 3 weeks (Cohort 10). The multiple dose cohorts will be initiated after single dose Cohort 4 (450 mg SC) and Cohort 5 (450 mg IV). All participants within each cohort will be recruited at a single site.

Table 2: ALXN1820-HV-101 Dosing Cohorts

Cohort	N	Study Drug	Route of Administration	Planned Dose (placeholders)	Number of Doses/Dose Interval
1	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	12.5 mg	1 single dose
2	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	50 mg	1 single dose
3	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	150 mg	1 single dose
4	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	450 mg	1 single dose
5	8 (6 active/2 placebo)	ALXN1820 and placebo	IV	450 mg	1 single dose
6	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	1200 mg	1 single dose
7 (optional)	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	TBD[a] (≤ 2250 mg)	1 single dose
8	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	150 mg	QW × 5
9	8 (6 active/2 placebo) Japanese participants	ALXN1820 and placebo	SC	150 mg	QW × 5
10	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	TBD[a]	QW × 3

[a] Dose in Cohort 7 to be determined based on the safety data up to Cohort 6 and interim PK/PD modeling with data up to Cohort 5. Dose in Cohort 10 to be determined based on safety data up to cohort 8 and interim PK/PD modeling with data up to Cohort 5.

Abbreviations: IV = intravenous; N = number of participants; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QW = once weekly; SC = subcutaneous; TBD = to be determined.

Details on timing of dosing in the cohorts are presented in Table 3.

The first 2 participants randomized to each cohort will be dosed as a sentinel pair with at least 1 participant on active treatment (either 1 participant on active treatment and 1 participant on placebo, or 2 participants on active treatment). This dosing strategy is justified given the large safety margin (approximately 20-fold at the highest planned dose) and the experience with properdin inhibition in healthy participants at Alexion. At the discretion of the Investigator, up to 3 more participants will be dosed at least 48 hours after dosing of the sentinel pair, followed by dosing of the remaining participants in the cohort no earlier than the 4th day, as long as no suspension/stopping criteria have been met (Section 7.2). At no time will more than 4 participants per cohort be dosed on a given day. The allowance for a maximum of 4 participants/day/cohort is intended to provide flexibility should a fourth participant need to be added (eg, if replacement of a participant is required). The intention for this dosing strategy is to ensure limited number of healthy participants will receive a dose and regimen that have not been previously tested. The limit of ≤ 4 participants/day/cohort does not apply to dose and regimen that has been tested previously.

Table 3: Dosing Chart for Single Ascending Dose and Multiple Ascending Dose Regimens

Cohort	Route of Administration	Number of participants dosed		
		Day 1[a]	Day 3	Day 4
1[b], 2[b], and 3[b]	Manual SC or via SP	2	3	3
4[b], 6[c], 7[c]	SC infusion via SP			
5[d]	IV infusion			
8[e], 9[e]	Manual SC, QW × 5			
10[f]	Manual SC or SC infusion via SP, QW × 3			

Note: At no time > 4 participants/cohort to be dosed on a given day for dose and regimen that have not been tested previously.

[a] At least 1 participant on active treatment (either 1 participant on active treatment and 1 participant on placebo, or 2 participants on active treatment).

[b] Sequential dosing to occur in Cohorts 1 to 4, dependent on SRC review of safety data through Day 15 (336 hours) of previous cohort.

[c] Dosing in Cohort 6 to be administered based on SRC review of interim safety data from the Day 15 (336 hours) assessment after dosing of Cohorts 4 and 5. Dosing in Cohort 7 to be determined based on SRC review of interim safety data from the Day 15 (336 hours) assessment after dosing of Cohort 6 and PK/PD data from Day 29 (672 hours) assessment after dosing of Cohorts 4 and 5.

[d] Dosing in Cohort 5 is dependent on Investigator review of safety data through Day 8 (168 hours) of Cohort 4. However, should there be safety findings of concern in previous cohorts, an SRC review will be conducted for Cohort 5 to determine if participants will be dosed at the planned dose of 450 mg IV or a lower dose.

[e] Dosing in Cohorts 8 and 9 to be determined based on SRC review of all data from the Day 15 (336 hours) assessment for Cohorts 4 and 5. Dosing of Cohort 9 may start at the same time as Cohort 8 or later depending on scheduling at the clinical site

[f] Dosing in Cohort 10 to be determined based on SRC review of all data from the Day 29 (672 hours) assessment for Cohort 8 and PK/PD data from Day 29 (672 hours) after dosing of Cohorts 4 and 5.

Abbreviations: IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; QW = once weekly; SC = subcutaneous; SP = syringe pump; SRC = safety review committee.

At the Sponsor's discretion, and after consultation with the Safety Review Committee (SRC), up to 18 additional participants across the entire study may be enrolled as replacement participants if a participant discontinues prior to Day 43 for reasons other than drug-related adverse events (AEs).

Additional cohorts in healthy participants and patients may be added later if deemed necessary. These cohorts will only be added with a substantial amendment, and after regulatory agency and Ethics Committee (EC) approval. Screening for these cohorts can proceed prior to amendment approval, as long as the approved selection criteria apply. Randomization and dosing can only occur after approval of the amendment.

Number of Participants:

Approximately 80 participants (60 on active treatment, 20 on placebo) will be screened and randomly assigned to receive study drug or placebo to allow for study completion.

Intervention Groups and Duration:

The planned study duration is approximately 29 to 33 weeks: up to 79 days for screening and 126 and 154 days for dosing and follow-up for the single dose and multiple dose cohorts,

respectively. Participants will be admitted to an inpatient facility during the Dosing and Follow-up Period (first 5 days for the single dose cohorts, and first 5 days after the first and last dose and 2 days after each other dose for the multiple-dose cohorts). Dosing will be staggered within and between cohorts, but the end of study for each individual participant is anticipated to be Day 127 and Day 155 for SAD and MAD cohorts, respectively, or the time point at which complement activity has normalized, if later than Day 127 or Day 155.

Safety Review Committee: An SRC will be used to make dose escalation decisions.

Statistical Analyses:

Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Safety	All participants who receive at least 1 dose of study drug
Pharmacokinetic	All participants who receive at least 1 dose of the study drug and have at least 1 post-dose PK sample
Pharmacodynamic	All participants who receive at least 1 dose of study drug and who have evaluable properdin concentration data CAP or CCP activity data
Immunogenicity	All participants who have a predose and at least 1 postdose ADA sample collected that can be analyzed

Abbreviations: ADA = antidrug antibody; CAP = complement alternative pathway; CCP = complement classical pathway; PK = pharmacokinetic(s).

Safety Analysis

All safety analyses will be performed on the Safety Population and will be reported by each cohort and treatment arm (ALXN1820 versus placebo). In addition, healthy participants on placebo treatment will be pooled together across cohorts.

Safety analyses will include an analysis of all treatment-emergent AEs, electrocardiograms (ECG's), clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics. No inferential statistical analyses are planned on the safety parameters of this study. The prevalence of AEs and serious adverse events (SAEs) will be summarized, by System Organ Class (SOC) and Preferred Term for each cohort and treatment arm and overall, within each treatment arm, by relationship to study drug. Adverse events will also be summarized by cohort and by treatment arm, and overall, within each treatment arm, by severity. Serious AEs and AEs resulting in withdrawal from the study will be listed. Participants having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity tables, a participant's most severe event within a category will be counted.

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

Pharmacokinetic Analysis

The individual serum concentration data from participants who receive ALXN1820 SC or ALXN1820 IV with actual sampling dates and times, will be used to derive the PK parameters by noncompartmental analyses methods.

Pharmacodynamic Analysis

The PD effects of all ALXN1820 SC and ALXN1820 IV doses administered will be evaluated by assessing changes in serum total and free properdin concentrations and complement alternative pathway (CAP) activity using the Weislab alternative pathway (AP) assay. In addition, complement classical pathway (CCP) activity and other measures of properdin activity over time may be considered as deemed appropriate (Section 8.6).

Biomarker assays may be conducted as an exploratory analysis on collected samples.

Immunogenicity Analysis

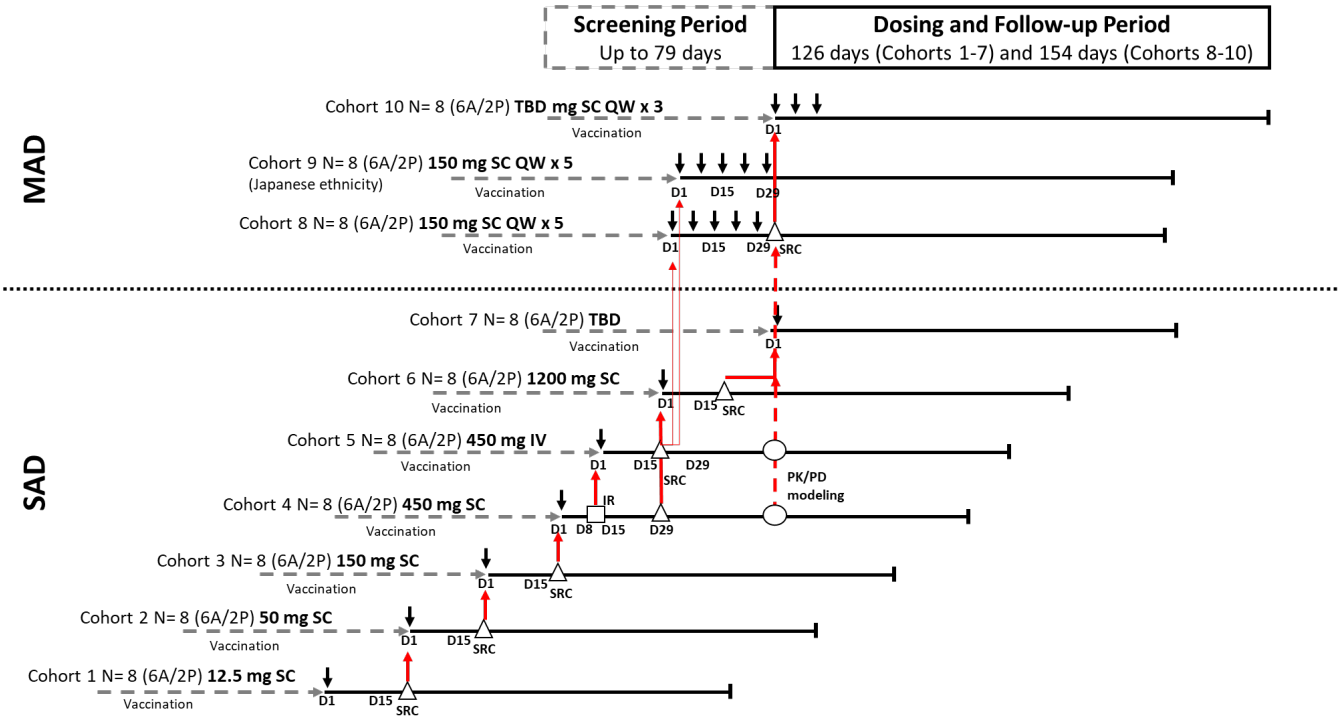
Immunogenicity, as measured by incidence of anti-drug antibody (ADA) to ALXN1820 will be summarized.

Interim Analyses

An assessment of all available PK/PD data will be performed when all participants in Cohorts 4 and 5 reach Day 29. These data will be used to project the exposure and duration of properdin and CAP activity inhibition (not to exceed 70 days) at the highest single dose planned in the study (Cohort 7) and the highest multiple dose in the study (Cohort 10). Further assessments of available data may be performed to inform Phase 2 study design in patients. Details of this analysis will be presented in the Statistical Analysis Plan (SAP).

1.2. Schema

Figure 1: Study ALXN1820-HV-101 Schematic



Note: black arrow(s) indicate dose(s) given; red arrow indicates decision for dose escalation.
Abbreviations: A = active (ALXN1820); D = day; IR = Investigator review; IV = intravenous; MAD = multiple ascending dose; N = number of participants; P = placebo; PD = pharmacodynamics; PK = pharmacokinetics;

QW = once weekly; SAD = single ascending dose; SC = subcutaneous; SRC = Safety Review Committee; TBD = to be determined.

1.3. Schedule of Activities (SoA)

As this is a FIH study, additional or fewer samples or assessments for safety, tolerability, PK, PD, and/or ADA may be taken or performed, or the timing of samples or assessments may be adjusted, in accordance with the evolving data and dosing schedule. The total blood volume will not exceed the study specified maximum blood volume (Section 8.2.4).

Schedules of activities are presented for single-dose Cohorts 1 to 7 for Screening through Day 5 in Table 4 and Day 8 through Day 127 in Table 5.

Schedules of activities are presented for multiple-dose Cohorts 8 and 9 for Screening through Day 5 and Days 28 through 33 in Table 6, Day 7 through Day 23 in Table 7, and Day 36 through Day 155 in Table 8. Schedules of activities are presented for multiple-dose Cohort 10 for Screening through Day 5 and Days 14 through 19 in Table 9, Day 7 through Day 9 in Table 10 and Day 22 through Day 155 in Table 11.

Table 4: Schedule of Activities – Screening Through Day 5 for Single-dose Cohorts 1 - 7

Study Day	Screening	Day –1	Day 1								Day 2	Day 3	Day 5
Assessments[a]	Day –79 to Day –2	Admit	Predose	0 h (SOI)	EOI	30 min post SOI[b]	2 h post SOI	4 h post SOI	8 h post SOI	12 h post SOI	24 h post SOI	48 h post SOI	96 h post SOI
Status (OP or CRU)	OP	Admit	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU[c]
Informed consent[d]	X												
MCV4 immunization[e]	X												
Meningococcal serogroup B immunization[e]	X												
Vaccine titer (meningococcal serogroups A, C, W135, and Y)[f]	X												
Medical history and demographics	X												
Physical examination	X	X											X
Height, weight, and BMI[g]	X	X											
QuantiFERON®-TB test	X												
Chemistry[h]	X	X									X		X
Serum albumin												X	
Hematology	X	X									X		X
Coagulation	X	X									X		X
Hepatitis B and C screen	X												
HIV (types 1 and 2) screen	X												
Complement activity[i]	X												
Serum pregnancy test[j]	X	X											
Alcohol breath test	X	X											
Urinalysis (via dipstick)	X	X									X		X
Urine drug screen	X	X											
Vital sign measurements[k]	X	X	X		X	X	X	X	X	X	X	X	X
Triplicate ECG	X		X[l]		X	X	X	X	X	X	X	X	X
24-h Holter ECG[m]	X												

Table 4: Schedule of Activities – Screening Through Day 5 for Single-dose Cohorts 1 - 7

Study Day	Screening	Day –1	Day 1								Day 2	Day 3	Day 5
Assessments[a]	Day –79 to Day –2	Admit	Predose	0 h (SOI)	EOI	30 min post SOI[b]	2 h post SOI	4 h post SOI	8 h post SOI	12 h post SOI	24 h post SOI	48 h post SOI	96 h post SOI
Randomization[n]			X										
Study drug administration				X									
PK samples			X		X[o]		X	X	X	X	X	X	X
PD panel (serum total and free properdin, CAP activity)			X		X[o]		X	X	X	X	X	X	X
Exploratory biomarkers[p]			X		X[o]						X		X
Injection/infusion site evaluation			X		X	X	X	X	X	X	X[q]		
Immunogenicity (ALXN1820 ADA)[r]			X										
Review safety card[s]	X	X									X	X	X
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→												
Adverse events[t]	←Monitor continuously (after ICF is signed at Screening)→												
Prophylactic antibiotic tx[u]		←Antibiotic prophylaxis→											

[a] Permissible windows for study assessments are described in the Study Operation Manual.
[b] For Cohorts 6 and 7, assessments will be performed 1 hour after SOI.
[c] Participant will be discharged from the CRU after completing all Day 5 assessments. Participants will be provided a "Study Participant ID card" with information for healthcare provider and participant on symptoms of meningitis infection.
[d] Signed and dated IEC-approved ICF must be obtained before any study-specific screening procedures are performed.
[e] For participants 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 dosing 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.
[f] For participants with a documented vaccine titer indicating sufficient protection within 6 months prior to Screening, the titer does not need to be repeated.
[g] Height and BMI only at Screening.
[h] Non-fasting blood samples will be obtained.
[i] Complement activity, confirmed by a suitable assay such as CAP ELISA/C5 (hemolysis) inhibition, will be performed at Screening to confirm participants do not have a complement deficiency.
[j] Serum pregnancy test for all female participants of childbearing potential to confirm that a female participant is not pregnant prior to dosing. A urine pregnancy test can be performed if the Screening visit is within 3 weeks of Day 1 visit.
[k] At Screening, supine and standing (orthostatic) blood pressures will be performed to exclude participants who are prone to orthostatic hypotension.
[l] Predose triplicate 12-lead ECGs will be performed 3 times at approximately 2, 1, and 0.5 hours before the start of dosing.

[m] A 24-hour Holter ECG will be performed up to 3 months prior to Day 1 to exclude pre-existing ECG abnormalities.
[n] Planned randomization may be up to 7 days prior to dosing on Day 1.
[o] Collection of post-dose PK/PD samples are to be collected from the non-infused arm and not the administration line in IV administered cohorts
[p] Collection of blood (for serum, citrated and K2-EDTA, or Plasma P100 plasma) and urine.
[q] Injection/infusion site reaction evaluation will continue until the reaction is fully resolved.
[r] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[s] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical study participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns of the participant.
[t] Collection of adverse events and serious adverse events will begin after ICF signing.
[u] Participants 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 through Day 127, or until complement activity has normalized (as determined by CAP assay). If penicillin is not tolerated, second line antibiotics will be initiated at the discretion of the Investigator.

Abbreviations: ADA = antidrug antibody; BMI = body mass index; C5 = complement component 5; CAP = complement alternative pathway; CRU = clinical research unit; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; EOI = end of infusion/injection; h = hour; HIV = human immunodeficiency virus; ICF = informed consent form; ID = identity; IEC = Independent Ethics Committee; IV = intravenous; K2-EDTA = dipotassium ethylenediaminetetraacetic acid; MCV4 = tetravalent meningococcal conjugate vaccine; min = minutes; OP = outpatient; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SC = subcutaneous; SOI = start of infusion/injection; TB = tuberculosis; tx = treatment.

Table 5: Schedule of Activities – Day 8 Through Day 127 for Single-dose Cohorts 1 - 7

Study Day[a]	Day 8 (168 h post SOI)	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 71	Day 85	Day 99	Day 127[h]/ET
Window (days)	0	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1
Status (OP or CRU)	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP
Physical examination	X			X								X
Vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate ECG	X	X		X				X	X		X	X
Chemistry[b]	X			X				X				X
Hematology	X			X				X				X
Coagulation	X			X				X				X
Urinalysis (via dipstick)	X			X				X				X
Serum pregnancy test				X				X		X		X
PK samples	X	X	X	X	X	X	X	X	X	X	X	X
PD panel (serum total and free properdin, CAP activity)	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory biomarkers[c]		X		X								X
Immunogenicity (ALXN1820 ADA)[e]		X		X				X		X		X[d]
Review safety card[f]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	←Monitor continuously→											
Adverse events[g]	←Monitor continuously→											
Prophylactic antibiotic tx[h]	←Antibiotic prophylaxis→											

[a] Permissible windows for study assessments are described in the Study Operations Manual.
[b] Non-fasting blood samples will be obtained.
[c] Collection of blood (for serum, citrated and K2-EDTA, or Plasma P100 plasma) and urine.
[d] Participants who are ADA positive at Day 127/ET will be followed up to 1 year from the study drug administration or ADA titers return to baseline levels (whichever occurs first).
[e] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the event.
[f] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical study participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns on the part of the participant
[g] Collection of adverse events and serious adverse events will begin after ICF signing.
[h] Participants 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 through Day 127, or until complement activity has normalized (as determined by CAP assay). If penicillin is not tolerated, second line antibiotics will be initiated at the discretion of the Investigator. Follow-up will be extended until individual CAP activity has normalized.

Abbreviations: ADA = antidrug antibody; CAP = complement alternative pathway; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; h = hour; ICF = informed consent form; K2-EDTA = dipotassium ethylenediaminetetraacetic acid; OP = outpatient; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SOI = start of infusion/injection; tx = treatment.

Table 6: Schedule of Activities – Screening Through Day 5 (First Dose), Day 28 to 33 (Last Dose) for Multiple-dose Cohorts 8 and 9

Study Day	**Screening**	**Day –1, 28[a]**	**Day 1, 29**								**Day 2, 30**	**Day 3, 31**	**Day 5, 33**
Assessments[b]	**Day –79 to Day –2**	**Admit**	**Pre-dose**	**0 h (SOI)**	**EOI**	**30 min post SOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**12 h post SOI**	**24 h post SOI**	**48 h post SOI**	**96 h post SOI**
Status (OP or CRU)	OP	Admit	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU[c]
Informed consent[d]	X												
MCV4 immunization[e]	X												
Meningococcal serogroup B immunization[e]	X												
Vaccine titer (meningococcal serogroups A, C, W135, and Y)[f]	X												
Medical history and demographics	X												
Physical examination	X	X									X		
Height, weight, and BMI[g]	X	X											
QuantiFERON®-TB test	X												
Chemistry[h]	X	X									X		
Serum albumin												X	X
Hematology	X	X									X		
Coagulation	X	X									X		
Hepatitis B and C screen	X												
HIV (types 1 and 2) screen	X												
Complement activity[i]	X												
Serum pregnancy test[j]	X	X											
Alcohol breath test	X	X											
Urinalysis (via dipstick)	X	X									X		
Urine drug screen	X	X											
Vital sign measurements[k]	X	X	X		X	X	X	X	X	X	X	X	X
Triplicate ECG	X		X[l]		X	X	X	X	X	X	X	X	X
Cardiac telemetry[m]			←Monitor continuously→										
24-h Holter ECG[n]	X												
Randomization[o]			X										
Study drug administration				X									
PK samples			X		X		X	X	X	X	X	X	X
PD panel (serum total and free properdin, CAP activity)			X		X		X	X	X	X	X	X	X
Exploratory biomarker[p]			X								X		

Table 6: Schedule of Activities – Screening Through Day 5 (First Dose), Day 28 to 33 (Last Dose) for Multiple-dose Cohorts 8 and 9

Study Day	Screening	Day –1, 28[a]	Day 1, 29								Day 2, 30	Day 3, 31	Day 5, 33
Assessments[b]	**Day –79 to Day –2**	**Admit**	**Pre-dose**	**0 h (SOI)**	**EOI**	**30 min post SOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**12 h post SOI**	**24 h post SOI**	**48 h post SOI**	**96 h post SOI**
Injection/infusion site evaluation			X		X	X	X	X	X	X	X[q]		
Immunogenicity (ALXN1820 ADA)[r]			X										
Review safety card[s]	X	X	X								X	X	X
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→												
Adverse events[t]	←Monitor continuously (after ICF is signed at Screening)→												
Prophylactic antibiotic tx[u]		←Antibiotic prophylaxis→											

[a] Schedule for Days 7 – 23 provided in Table 7.
[b] Permissible windows for study assessments are described in the Study Operations Manual.
[c] Participant will be discharged from the CRU after completing all Day 5 or Day 33 assessments. Participants will be provided a "Study Participant ID card" with information for healthcare provider and participant on symptoms of meningitis infection.
[d] Signed and dated IEC-approved ICF must be obtained before any study-specific screening procedures are performed.
[e] For participants 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 dosing 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.
[f] For participants with a documented vaccine titer indicating sufficient protection within 6 months prior to Screening, the titer does not need to be repeated.
[g] Height and BMI only at Screening.
[h] Non-fasting blood samples will be obtained.
[i] Complement activity, confirmed by a suitable assay such as CAP ELISA/C5 (hemolysis) inhibition, will be performed at Screening to confirm participants do not have a complement deficiency.
[j] Serum pregnancy test for all female participants of childbearing potential to confirm that a female participant is not pregnant prior to dosing. A urine pregnancy test can be performed if the Screening visit is within 3 weeks of Day 1 visit.
[k] At Screening, supine and standing (orthostatic) blood pressures will be performed to exclude participants who are prone to orthostatic hypotension.
[l] Predose triplicate 12-lead ECGs will be performed 3 times at approximately 2, 1, and 0.5 hours before the start of dosing.
[m] Continuous cardiac monitoring from 1 hour pre-dose to 2 hours after the start of study drug administration.
[n] A 24-hour Holter ECG will be performed up to 3 months prior to Day 1 to exclude pre-existing ECG abnormalities.
[o] Planned randomization may be up to 7 days prior to dosing on Day 1.
[p] Collection of blood (for serum, citrated and K2-EDTA, or Plasma P100 plasma) and urine
[q] Injection/infusion site reaction evaluation will continue until the reaction is fully resolved.
[r] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[s] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical study participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns of the participant.
[t] Collection of adverse events and serious adverse events will begin after ICF signing.

[u] Participants 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 through Day 127, or until complement activity has normalized (as determined by CAP assay). If penicillin is not tolerated, second line antibiotics will be initiated at the discretion of the Investigator.

Abbreviations: ADA = antidrug antibody; BMI = body mass index; C5 = complement component 5; CAP = complement alternative pathway; CRU = clinical research unit; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; EOI = end of infusion/injection; h = hour; HIV = human immunodeficiency virus; ICF = informed consent form; ID = identity; IEC = independent ethics committee; MCV4 = tetravalent meningococcal conjugate vaccine; min = minutes; OP = outpatient; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SC = subcutaneous; SOI = start of infusion/injection; TB = tuberculosis; tx = treatment.

Table 7: Schedule of Activities – Day 7 Through Day 23 for Multiple-dose Cohorts 8 and 9

Study Day	**Days 7, 14, 21**	**Days 8, 15, 22**								**Days 9, 16, 23**
Assessments[a]	**Admit**	**Pre-dose**	**0 h (SOI)**	**EOI**	**30 min post SOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**12 h post SOI**	**24 h post SOI**
Status (OP or CRU)	Admit	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU[b]
Physical examination	X									
Body weight	X									
Chemistry[c]	X									X
Hematology	X									X
Coagulation	X									X
Serum pregnancy test[d]	X									
Alcohol breath test	X									
Urinalysis (via dipstick)	X									X
Urine drug screen	X									
Vital sign measurements	X	X		X				X		X
Triplicate ECG		X		X				X		X
Cardiac telemetry[e]		←Monitor continuously→								
Study drug administration			X							
PK samples		X		X				X		X
PD panel (serum total and free properdin, CAP activity)		X		X				X		X
Injection/infusion site evaluation[f]		X		X	X	X	X	X	X	X
Immunogenicity (ALXN1820 ADA)[g]		X								
Review safety card[h]	X	X								X
Concomitant medications	←Monitor continuously→									
Adverse events[i]	←Monitor continuously→									
Prophylactic antibiotic tx[j]	←Antibiotic prophylaxis→									

[a] Permissible windows for study assessments are described in the Study Operations Manual.
[b] Participant will be discharged from the CRU after completing all Day 9, Day 16 or Day 23 assessments. Participants will be provided a "Study Participant ID card" with information for healthcare provider and participant on symptoms of meningitis infection.
[c] Non-fasting blood samples will be obtained.
[d] Serum pregnancy test for all female participants of childbearing potential to confirm that a female participant is not pregnant prior to dosing.
[e] Continuous cardiac monitoring from 1 hour pre-dose to 2 hours after the start of study drug administration.
[f] Injection/infusion site reaction evaluation will continue until the reaction is fully resolved.
[g] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[h] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical trial participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns of the participant.
[i] Collection of adverse events and serious adverse events will begin after ICF signing.

[j] Participants 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 through Day 155, or until complement activity has normalized (as determined by CAP assay). If penicillin is not tolerated, second line antibiotics will be initiated at the discretion of the Investigator.

Abbreviations: ADA = antidrug antibody; CAP = complement alternative pathway; CRU = clinical research unit; ECG = electrocardiogram; EOI = end-of-infusion/injection; h = hour; ICF = informed consent form; ID = identity; min = minutes; OP = outpatient; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SOI = start of infusion/injection; tx = treatment.

Table 8: Schedule of Activities – Day 36 Through Day 155 for Multiple Dose Cohorts 8 and 9

Study Day[a]	Day 36 (168 h post SOI)	Day 43	Day 50	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155[h]/ET
Window (Day)		±1	±1	±1	±1	±1	±1	±1	±1	±1	±1
Status (OP or CRU)	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP
Physical examination	X										X
Abbreviated physical exam (optional)		X	X	X	X	X	X	X	X	X	X
Vital sign measurements	X	X	X	X	X	X	X	X	X	X	X
Triplicate ECG	X			X	X		X		X		X
Chemistry[b]	X			X							X
Hematology	X			X							X
Coagulation	X			X							X
Urinalysis (via dipstick)	X			X							X
Serum pregnancy test	X			X		X		X			X
PK samples	X	X	X	X	X	X	X	X	X	X	X
PD panel (serum total and free properdin, CAP activity)	X	X	X	X	X	X	X	X	X	X	X
Exploratory biomarkers[c]				X							X
Immunogenicity (ALXN1820 ADA)[d]			X		X		X		X		X[e]
Review safety card[f]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	←Monitor continuously→										
Adverse events[g]	←Monitor continuously→										
Prophylactic antibiotic tx[h]	←Antibiotic prophylaxis→										

[a] Permissible windows for study assessments are described in the Study Operations Manual.
[b] Non-fasting blood samples will be obtained.
[c] Collection of blood (for serum, citrated and K2-EDTA, or Plasma P100 plasma) and urine.
[d] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[e] Participants who are ADA positive at Day 155/ET will be followed up to 1 year from the study drug administration or ADA titers return to baseline levels (whichever occurs first).
[f] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical trial participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns on the part of the participant.
[g] Collection of adverse events and serious adverse events will begin after ICF signing.
[h] Participants will be administered prophylactic antibiotic treatment, oral penicillin V 500 mg twice daily (equivalent to 1×10^6 units) through Day 155 or until complement activity has normalized (as determined by CAP assay). If penicillin is not tolerated, second line antibiotics will be initiated at the discretion of the Investigator. Follow-up will be extended until individual CAP activity has normalized.
Abbreviations: ADA = antidrug antibody; CAP: Complement alternative pathway; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; h = hour; ICF = informed consent form; K2-EDTA = dipotassium ethylenediaminetetraacetic acid; OP = outpatient; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SOI = start of infusion/injection; tx = treatment.

Table 9: Schedule of Activities – Screening Through Day 5 (First Dose), Day 14 to 19 (Last Dose) for Multiple-dose Cohort 10

Study Day	**Screening**	**Day –1, 14[a]**	**Day 1, 15**								**Day 2, 16**	**Day 3, 17**	**Day 5, 19**
Assessments[b]	**Day –79 to Day –2**	**Admit**	**Pre-dose**	**0 h (SOI)**	**EOI**	**30 min post SOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**12 h post SOI**	**24 h post SOI**	**48 h post SOI**	**96 h post SOI**
Status (OP or CRU)	OP	Admit	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU[c]
Informed consent[d]	X												
MCV4 immunization[e]	X												
Meningococcal serogroup B immunization[e]	X												
Vaccine titer (meningococcal serogroups A, C, W135, and Y)[f]	X												
Medical history and demographics	X												
Physical examination	X	X									X		
Height, weight, and BMI[g]	X	X											
QuantiFERON®-TB test	X												
Chemistry[h]	X	X									X		
Serum albumin												X	X
Hematology	X	X									X		
Coagulation	X	X									X		
Hepatitis B and C screen	X												
HIV (types 1 and 2) screen	X												
Complement activity[i]	X												
Serum pregnancy test[j]	X	X											
Alcohol breath test	X	X											
Urinalysis (via dipstick)	X	X									X		
Urine drug screen	X	X											
Vital sign measurements[k]	X	X	X		X	X	X	X	X	X	X	X	X
Triplicate ECG	X		X[l]		X	X	X	X	X	X	X	X	X
Cardiac telemetry[m]			←Monitor continuously→										
24-h Holter ECG[n]	X												
Randomization[o]			X										
Study drug administration				X									
PK samples			X		X		X	X	X	X	X	X	X
PD panel (serum total and free properdin, CAP activity)			X		X		X	X	X	X	X	X	X

Table 9: Schedule of Activities – Screening Through Day 5 (First Dose), Day 14 to 19 (Last Dose) for Multiple-dose Cohort 10

Study Day	Screening	Day –1, 14[a]	Day 1, 15								Day 2, 16	Day 3, 17	Day 5, 19
Assessments[b]	**Day –79 to Day –2**	**Admit**	**Pre-dose**	**0 h (SOI)**	**EOI**	**30 min post SOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**12 h post SOI**	**24 h post SOI**	**48 h post SOI**	**96 h post SOI**
Exploratory biomarker[p]			X								X		
Injection/infusion site evaluation			X		X	X	X	X	X	X	X[q]		
Immunogenicity (ALXN1820 ADA)[r]			X										
Review safety card[s]	X	X	X								X	X	X
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→												
Adverse events[t]	←Monitor continuously (after ICF is signed at Screening)→												
Prophylactic antibiotic tx[u]		←Antibiotic prophylaxis→											

[a] Schedule for Days 7 – 9 provided in Table 10.
[b] Permissible windows for study assessments are described in the Study Operations Manual.
[c] Participant will be discharged from the CRU after completing all Day 5 or Day 19 assessments. Participants will be provided a "Study Participant ID card" with information for healthcare provider and participant on symptoms of meningitis infection.
[d] Signed and dated IEC-approved ICF must be obtained before any study-specific screening procedures are performed.
[e] For participants 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 dosing 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.
[f] For participants with a documented vaccine titer indicating sufficient protection within 6 months prior to Screening, the titer does not need to be repeated.
[g] Height and BMI only at Screening.
[h] Non-fasting blood samples will be obtained.
[i] Complement activity, confirmed by a suitable assay such as CAP ELISA/C5 (hemolysis) inhibition, will be performed at Screening to confirm participants do not have a complement deficiency.
[j] Serum pregnancy test for all female participants of childbearing potential to confirm that a female participant is not pregnant prior to dosing. A urine pregnancy test can be performed if the Screening visit is within 3 weeks of Day 1 visit.
[k] At Screening, supine and standing (orthostatic) blood pressures will be performed to exclude participants who are prone to orthostatic hypotension.
[l] Predose triplicate 12-lead ECGs will be performed 3 times at approximately 2, 1, and 0.5 hours before the start of dosing.
[m] A 24-hour Holter ECG will be performed up to 3 months prior to Day 1 to exclude pre-existing ECG abnormalities.
[n] Continuous cardiac monitoring from 1 hour pre-dose to 2 hours after the start of study drug administration.
[o] Planned randomization may be up to 7 days prior to dosing on Day 1.
[p] Collection of blood (for serum, citrated and K2-EDTA, or Plasma P100 plasma) and urine
[q] Injection/infusion site reaction evaluation will continue until the reaction is fully resolved.
[r] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[s] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical study participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns of the participant.
[t] Collection of adverse events and serious adverse events will begin after ICF signing.

Table 9: Schedule of Activities – Screening Through Day 5 (First Dose), Day 14 to 19 (Last Dose) for Multiple-dose Cohort 10

Study Day	Screening	Day –1, 14[a]	Day 1, 15								Day 2, 16	Day 3, 17	Day 5, 19
Assessments[b]	**Day –79 to Day –2**	**Admit**	**Pre-dose**	**0 h (SOI)**	**EOI**	**30 min post SOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**12 h post SOI**	**24 h post SOI**	**48 h post SOI**	**96 h post SOI**

[u] Participants 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 through Day 155, or until complement activity has normalized (as determined by CAP assay). If penicillin is not tolerated, second line antibiotics will be initiated at the discretion of the Investigator.
Abbreviations: ADA = antidrug antibody; BMI = body mass index; C5 = complement component 5; CAP = complement alternative pathway; CRU = clinical research unit; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; EOI = end of infusion/injection; h = hour; HIV = human immunodeficiency virus; ICF = informed consent form; ID = identity; IEC = independent ethics committee; MCV4 = tetravalent meningococcal conjugate vaccine; min = minutes; OP = outpatient; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SC = subcutaneous; SOI = start of infusion/injection; TB = tuberculosis; tx = treatment.

Table 10: Schedule of Activities – Day 7 Through Day 9 for Multiple-dose Cohort 10

Study Day	Day 7	Day 8								Day 9
Assessments[a]	**Admit**	**Pre-dose**	**0 h (SOI)**	**EOI**	**30 min post SOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**12 h post SOI**	**24 h post SOI**
Status (OP or CRU)	Admit	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU[b]
Physical examination	X									
Body weight	X									
Chemistry[c]	X									X
Hematology	X									X
Coagulation	X									X
Serum pregnancy test[d]	X									
Alcohol breath test	X									
Urinalysis (via dipstick)	X									X
Urine drug screen	X									
Vital sign measurements	X	X		X				X		X
Triplicate ECG		X		X				X		X
Cardiac telemetry[e]		←Monitor continuously→								
Study drug administration			X							
PK samples		X		X		X	X	X	X	X
PD panel (serum total and free properdin, CAP activity)		X		X		X	X	X	X	X
Injection/infusion site evaluation		X		X	X	X	X	X	X	X[f]
Immunogenicity (ALXN1820 ADA)[g]		X								
Review safety card[h]	X									X
Concomitant medications	←Monitor continuously→									
Adverse events[i]	←Monitor continuously→									
Prophylactic antibiotic tx[j]	←Antibiotic prophylaxis→									

[a] Permissible windows for study assessments are described in the Study Operations Manual.
[b] Participant will be discharged from the CRU after completing all Day 9 assessments. Participants will be provided a "Study Participant ID card" with information for healthcare provider and participant on symptoms of meningitis infection.
[c] Non-fasting blood samples will be obtained.
[d] Serum pregnancy test for all female participants of childbearing potential to confirm that a female participant is not pregnant prior to dosing.
[e] Continuous cardiac monitoring from 1 hour pre-dose to 2 hours after the start of study drug administration.
[f] Injection/infusion site reaction evaluation will continue until the reaction is fully resolved.
[g] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[h] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical trial participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns of the participant.
[i] Collection of adverse events and serious adverse events will begin after ICF signing.
[j] Participants 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 through Day 155, or until complement activity has normalized (as determined by CAP assay). If penicillin is not tolerated, second line antibiotics will be initiated at the discretion of the

Investigator.
Abbreviations: ADA = antidrug antibody; CAP = complement alternative pathway; CRU = clinical research unit; ECG = electrocardiogram; EOI = end-of-infusion/injection; h = hour; ICF = informed consent form; ID = identity; min = minutes; OP = outpatient; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SOI = start of infusion/injection; tx = treatment.

Table 11: Schedule of Activities – Day 22 Through Day 155 for Multiple Dose Cohorts 10

Study Day[a]	Day 22 (168 h post SOI)	Day 29	Day 36	Day 43	Day 50	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155[h]/ET
Window (Day)		±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1
Status (OP or CRU)	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP
Physical examination	X												X
Abbreviated physical exam (optional)		X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate ECG	X					X	X		X		X		X
Chemistry[b]	X					X							X
Hematology	X					X							X
Coagulation	X					X							X
Urinalysis (via dipstick)	X					X							X
Serum pregnancy test		X				X		X		X			X
PK samples	X	X	X	X	X	X	X	X	X	X	X	X	X
PD panel (serum total and free properdin, CAP activity)	X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory biomarkers[c]	X				X								X
Immunogenicity (ALXN1820 ADA)[e]		X			X		X		X		X		X[d]
Review safety card[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	←Monitor continuously→												
Adverse events[g]	←Monitor continuously→												
Prophylactic antibiotic tx[h]	←Antibiotic prophylaxis→												

[a] Permissible windows for study assessments are described in the Study Operations Manual.
[b] Non-fasting blood samples will be obtained.
[c] Collection of blood (for serum, citrated and K2-EDTA, or Plasma P100 plasma) and urine.
[d] Participants who are ADA positive at Day 155/ET will be followed up to 1 year from the study drug administration or ADA titers return to baseline levels (whichever occurs first).
[e] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[f] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical trial participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns on the part of the participant.
[g] Collection of adverse events and serious adverse events will begin after ICF signing.
[h] Participants will be administered prophylactic antibiotic treatment, oral penicillin V 500 mg twice daily (equivalent to 1×10^6 units) through Day 155 or until complement activity has normalized (as determined by CAP assay). If penicillin is not tolerated, second line antibiotics will be initiated at the discretion of the Investigator. Follow-up will be extended until individual CAP activity have normalized.

Abbreviations: ADA = antidrug antibody; CAP: complement alternative pathway; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; h = hour; ICF = informed consent form; K2-EDTA = dipotassium ethylenediaminetetraacetic acid; OP = outpatient; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SOI = start of infusion/injection; tx = treatment.

2. INTRODUCTION

2.1. Study Rationale

ALXN1820 (anti-properdin/anti-serum albumin bispecific VHH antibody) is a novel properdin blocking agent being developed for the treatment of diseases involving dysregulated complement alternative pathway (CAP) activity. The ALXN1820 molecule is bispecific, comprising a VHH antibody domain that binds and blocks properdin connected via a linker to a VHH domain that binds serum albumin, thereby conferring an extended circulatory half-life to the molecule.

ALXN1820 binds to properdin with a high affinity to prevent stabilization of the CAP C3 and C5 convertases that cleave C3 and C5 into their activation products. Quantitative blockade of properdin has been shown to be safe in human based on experience with the properdin binding antibody ALXN1510 (see Section 4.3). There is a need to provide patients the opportunity for self-administration and an extended dose interval with complement pathway inhibitors. With this goal in mind, ALXN1820 was designed to enable SC self-administration.

The purpose of this FIH study is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of single ascending doses and multiple ascending doses of ALXN1820 administered SC (ALXN1820 SC) and bioavailability of a single dose of ALXN1820 administered intravenously (ALXN1820 IV). The study will be conducted in healthy adult participants and will also include a multiple SC dose cohort in healthy participants of Japanese descent. Data from this study are anticipated to help inform the design of future studies in patients with complement-mediated diseases.

2.2. Background

A detailed description of the chemistry, pharmacology, and toxicology data available for ALXN1820 is provided in the Investigator's Brochure (IB).

2.2.1. Chemistry

ALXN1820 is a recombinant, humanized VHH bispecific antibody that binds to human properdin and serum albumin. The antibody consists of a single polypeptide chain of 256 amino acids, which is comprised of an anti-albumin domain at the N-terminus that is fused to a C-terminal anti-properdin domain via a 15 amino acid linker. The variable region domains that form the serum albumin and properdin binding sites consist of llama complementarity determining regions grafted into human germline frameworks. Within the framework regions, llama residues at 11 positions were left unchanged to maintain antigen binding, aqueous solubility, and overall stability. There are 2 intrachain disulfide bonds, one disulfide bond localized in each VHH domain. The theoretical average molecular mass of the antibody is 27,350.2 Da. At pH 7.4, ALXN1820 exhibited a binding dissociation constant (K_D) of 323 pM for human properdin and K_D of 439 pM for human serum albumin. The IC_{50} for blockade of human CAP hemolysis by ALXN1820 (20% v/v final serum) was 29 nM. ALXN1820 blocked C3 fragment, properdin and C9 deposition onto a myeloperoxidase substrate by human serum (20%v/v) with IC_{50} values of approximately 20 nM (C3), 15 nM (properdin) and 19 nM (C9).

2.2.2. Nonclinical Pharmacology

In a study of the potency of blockade of in vitro CAP hemolysis by ALXN1820 using sera across a range of species, significant species cross reactivity was observed only when using sera from cynomolgus and rhesus macaque. CAP hemolytic activities in the sera of mouse, rat, guinea pig, minipig, beagle and rabbit were not inhibited by the highest concentration of ALXN1820 examined (> 100 µg/mL). The IC_{50} for blockade of cynomolgus CAP hemolysis by ALXN1820 (20% v/v final serum) was 47 nM. ALXN1820 exhibited a binding K_D of 2.9 nM for cynomolgus properdin and K_D of 2.1 nM for cynomolgus serum albumin. ALXN1820 blocked C3 fragment, properdin and C9 deposition onto a myeloperoxidase substrate by cynomolgus monkey serum (20%v/v) with IC_{50} values of approximately 11 nM (C3), 9 nM (properdin) and 17 nM (C9). The lack of species cross reactivity beyond primates described above, prevented testing of the biologic activity of ALXN1820 in traditional rodent models of diseases involving dysregulated complement activity. Collectively therefore, the nonclinical in vitro and in vivo studies to assess the pharmacologic, PK, PD and toxicologic properties of ALXN1820 are being performed in cynomolgus monkeys.

2.2.3. Toxicology

Nonclinical safety profile of ALXN1820 has been evaluated in an in vitro Good Laboratory Practice (GLP) tissue cross reactivity (TCR) study and in both a non-GLP and GLP in vivo study in cynomolgus monkeys. In the GLP toxicology study ALXN1820 was administered both by IV administration (up to single dose of 100 mg/kg) and SC administration (up to 6 weekly doses of 300 mg/kg/week). ALXN1820 did not demonstrate any non-specific binding to human tissues in the TCR study. Based on the absence of any adverse systemic or local toxicity in cynomolgus monkeys, 300 mg/kg/week was considered the no observed adverse effect level (NOAEL) for SC administration and 100 mg/kg was considered as the NOAEL for IV administration of ALXN1820. Systemic exposures (C_{max} and $AUC_{0\text{-}168hr}$ of 9,220 µg/mL and 1,230,000 µg·hr/mL, respectively), after the last dose at the NOAEL in the SC group, yielded exposure multiples of 40-fold to the C_{max} and 37-fold to the $AUC_{0\text{-}168hr}$ to the projected exposures at the highest anticipated human dose of 1200 mg (Table 16). Antidrug antibodies were only observed in 1 monkey (out of a total of 40 monkeys) administered with ALXN1820 and did not have any impact on systemic exposure or toxicity profile.

2.3. Benefit/Risk Assessment

This is a healthy participant study, and there is no direct benefit to study participants. Identified and potential risks are described below. More detailed information about the known and expected benefits and risks and reasonably expected AEs of ALXN1820 may be found in the IB.

2.3.1. Risk Assessment

This study is the first human exposure to ALXN1820, and as there is no clinical experience to date, the potential risks are based on the class of the molecule and its mechanism of action. No potential risks were identified from the repeat dose toxicity study in cynomolgus monkeys with ALXN1820 after 6 weekly SC doses up to 300 mg/kg/week or after a single IV dose up to 100 mg/kg.

2.3.1.1. Neisseria meningitidis Infections

Increased susceptibility to infection with *Neisseria* (*N.*) *meningitidis* is a known risk associated with properdin deficiency and has been well described with properdin deficient patients (Figueroa, 1991). Similar to properdin deficiency, the main risk associated with the use of ALXN1820 (properdin inhibitor) is the risk of meningococcal infections. Specific risk mitigation measures are in place to address this risk. All participants must be vaccinated against meningococcal infections at least 56 days before the time of initiating study drug and should receive treatment with appropriate prophylactic antibiotics during the duration of reduced complement activity.

Clinically, the risk of *N. meningitidis* is mitigated in patients with properdin deficiency by vaccinating all patients against *N. meningitidis* with tetravalent meningococcal conjugate (MCV4) and serogroup B vaccines before dosing. In this clinical study, participants will experience an induced transient state of properdin deficiency, therefore participants will receive the MCV4 vaccination at least 56 days prior to dosing with ALXN1820 (if not vaccinated with MCV4 within the last 2 years and 6 months, or if adequate documentation to verify previous vaccination is unavailable). A titer to MCV4 will be established prior to enrollment to confirm immunization status. Participants who are not already vaccinated for serogroup B meningococcal infections will also receive that vaccination 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 participants will be treated with prophylactic antibiotics (oral penicillin V 500 mg twice daily) for the duration of reduced complement activity. Unless the Investigator and Sponsor agree to an alternative regimen, all participants will take prophylactic antibiotics (oral penicillin V 500 mg twice daily) until complement activity has normalized. Penicillin is the drug of choice in eradication of *N. meningitidis* in carriers, as supported by the following:

1. High levels of resistance to penicillin caused by plasmid-encoded β-lactamases are rarely encountered in meningococcal strains (Yazdankhah, 2004).
2. Antibiotic prophylaxis with orally administered penicillin V 500 mg twice daily has been provided in the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) patients with eculizumab by some physicians and is generally well-tolerated (Kelly, 2011; Leeds Teaching Hospitals NHS Trust, 2013).

If penicillin is not tolerated, or the participant has a known penicillin allergy, second-line antibiotics will be initiated at the discretion of the Investigator.

2.3.1.2. Immunogenicity and Hypersensitivity

ALXN1820 has the potential to be immunogenic and may be associated with hypersensitivity reactions. Some healthy participants are also known to have pre-existing antibody to VHH antibodies. Antibodies to ALXN1820 have been observed in 14 of 100 healthy participant serum samples tested in an in vitro screening assay.

Monitoring of immunogenicity for ALXN1820 is in place for this study as specified in the SoA (Section 1.3).

Table 12: Potential Risks and Mitigation Strategies

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Treatment with ALXN1820		
Meningococcal infection	ALXN 1820 blocks properdin which can result in increased susceptibility to *Neisseria meningitidis*, likely with fulminant clinical manifestations.	Participants must be vaccinated against all available serotypes of *N. meningitidis* (A, C, Y, W 135, and B). However, vaccination may not be sufficient to prevent meningococcal infection. Participants will be put on prophylactic antibiotics for the entire Treatment Period until CAP activity returns to baseline (See Sections 1.3, 2.3.1.1 and 8.2.9) Participants will be provided a safety card to carry at all times and for 5 months after the final dose of ALXN1820.
Immunogenicity	Treatment with any therapeutic protein may induce an immune response. Occasionally, this immune response is clinically meaningful. The consequences of an immune reaction to a therapeutic protein range from transient appearance of antibodies, without any clinical consequence, to severe, life-threatening conditions. Potential clinical consequences also may include severe hypersensitivity-type reactions, decrease in efficacy and induction of autoimmunity.	Algorithm for hypersensitivity reaction management; Stopping rules and staggered dosing

Abbreviation: CAP = complement alternative pathway.

2.3.1.3. Coronavirus Disease 2019

The SARS-COV-2 disease (COVID-19) global pandemic is active in many countries at the time of this protocol. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they may be related to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.7, Appendix 7.

2.3.2. Benefit Assessment

This is a healthy participant study, and there is no direct benefit to study participants.

2.3.3. Overall Benefit: Risk Conclusion

This is the first time that ALXN1820 will be administered to humans. Healthy participants are the appropriate population for this study, as they will enable PK and PD assessments without the potential of confounding effects due to other disease activity, comorbidities, or medications. This study has been designed to minimize risk to participants; there is strict inclusion/exclusion criteria with a robust safety monitoring and risk mitigation plan in place. This dosing strategy is

justified given the large safety margin and the experience with complete properdin inhibition in healthy participants at Alexion (Section 4.3). An SRC, consisting of the Investigator, Medical Monitor, safety physician, study statistician and clinical pharmacologist, will evaluate the available study data at prespecified time points for participant safety and make recommendations on dose escalation, dose modification, or termination of the study. The single and multiple SC and IV doses to be studied in healthy participants in this study are predicted to be within the safety exposure margins established from a cynomolgus monkey 6-week GLP toxicology study.

The data obtained from this healthy participant study may inform future clinical studies in patients.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 13.

Table 13: Study ALXN1820-HV-101 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of ALXN1820 SC and ALXN1820 IV	Safety assessed by incidence of TEAEs and SAEs, physical examination, vital sign measurements, clinical laboratory, and electrocardiogram results
Secondary	
To assess the single- and multiple-dose PK of ALXN1820 SC and single-dose PK of ALXN1820 IV	Serum ALXN1820 single- and multiple-dose PK profiles and PK parameters
To explore the PD effects of ALXN1820 SC and ALXN1820 IV	Change in serum concentrations of total and free properdin over time Change in CAP activity using the Wieslab AP assay
To assess the immunogenicity of ALXN1820 SC and ALXN1820 IV	Incidence of treatment-emergent ADAs to ALXN1820
To estimate the absolute bioavailability of ALXN1820 SC	ALXN1820 PK parameters (AUC) SC versus IV will be compared
To compare safety, tolerability, PK, PD, and immunogenicity of ALXN1820 SC between Japanese and non-Japanese healthy participants	Quantitative assessment of safety, PK, PD parameters, and immunogenicity (ADA) between healthy non-Japanese participants and participants of Japanese descent

Abbreviations: ADA = antidrug antibody; AP = alternative pathway; AUC = area under the concentration-time curve; CAP = complement alternative pathway; IV = intravenous; PD = pharmacodynamics(s); PK = pharmacokinetic(s); SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, double-blind, placebo-controlled single and multiple ascending dose study designed to evaluate the safety, tolerability, PK, PD, and immunogenicity of ALXN1820 administered SC (ALXN1820 SC) and IV (ALXN1820 IV). ALXN1820 SC will be evaluated in single and multiple ascending doses while ALXN1820 IV will be evaluated in a single dose only. A total of 80 healthy adult participants (60 on ALXN1820, 20 on placebo) will be enrolled in up to 10 cohorts. All participants within each cohort will be recruited at a single site.

Eight participants will be randomly assigned in a 3:1 ratio to each cohort to receive either a single or multiple doses of ALXN1820 SC, a single dose of ALXN1820 IV (n = 6 per cohort), or a single or multiple doses of placebo (n = 2 per cohort). Details on dosing are presented in Table 14.

Table 14: ALXN1820-HV-101 Dosing Cohorts

Cohort	N	Study Drug	Route of Administration	Planned Dose (placeholders)	Number of Doses/Dose Interval
1	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	12.5 mg	1 single dose
2	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	50 mg	1 single dose
3	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	150 mg	1 single dose
4	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	450 mg	1 single dose
5	8 (6 active/2 placebo)	ALXN1820 and placebo	IV	450 mg	1 single dose
6	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	1200 mg	1 single dose
7 (optional)	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	TBD[a] (≤ 2250 mg)	1 single dose
8	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	150 mg	QW × 5
9	8 (6 active/2 placebo) Japanese participants	ALXN1820 and placebo	SC	150 mg	QW × 5
10	8 (6 active/2 placebo)	ALXN1820 and placebo	SC	TBD[a]	QW × 3[a]

[a] Dosing in Cohorts 7 and 10 to be determined based on the observed data up to Cohort 5 and PK/PD modeling.
Abbreviations: IV = intravenous; N = number of participants; PD = pharmacodynamic (s); PK = pharmacokinetic(s); QW = once weekly; SC = subcutaneous; TBD = to be determined.

Details on timing of dosing in the cohorts are presented in Table 15.

The first 2 participants randomized to each cohort will be dosed as a sentinel pair with at least 1 participant on active treatment (either 1 participant on active treatment and 1 participant on placebo, or 2 participants on active treatment). This dosing strategy is justified given the large

safety margin (approximately 20-fold at the highest planned dose) and the experience with properdin inhibition in healthy participants at Alexion. At the discretion of the Investigator, up to 3 more participants will be dosed at least 48 hours after dosing of the sentinel pair, followed by dosing of the remaining participants in the cohort no earlier than the 4th day, as long as no suspension/stopping criteria have been met (Section 7.2). At no time will more than 4 participants per cohort be dosed on a given day. The allowance for a maximum of 4 participants/day/cohort is intended to provide flexibility should a 4th participant need to be added (eg, if replacement of a participant is required). The intention for this dosing strategy is to ensure a limited number of healthy participants will receive a dose and regimen that have not been previously tested. The limit of ≤ 4 participants/day/cohort does not apply to the dose and regimens tested previously.

The timing and dependencies of the dosing cohorts are in Table 15 and in Figure 1. Enrollment may be stopped at the discretion of the SRC. Should they be required, dose modifications are described in Table 19.

Table 15: Dosing Chart for Single Ascending Dose and Multiple Ascending Dose Regimens

Cohort	Route of Administration	Number of participants dosed		
		Day 1[a]	Day 3	Day 4
1[b], 2[b], and 3[b]	Manual SC or via SP	2	3	3
4[b], 6[c], 7[c]	SC infusion via SP			
5[d]	IV infusion			
8[e], 9[e]	Manual SC, QW × 5			
10[f]	Manual SC or SC infusion via SP, QW × 3			

Note At no time > 4 participants/cohort to be dosed on a given day for dose and regimen that have not been tested previously.

[a] At least 1 participant on active treatment (either 1 participant on active treatment and 1 participant on placebo, or 2 participants on active treatment).

[b] Sequential dosing to occur in Cohorts 1 to 4, dependent on SRC review of safety data through Day 15 (336 hours) of previous cohort.

[c] Dosing in Cohort 6 to be administered based on SRC review of interim safety data from the Day 15 (336 hours) assessment after dosing of Cohorts 4 and 5. Dosing in Cohort 7 to be determined based on SRC review of interim safety data from the Day 15 (336 hours) assessment after dosing of Cohort 6 and PK/PD data from Day 29 (672 hours) assessment after dosing of Cohorts 4 and 5.

[d] Dosing in Cohort 5 is dependent on Investigator review of safety data through Day 8 (168 hours) of Cohort 4. However, should there be safety findings of concern in previous cohorts, an SRC review will be conducted for Cohort 5 to determine if participants will be dosed at the planned dose of 450 mg IV or a lower dose.

[e] Dosing in Cohorts 8 and 9 to be determined based on SRC review of all data from the Day 15 (336 hours) assessment for Cohorts 4 and 5. Dosing of Cohort 9 may start at the same time as Cohort 8 or later depending on scheduling at the clinical site

[f] Dosing in Cohort 10 to be determined based on SRC review of all data from the Day 29 (672 hours) assessment for Cohort 8 and PK/PD data from Day 29 (672 hours) after dosing of Cohorts 4 and 5.

Abbreviations: IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; QW = once weekly; SC = subcutaneous; SP = syringe pump; SRC = safety review committee.

An SRC, consisting of the Investigator, Medical Monitor, safety physician, study statistician and clinical pharmacologist, will evaluate the available study data at prespecified time points for participant safety and make recommendations on dose escalation, dose modification, or

termination of the study (see SRC charter for description of membership, schedule of meetings, data required for each safety review, and requirements for documenting meeting discussions and outcome). At the Sponsor's discretion, and after consultation with the SRC, up to 18 additional participants across the entire study may be enrolled as replacement participants if a participant discontinues prior to Day 43 for reasons other than drug-related AEs.

The highest single-dose cohort (Cohort 7) will be optional and determined based on SRC review of interim safety data from Day 15 (336 hours) assessment after dosing of Cohort 6 and PK/PD data from Day 29 (672 hours) after dosing of Cohorts 4 and 5 (450 mg SC and IV, respectively). Based on properdin and CAP activity, the highest dose administered in this study will not exceed 2250 mg or the NOAEL exposure established in the GLP toxicology study, whichever is lower. For comparison with NOAEL exposure, instead of using the common practice of the mean predicted AUC0-168 and Cmax of all participants in a cohort, the upper limit of the 95% prediction interval (PI) of the model predicted AUC0-168 and Cmax will be used. This approach will ensure that each participant in this cohort will have a lower exposure than the NOAEL exposure. The highest dose will have on average ≤ 70 days complete inhibition of properdin and CAP activity.

Dosing in the multiple-dose Cohort 10 will start after SRC review of all available data through Day 29 (672 hours) for Cohort 8 (ALXN1820 150 mg SC weekly for 5 weeks) and all available data from the single dose cohorts at the time of the SRC meeting. The final dose will be determined based on the interim PK/PD modeling using PK/PD data from Day 29 (672 hours) after dosing of Cohorts 4 and 5. Administration of ALXN1820 to participants in Cohort 10 is expected to completely inhibit properdin and CAP activity during the dosing period. The dose regimen determined for this cohort will not exceed the NOAEL exposure established in the GLP toxicology study. For comparison with NOAEL exposure, instead of using the common practice of the mean predicted $AUC_{0\text{-}168}$ and C_{max} of all participants in a cohort, the upper limit of the 95% prediction interval (PI) of the model predicted $AUC_{0\text{-}168}$ and C_{max} will be used. This approach will ensure that each participant in this cohort will have an exposure lower than the NOAEL exposure.

Additional cohorts in healthy participants and patients may be added later if deemed necessary. These cohorts will only be added as part of a substantial amendment to the protocol, and after SRC review and regulatory agency and EC approval. Screening for these cohorts can proceed prior to amendment approval, as long as the approved selection criteria apply. Randomization and dosing can only occur after approval of the amendment.

All ALXN1820 dose levels/dosing regimens can be adjusted in accordance with safety, tolerability, and PK/PD data collected up to the decision-making time point (see Table 19 for dose escalation rules). As used here, the term "dosing regimen" includes (1) the dose level administered, (2) the number of doses administered each day, (3) the interval between individual doses, and (4) the duration of dosing, i.e., the total number of doses administered. Accordingly, these can be adjusted individually or in combination.

4.2. Scientific Rationale for Study Design

As this is the first time ALXN1820 will be dosed in humans, a randomized, double-blind, placebo-controlled, single- and multiple ascending dose design was chosen for initial assessment of the safety, tolerability, PK/PD, and immunogenicity of ALXN1820 SC and ALXN1820 IV.

The ALXN1820 IV cohort will provide the reference arm for assessing ALXN1820 SC absolute bioavailability.

This study is being conducted in healthy participants, not patients, so that the assessments are not confounded by disease activity, comorbidities, or concomitant medications. A sentinel dosing paradigm is being used since this is the first administration of ALXN1820 to healthy participants.

The ALXN1820 multiple-dose SC cohorts will assess safety, tolerability, PK/PD, and immunogenicity after multiple doses of ALXN1820 administration. The ALXN1820 multiple-dose SC cohort in participants of Japanese ethnicity will assess safety, tolerability, PK/PD, and immunogenicity after multiple doses of ALXN1820 administration in participants of Japanese ethnicity and comparison of safety and PK/PD between Japanese and non-Japanese participants.

The expected terminal elimination half-life for the highest SC dose being evaluated in this study is expected to be approximately 24 days. The 126 and 154-day washout periods for the single and multiple dose cohorts, respectively, correspond to more than 5 half-lives, at which point ALXN1820 is expected to be nearly completely eliminated from the systemic circulation and complement activity restored to normal levels in the study participants.

As this is a FIH study, placebo control is implemented in each cohort. Due to the difficulty of providing a matching placebo, participants randomized to placebo will receive an equivalent volume of normal saline (SC administration) or 5% dextrose or glucose (IV administration) at the same injection/infusion rate as the active treatment. To ensure double-blinded conditions, the pharmacist preparing the study drug and the physician(s) administering the active treatment or placebo will be unblinded to treatment assignment. All other study personnel will remain blinded to treatment assignment, unless pre-specified in the protocol. All necessary steps will be taken to avoid inadvertent unblinding.

4.3. Justification for Dose

The proposed doses in this study are justified based on the experience of properdin deficient patients reported in the literatures and Alexion's own nonclinical and clinical experience with other properdin inhibitors (ALXN1510 and ALXN1610).

A number of individuals have been described in the literature with properdin deficiency (Figueroa, 1991; Fijen, 1996). Properdin deficiency is an X-linked recessive disease that occurs in males. The main clinical characteristic of properdin deficiency is significant risk of meningococcal infection. Recurrent meningococcal infection is rare possibly in part because the CCP remains intact and can be activated by antibodies elicited in the initial meningococcal infection. Properdin-deficient patients respond well to meningococcal vaccination (Fijen, 1998). Obligate carrier females had approximately half the normal level of properdin but normal AP activity and no increased risk of meningococcal infection (Densen, 1987).

Alexion has previously conducted nonclinical and clinical studies with other properdin inhibitors, ALXN1510 and ALXN1610. ALXN1510 is a full-length IgG1 monoclonal antibody (mAb) that binds and blocks properdin. A FIH healthy participant SAD study of ALXN1510 was conducted with 6 dose cohorts from 0.1 to 20 mg/kg administered as IV infusions (Study ALXN1510-HV-101). A total of 48 participants (36 active and 12 placebo) were enrolled

with 8 participants (6 active and 2 placebo) in each of the 6 cohorts. ALXN1510 was well tolerated up to the highest dose tested (20 mg/kg) with no SAEs. Adverse events (AEs) were mild (mostly Grade 1). Risk of *Neisseria* infection in this study was mitigated by a combination of immunizations (ACWY and Serogroup B) and antibiotic prophylaxis. At doses ≥ 1 mg/kg a complete inhibition (defined as < 20% of the baseline value) of CAP-mediated hemolysis was observed. At doses above 10 mg/kg, the complete inhibition of CAP hemolysis persisted for 22 to 36 days post dose, returning to baseline (defined as > 80% of the baseline value) around 36 to 50 days post dose. There was no effect on hemolysis mediated through CCP at any dose level in this study. Antidrug antibody against ALXN1510 was observed in only one of 36 ALXN1510-treated participants in this study at the lowest dose cohort starting around Day 90 and was not associated with any clinical sequelae or accelerated clearance.

A 26-week, QW IV GLP toxicology study with 8-week recovery period performed in rhesus monkeys with ALXN1510 was conducted in parallel with the FIH healthy volunteer study ALXN1510-HV-101. In this study, poor tolerability was observed which was due to significant immunogenicity towards ALXN1510 with subsequent deposition of immune complexes and was unrelated to inhibition of free properdin and CAP-mediated hemolysis. ALXN1610, derived from ALXN1510 by removing 19 murine back mutations from ALXN1510 and replacing the aglyco-Ig1-Fc with a G2-G4 Fc, had substantially reduced ADA levels and was well tolerated in a 26-week QW toxicology study in rhesus monkeys up to the highest dose tested (100 mg/kg) where complete inhibition of free properdin and CAP-mediated hemolysis was achieved.

A PK/PD model of ALXN1820 was developed using data from the following:

- a non-GLP single dose and a GLP multiple dose toxicology PK/PD study in cynomolgus monkeys
- in vitro binding of ALXN1820 to human properdin
- the relationship between in vitro human properdin and CAP activity

The ALXN1820 PK/PD model was based and refined upon the PK/PD model used in the ALXN1510 FIH study. ALXN1510 PK/PD model was a semi-mechanistic target-mediated drug disposition model, incorporating ALXN1510, human properdin, binding kinetics of ALXN1510 to human properdin, and in vitro properdin vs. CAP hemolysis relationship. ALXN1510 PK/PD model was used to predict the ALXN1510 PK, properdin inhibition and duration of CAP hemolysis inhibition for the ALXN1510 FIH single ascending dose study with reasonable accuracy when compared to the observed data. The ALXN1820 PK/PD model in cynomolgus monkeys was scaled to simulate ALXN1820 concentrations and the inhibition of properdin and CAP activity in humans, which in turn were used to estimate exposure and select a starting dose that will produce a minimal on-target pharmacologic effect.

A summary of the predicted exposure, safety margin, duration of inhibition of properdin, and CAP activity for ALXN1820 based on the PK/PD model described above is provided in Table 16. Based on the results of PK/PD modeling for ALXN1820, a single dose of 12.5 mg ALXN1820 SC is expected to result in < 50% inhibition of free properdin. This dose is considered as the minimally anticipated biologically effective dose (MABEL) based upon studies of individuals that exhibit heterozygous deficiency in properdin (Bathum, 2006; Densen, 1987). In these studies, obligate carrier females had approximately half the normal level of properdin but normal CAP activity; no meningococcal infections were reported. In addition, given

Alexion's previous clinical study experience with ALXN1510 as described above, a 50% inhibition of free properdin would have little impact on the CAP activity. The MABEL dose is estimated to occupy only about 0.02 - 0.03% of human serum albumin on a molar basis at C_{max}.

Single SC doses will be escalated by 4-fold from 12.5 mg to 50 mg and by 3-fold from 50 mg to 150 mg and from 150 mg to 450 mg and by 2.67-fold from 450 mg to 1200 mg. At 1200 mg SC, ALXN1820 is predicted to produce complete inhibition of properdin (> 99.6% from the baseline) and CAP activity (> 80% from the baseline) for about 68 days and 67 days, respectively. The properdin and CAP activity are expected to return to 80% of baseline levels by 92 days and 84 days, respectively. The predicted exposure at the 1200 mg dose is around 1/37 of the predicted NOAEL exposure, based on the NOAEL in the toxicology study (300 mg/kg). At this dose, the occupancy of human serum albumin at the C_{max} is approximately 1.12% to 1.69%.

A single dose of 450 mg will be administered by the IV route (Cohort 5) to healthy participants after completion of the 450 mg SC cohort (Cohort 4) to estimate the absolute bioavailability of ALXN1820 following SC administration (Table 16). Given the high SC bioavailability in the cynomolgus monkey, the SC bioavailability in humans is expected to be close to 100%. Hence, the exposure of ALXN1820 following a 450 mg IV dose is anticipated to be similar to that following a 450 mg SC dose. Dosing of Cohort 5 will start based on the Investigator's review of all available safety data through Day 8 (168 hours) for Cohort 4. However, in case there are safety findings in previous cohorts, an SRC review will be conducted and dosing for Cohort 5 may be started at the planned dose of 450 mg IV or at a lower dose than 450 mg IV.

The highest single-dose cohort (Cohort 7) will be determined based on SRC review of interim safety data from the Day 15 (336-hour) assessment after dosing of Cohort 6 and PK/PD data from Day 29 (672 hours) after dosing of Cohorts 4 and 5. As shown in Table 16, for participants in Cohort 4 and 5 (450 mg SC and IV, respectively), properdin is projected to be completely suppressed for 39 days, and CAP activity is projected to be completely suppressed for approximately 39 days. The interim PK/PD data from the 450 mg SC and IV doses would be sufficient for prediction of higher doses in which an extended duration of inhibition of properdin and CAP activity is expected. The highest dose administered in this study will not exceed 2250 mg or the NOAEL exposure established in the GLP toxicology study, whichever is lower. For comparison with NOAEL exposure, instead of using the common practice of the mean predicted $AUC_{0\text{-}168}$ and C_{max} of all participants in a cohort, the upper limit of the 95% PI of the model predicted $AUC_{0\text{-}168}$ and C_{max} will be used. This approach will ensure that each participant in this cohort will have an exposure lower than the NOAEL exposure. The highest dose also will have on average ≤ 70 days complete inhibition of properdin and CAP activity. The limit of 70 days of complete inhibition is selected to enable evaluation of extended dosing intervals (eg, Q8W), leveraging our previous nonclinical (up to 6-month monkey toxicology data) and clinical (up to 36 days of complete inhibition of properdin and CAP hemolysis in human) experience with other antiproperdin inhibitors (ALXN1510 and ALXN1610), and properdin deficiency patients as described above. As shown in Table 16, a 1200 mg dose of ALXN1820 (Cohort 6) is projected to suppress properdin and CAP activity for approximately 68 days. If this level of suppression is confirmed based on the observed data and interim PK/PD analysis, Cohort 7 may not be initiated.

Three MAD cohorts will also be included in this study. The first 2 multiple-dose cohorts (Cohorts 8 and 9) will receive 150 mg SC weekly for 5 doses. These cohorts will start after SRC review of all available data through Day 15 for the 450 mg SC and IV single-dose cohort (Cohorts 4 and 5) and administration of ALXN1820 is predicted to provide a duration of complete inhibition of properdin and CAP activity of approximately 67 and 66 days, respectively, following the first dose, with properdin and CAP activity returning to baseline level approximately 91 and 83 days, respectively, after the first dose. The binding to human serum albumin is predicted to be approximately 0.51% to 0.77% at the C_{max} after the last dose. Cohort 9 will assess the safety, tolerability, PK, PD, safety, and immunogenicity of ALXN1820 at a dose level of 150 mg SC weekly for 5 doses in participants of Japanese descent.

Study drug administration in Cohort 10 will start after the completion of the Day 29 SRC assessment of the safety and tolerability of Cohort 8 in conjunction with all available safety, tolerability, and PK/PD data from the single-dose cohorts. The dose will be determined based on the interim PK/PD modeling using PK/PD data from Day 29 after dosing of Cohorts 4 and 5. Administration of ALXN1820 to participants in Cohort 10 is expected to completely inhibit properdin and CAP activity during the dosing period. The dose regimen determined for this cohort will not exceed the NOAEL exposure established in the GLP toxicology study. For comparison with NOAEL exposure, instead of using the common practice of the mean predicted $AUC_{0\text{-}168}$ and C_{max} of all participants in a cohort, the upper limit of the 95% PI of the model predicted $AUC_{0\text{-}168}$ and C_{max} will be used. This approach will ensure that each participant in this cohort will have an exposure lower than the NOAEL exposure. The dose regimen also will have on average $\leq$ 70 days complete inhibition of properdin and CAP activity.

Table 16: Predicted ALXN1820 Exposure and Duration of Properdin and CAP Activity Inhibition

Cohort	Planned Dose	Predicted $AUC_{human\ (0\text{-}168h)}$ (h × µg/mL)	Predicted C_{max} (µg/mL)	Expected Safety Margin for AUC	Expected Safety Margin for C_{max}	Duration of ≥ 99.6% Properdin Inhibition (Days)	Time of Properdin Return to 80% Baseline (Days)	Duration of Complete Inhibition of CAP Activity (Days)	Time of CAP Activity Return to 80% Baseline (Days)	Max Free and Partially Free Properdin Inhibition (%)	Maximum Albumin Occupancy (%)
1	12.5 mg SC	503	4	2447	2460	0	4	0	0	44	0.02 - 0.03
2	50 mg SC	1685	12	730	771	4	14	4	9	99.717	0.06 - 0.09
3	150 mg SC	4414	31	279	300	16	33	16	26	99.936	0.15 - 0.23
4	450 mg SC	12579	88	98	105	39	62	39	54	99.981	0.43 - 0.64
5	450 mg IV	17271	178	71	52	39	61	39	53	99.995	0.87 - 1.30
6	1200 mg SC	32984	230	37	40	68	92	67	84	99.993	1.12 - 1.69
7	TBD[a] (≤ 2250 mg SC)										
8 and 9	150 mg SC QW × 5	4414 (after the 1st dose)	31 (after the 1st dose)	73 (after the 5th dose)	88 (after the 5th dose)	67 (after the 1st dose)	91 (after the 1st dose)	66 (after the 1st dose)	83 (after the 1st dose)	99.936	0.51 – 0.77
		16802 (after the 5th dose)	105 (after the 5th dose)			39 (after the 5th dose)	63 (after the 5th dose)	38 (after the 5th dose)	55 (after the 5th dose)		
10	TBD[a] SC QW × 3	8497 (after the 1st dose)	59 (after the 1st dose)	54 (after the 3rd dose)	64 (after the 3rd dose)	65 (after the 1st dose)	90 (after the 1st dose)	65 (after the 1st dose)	81 (after the 1st dose)	99.97	0.71 – 1.06
		22901 (after the 3rd dose)	145 (after the 3rd dose)			51 (after the 3rd dose)	76 (after the 3rd dose)	51 (after the 3rd dose)	67 (after the 3rd dose)		

[a] Dose will be determined based on the interim PK/PD analysis using the PK/PD limits specified in Sections 4.1 and 4.3.

Note: Expected safety margin for AUC = $AUC_{cyno\ (0\text{-}168h)\ after\ last\ dose}/AUC_{human\ (0\text{-}168h)}$.

Abbreviations: AUC = area under the concentration-time curve; $AUC_{cyno\ (0\text{-}168h)\ after\ last\ dose}$ = area under the concentration-time curve from time 0 through 168 hours after the last dose in cynomolgus monkeys; $AUC_{human\ (0\text{-}168h)}$ = area under the concentration-time curve from time 0 through 168 hours in humans; CAP = complement alternative pathway; C_{max} = maximum concentration; IV = intravenous; Max = maximum; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QW = once weekly; SC = subcutaneous; TBD = to be determined.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as the date the last participant completes the last visit as shown in the SoA (Section 1.3).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Male and female participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by medical evaluation with no clinically significant or relevant abnormalities as determined by medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluation (hematology, biochemistry, coagulation, and urinalysis) that is reasonably likely to interfere with participation in or ability to complete the study, or to potentially confound interpretation of study results, as assessed by the Investigator and Sponsor Medical Monitor.
3. Cohort 9 only: Participants of Japanese descent (defined as those participants whose parents and grandparents are both Japanese and who have spent less than 5 years outside of Japan).

Weight

4. Body weight within 50 – 100 kg (inclusive), and body mass index (BMI) within the range 17 – 32 kg/m^2, (inclusive).

Sex

5. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Female participants of childbearing potential and male participants with female partners of childbearing potential must be willing to follow protocol-specified contraception guidance while on treatment and for at least 5 months after last dose of study drug (described in Section 10.4).

Other Inclusion Criteria

6. Serum albumin above lower limit of the normal range (local laboratory) at Screening.
7. QT interval corrected using the Fridericia's formula (QTcF) ≤ 450 msec at Screening and prior to dosing on Day 1.
8. Documented vaccination with MCV4 at least 56 days and not more than 2 years and 6 months prior to dosing. Documentation must include a positive titer to confirm an immune response before study drug administration.
9. Documented vaccination with serogroup B meningococcal vaccine at least 56 days and not more than 2 years and 6 months prior to dosing. For participants not previously

vaccinated with serogroup B meningococcal vaccine, vaccination 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. For participants vaccinated more than 2 years and 6 months prior to dosing, a booster administrated at least 28 days prior to dosing on Day 1.

Informed Consent

10. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Current or recurrent disease (eg, cardiovascular, hematologic, neurologic, endocrine, immunologic, rheumatologic, renal, hepatic or gastrointestinal, or other conditions) that could affect clinical assessments or clinical laboratory evaluations.
2. Current or relevant history of physical or psychiatric illness that is not stable or may require a change in treatment, use of prohibited therapies during the study, make the participant unlikely to fully comply with the requirements of the study or complete the study, or, any condition that presents undue risk from the study drug or study procedures.
3. Any other significant disease or disorder which, in the opinion of the Investigator, may put the participant at risk.
4. History of any *Neisseria* infection.
5. History of unexplained, recurrent infection, or infection requiring treatment with systemic antibiotics within 90 days prior to dosing on Day 1.
6. History of complement deficiency or complement activity below the reference range as evaluated at Screening.
7. 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 within 5 years.
8. Positive test for hepatitis B surface antigen (HbsAg) or human immunodeficiency virus antibody (HIV Ab) at Screening.
9. Acute or chronic hepatitis C virus infection (evidenced by antibody titer).
10. Active systemic bacterial, viral, or fungal infection within 14 days prior to dosing.
11. History of latent or active tuberculosis (TB) or exposure to endemic areas within 8 weeks prior to the Screening Visit.
12. History of significant allergic reaction to any product, including documented history of allergy to penicillin or cephalosporin.

Prior/Concomitant Therapy

13. Use of prescription medications (excluding oral contraceptives) within 7 days prior to dosing on Day 1, except with prior approval of the Sponsor.
14. Regular use of nonprescription, over-the-counter medications, including herbal remedies and supplements, within 7 days prior to dosing on Day 1. Multivitamins and paracetamol (acetaminophen) ≤ 2 g per day are allowed.

Prior/Concurrent Clinical Study Experience

15. Participation (ie, last protocol-required study visit) in a clinical study within 90 days or 5 half-lives of the investigational agent, whichever is longer, before initiation of dosing on Day 1.
16. Participation in more than 1 clinical study of a mAb, or participation (ie, last protocol-required study visit) in a clinical study of a mAb within the 6 months or 5 half-lives of the mAb, whichever is longer, prior to Screening, during which the participant was exposed to the active study drug.

Diagnostic assessments

17. Positive or indeterminate QuantiFERON®-TB test indicating possible TB infection.
18. Presence of fever (confirmed body temperature > 37.6°C) within 14 days prior to dosing on Day 1.
19. Serum creatinine greater than the upper limit of normal (ULN) of the reference range of the testing laboratory at Screening or on Day -1.
20. 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.
21. Any clinically significant abnormal hematological parameters (per the Investigator's discretion with agreement of the Sponsor).
22. Positive urine drug toxicology screen at Screening or on Day -1.
23. Alcohol consumption within 48 hours prior to study drug administration or positive alcohol breath test on Day -1.
24. Donation of plasma within 7 days prior to dosing on Day 1. Donation or loss (excluding volume drawn at Screening) of more than 400 mL of blood within the last 16 weeks prior to dosing on Day 1.

Other Exclusions

25. Female participants who are pregnant or breastfeeding.
26. Participants who are in intimate and prolonged contact with (defined as living under the same roof, living in dormitory-style accommodations, 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 HIV.

27. Participants who are one of the following:
    a. Professionals who are exposed to environments of greater risk for meningococcal disease.
    b. Research, industrial, and clinical laboratory personnel who are routinely exposed to *N. meningitidis*.
    c. Military personnel during recruit training (military personnel may be at increased risk of meningococcal infection when accommodated in close quarters).
    d. Daycare center workers.
    e. Those living on a college or university campus.
    f. 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, Saudi Arabia) within 6 months prior to dosing.
28. Immunization with a live-attenuated vaccine 28 days prior to dosing on Day 1 or planned vaccination during the course of the study (except for the vaccination planned by the study protocol).
29. Major surgery or hospitalization within 90 days prior to dosing on Day 1.
30. History of allergy or hypersensitivity to excipients of ALXN1820 (eg, polysorbate 80)
31. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch, electronic cigarettes) within 24 hours prior to the planned first day of dosing (Former smokers may be permitted to enroll at the Investigator's discretion). Unwilling to comply with the smoking restrictions detailed in Section 5.3.
32. History of illicit drug abuse, history of significant alcohol abuse within 1 year prior to the Screening Visit, or clinical evidence of substance and/or alcohol abuse within the 2 years before Screening. Alcohol abuse is defined as regular weekly intake of more than 14 units (for both males and females.

5.3. Lifestyle Considerations

Table 17: Healthy Participant Lifestyle Considerations

Items participants must not consume or do	When participants must stop	When participants can restart
Food containing poppy seeds	Within 24 hours prior to admission to the inpatient facility	After study completion/last visit.
Consume meals/snacks/water while confined in the inpatient facility. Meals/snacks/water provided by the study personnel will be allowed. Standard meals will be provided at the standard unit times, and meals should be completed each time.	While confined to the inpatient facility.	After discharge from the facility

Table 17: Healthy Participant Lifestyle Considerations

Items participants must not consume or do	When participants must stop	When participants can restart
Caffeine-containing or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate).	From 24 hours before admission through discharge from the inpatient facility and 24 hours before each study follow-up visit.	After discharge from the facility and after each study follow-up visit.
Alcohol	From 24 hours before admission through discharge from the inpatient facility and 24 hours before each study follow-up visit.	After discharge from the facility and after each study follow-up visit.
Tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch, electronic cigarettes).	From 24 hours before admission through discharge from the inpatient facility.	After discharge from the facility.
Strenuous physical activity.	48 hours before blood draws for clinical safety laboratory testing.	After blood draws for clinical safety laboratory testing. Participants should not start new physical training activities during the study until study completion (last visit).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study drug due to failure to meet eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any AEs, including any SAEs and any related concomitant medication, occurring during the screening period.

Participants who do not meet the criteria for participation in this study (ie, screen failures) may be rescreened. Any abnormal laboratory parameter(s) results outside of the reference range at Screening may be repeated per the Investigator's discretion for the purpose of further determining eligibility.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention Administered

The study drug composition and doses to be administered in this study are presented in Table 18. Placebo will be commercially available normal saline for SC administration, and 5% dextrose or glucose for IV administration. Placebo will be sourced from the site.

Table 18: Dose Reference Chart for Study ALXN1820-HV-101

Characteristics	ALXN1820 SC	ALXN1820 IV
Dosage formulation	ALXN1820 is formulated at pH 5.4 and each vial contains 300 mg of ALXN1820 in 20 mM sodium acetate, 250 mM sucrose, and 0.05% polysorbate-80. The concentration is 150 mg/mL.	ALXN1820 is formulated at pH 5.4 and each vial contains 300 mg of ALXN1820 in 20 mM sodium acetate, 250 mM sucrose, and 0.05% polysorbate-80. The concentration is 150 mg/mL.
Unit dose strength(s)/dosage level(s)	12.5 mg, 50 mg, 150 mg, 300 mg, 450 mg, 1200 mg, and a dose that will not exceed 2250 mg	450 mg
Route of administration	SC	IV
Dosing instructions	The SC doses will be administered as a manual SC push (for doses ≤ 300 mg) or as a SC infusion via a syringe pump (for doses > 300 mg).	ALXN1820 IV will be administered as an IV infusion
Packaging and labeling	Each vial will be packaged into a kit. There will be 1 vial per kit. Both vials and kits will be labeled according to the protocol and local regulatory requirements.	Each vial will be packaged into a kit. There will be 1 vial per kit. Both vials and kits will be labeled according to the protocol and local regulatory requirements.
Manufacturer	Alexion	Alexion

Abbreviations: IV = intravenous; SC = subcutaneous.

6.2. Preparation/Handling/Storage/Accountability

Details regarding preparation, handling, storage, accountability, and administration of the study drug are discussed below. Additional guidance is provided in the pharmacy manual.

1. ALXN1820 is to be stored at 2 - 8°C. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
2. Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

3. The pharmacy staff at the Investigator's site will be responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). The site's pharmacy will assemble the supplies into individual, labelled participant dose syringes and perform Qualified Person certification of the assembled product.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study. Eligible participants who meet all inclusion and no exclusion criteria will be assigned unique numbers for enrollment and randomization.

For all cohorts, dosing will be double-blinded to active versus placebo. Participants will be randomly assigned in a 3:1 ratio to active treatment or placebo.

During dosing, the participants and on site medical/nursing staff at the study center, and the Sponsor will be blinded to study drug assignment. The pharmacy staff preparing the SC/IV doses 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. Because the appearance of the placebo does not match that of the active study drug, a masking technique will be used at the time of administration (see pharmacy manual for details).

Sponsor staff will be unblinded only when necessary (eg, to monitor that the SC/IV dosing are being prepared appropriately, to determine reportability of SAEs, and evaluate PK/PD data for dose escalation decisions), and will refrain from sharing any information on study drug assignment with the study center staff or others at the Sponsor, especially with regard to assessment and reporting of safety. An unblinded study drug administrator will administer study drug; an appropriate unblinded physician or senior pharmacy staff member will review CAP activity results and make decisions regarding antibiotic treatment.

In the event of an emergency, an envelope for each participant containing his or her study drug assignment will be available from the pharmacy staff preparing the study drugs. There is no antidote to reverse the effects of ALXN1820; therefore, unblinding would not be helpful in the planning of participant treatment for a given event.

Except for reasons stated above, unblinding should only be considered for the safety of the participant. If unblinding is deemed necessary by the Investigator, the Investigator can unblind the participant's treatment allocation using the envelope available from the secure location accessible to the clinical staff. The Investigator must note the date, time, and reason for unblinding. The Investigator should inform the Medical Monitor that the participant was unblinded; however, the Investigator should not reveal to the Medical Monitor the participant's treatment allocation. When an AE is serious, unexpected, and related, the blind will be broken by the Sponsor only for that specific participant. 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, Independent Ethics Committees (IECs), 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.

6.4. Study Drug Compliance

Participants will be administered study drug in a controlled setting directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

For additional information on study intervention compliance and management, refer to the Pharmacy Manual.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Allowed Medicine and Therapy

Multivitamins, contraceptives, and paracetamol (ie, acetaminophen, at doses of ≤ 2 g/day) are permitted for use during the study at the Investigator's discretion. Topical skin products should not be administered at the site of study drug injection from 24 hours prior until 24 hours following study drug administration. Participants are also permitted to receive a booster vaccine, if required.

See Section 8.2.9 for details on administration and duration of treatment with prophylactic antibiotics that are required concomitant medication to mitigate the risk of *N. meningitidis* infection associated with complement inhibition.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required. Concomitant procedures are not allowed unless medically indicated.

6.5.2. Disallowed Medicine and Therapy

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Alexion, the medication will not interfere with the study.

6.6. Dose Modification

Decisions to continue or modify dosing will be made by the Investigator and/or SRC after review of the blinded data as described in Table 19. The SRC may also make recommendations regarding safety issues, study conduct, or study suspension.

Table 19: Study ALXN1820-HV-101 Dose Continuation/Escalation Decision Pathway

Dosing Decision	Responsible Party	Data to be Reviewed	Documentation/Communication Methods
Continuation from the sentinel participant to the remaining participants	Investigator	A minimum of 48 hours post-dose safety and tolerability data from the sentinel participant.	The Investigator will document the decision in an email to the Sponsor. The email does not require the Sponsor's response, unless there is disagreement with the Investigator's decision.
Dose escalation from Cohort 1 to 2, Cohort 2 to 3, Cohorts 3 to 4	SRC	All available data up to a minimum of 336 hours post-dose safety and tolerability data from at least 7 participants (of whom at least 5 will have received treatment) from the previous cohort.	The SRC will document the decision on the escalation/progression approval form.
Proceed to Cohort 5	Investigator or SRC	A minimum of 168 hours post-dose safety and tolerability data from at least 7 participants (of whom at least 5 will have received treatment) from Cohort 4.	The Investigator will document the decision in an email to the Sponsor. The email does not require the Sponsor's response, unless there is disagreement with the Investigator's decision. In case there are safety findings in previous cohorts, an SRC review will be conducted and dosing for Cohort 5 may be started at the planned dose of 450 mg IV or a lower dose.
Escalation to Cohort 6	SRC	All available data up to a minimum of 336 hours post-dose safety and tolerability data from at least 7 participants (of whom at least 5 will have received treatment) from each of cohorts 4 and 5.	The SRC will document the decision on the escalation/progression approval form.
Escalation to Cohort 7 (optional)	SRC	All available data up to a minimum of 336 hours post-dose safety and tolerability data from at least 7 participants (of whom at least 5 will have received treatment) from Cohort 6 and 672 hours post-dose PK/PD data for Cohorts 4 and 5 from at least 7 participants (of whom at least 5 will have received treatment) from each cohort. Cohort 7 may not be initiated based on SRC review.	The SRC will document the decision on the escalation/progression approval form.

Table 19: Study ALXN1820-HV-101 Dose Continuation/Escalation Decision Pathway

Dosing Decision	Responsible Party	Data to be Reviewed	Documentation/Communication Methods
Proceed to Cohort 8 and 9	SRC	All available data up to a minimum of 336 hours post-dose safety and tolerability data from at least 7 participants (of whom at least 5 will have received treatment) from Cohorts 4 and 5.	The SRC will document the decision on the escalation/progression approval form.
Escalation to Cohort 10	SRC	All available data up to a minimum of 672 hours post-dose safety and tolerability data from at least 7 participants (of whom at least 5 will have received treatment) from Cohort 8, and 672 hours post-dose PK/PD data for Cohorts 4 and 5 from at least 7 participants (of whom at least 5 will have received treatment) from each cohort.	The SRC will document the decision on the escalation/progression approval form.

Abbreviations: IV = intravenous; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SRC = Safety Review Committee.

6.7. Intervention After the End of the Study

This is a healthy participant study and no follow-up intervention is planned.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study intervention. If the study intervention is definitively discontinued, the participant should remain in the study to be evaluated for safety follow-up. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Participants should be considered for discontinuation from intervention if any of the following occur during the study:

- Serious hypersensitivity reaction;
- Severe uncontrolled infection;
- Use of disallowed medication as defined in Section 6.5;
- Pregnancy or planned pregnancy; or
- Alexion or the Investigator deems it is necessary for the participant.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Stopping Criteria

7.2.1. Individual Stopping Rules

Study drug administration to an individual participant will be continued, delayed, temporarily suspended, or discontinued immediately (if applicable) and permanently if AEs related to the study drug occur as detailed in Table 20:

Table 20: Individual Stopping Rules

Adverse Events Related to ALXN1820	Action[a]
Moderate (CTCAE Grade II except for injection site reactions, QT interval prolongation, hematology, and liver function, which are specified below)	Study drug administration may be continued, delayed, temporarily suspended, or discontinued in accordance with Investigator's clinical judgment, in consultation with the Sponsor
Injection site reactions: Moderate (CTCAE Grade II)	Study drug administration will be discontinued if not reduced at least to Grade 1 by the time of next dose
QT interval prolongation: A prolongation of the uncorrected QT interval of greater than 500 ms, using consistent, technically valid triplicate ECG	Study drug administration will be discontinued
Hematology: Hb drop to absolute values of < 10 g/dL (100 g/L) Platelet count drop to absolute values of < 75,000/mm^3	
Severe (CTCAE Grade III)	
CTCAE Grade IV **Or** Serious **Or** Hy's law: ALT or AST value > 3 × ULN together with bilirubin increase > 2 × ULN, without other evidence of cholestasis **Or** ALT or AST value > 8 × ULN ALT or AST value > 3 × ULN, and symptomatic	

[a] Actions are only relevant for multiple dosing regimens where additional doses are planned for administration.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; Hb = hemoglobin; IV = intravenous; ULN = upper limit of normal.

7.2.2. Cohort and Study Safety Stopping Rules

A cohort and other cohort with a dose at an equal or higher level will be stopped or not initiated if any of the following occurs (Table 21):

Table 21: Cohort and Study Stopping Rules

Adverse Events Related to ALXN1820	Showing Signs of Reversibility	Number of Participants	Action
Moderate (CTCAE Grade II except for injection site reactions, QT interval prolongation, hematology, and liver function, which are specified below)	Yes	≥ 3 in 1 SOC ≥ 4 total in different SOCs	Cohort: Dosing of the remainder of the cohort suspended Study: Dosing of equal or higher doses suspended Dosing of lower dose levels can continue Continuation of dosing of equal or higher doses requires a substantial amendment[b]
	No	≥ 2 total in different SOCs	
Injection site reactions: Moderate (CTCAE Grade II)	No[a]	≥ 3	
QT interval prolongation: A prolongation of the uncorrected QT interval of greater than 500 msec, using consistent, technically valid triplicate ECG	NA	≥ 2	
Hematology: Hemoglobin drop to absolute values of < 10g/dL (100 g/L). Platelet count drop to absolute values of < 75,000/mm^3	NA	≥ 2	
Severe (CTCAE Grade III)	NA	2	Study suspended (all dosing [lower, equal or higher doses] suspended) Continuation of the cohort or study requires a substantial amendment[b]
CTCAE Grade IV **Or** Serious **Or** Hy's law: ALT or AST value > 3 × ULN together with bilirubin increase > 2 × ULN, without other evidence of cholestasis **Or** ALT or AST value > 8 × ULN ALT or AST value > 3 × ULN, and symptomatic	NA	1	

[a] For injection-site reactions, a cohort and/or the study will be suspended when ≥ 3 participants are observed. If all but 1 affected participant show signs of recovery (at least to Grade 1), cohort and study continuation can then proceed. If ≥ 2 participants remain at Grade 2 after the minimum data review period, the period of observation should be extended for up to 168 hours. If all but 1 affected participant show sign of recovery (at least to Grade 1), cohort and study continuation can then proceed. If ≥ 2 affected participants remain at Grade 2 after the first 168-hour extension period, the SRC will make the decision to either prolong further the observation period up to a maximum of another 168 hours, or suspend the remainder of the cohort and study. At the end of the second extension period, if all but 1 participant show sign of recovery (at least to Grade 1), cohort and study continuation can then proceed. If, however, ≥ 2 affected participants remain at Grade 2, cohort and study will be suspended.

[b] A substantial amendment may include an amendment to the protocol, the ICF, or other study-related documents as appropriate.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; Hb = hemoglobin; ICF = informed consent form; IV = intravenous; NA = not applicable; SOC = System Organ Class; SRC = Safety Review Committee; ULN = upper limit of normal.

7.3. Participant Discontinuation/Withdrawal From the Study

All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and eCRF.

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

In order to meet minimum data requirements for SRC meetings, participants who withdraw consent from the study within the first 14 days may be replaced. At the Sponsor's discretion, and after consultation with the SRC, up to 18 additional participants may be enrolled as replacement participants if a participant discontinues prior to Day 43 for reasons other than drug-related AEs.

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, email, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA, if consistent with site SOP.

8.1. Efficacy Assessments

No efficacy assessments will be obtained during this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examination

A complete physical examination will include, at a minimum, assessments of the general appearance; skin; head, ears, eyes, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limbs; central nervous system; and musculoskeletal system. Weight will also be measured and recorded.

Height and BMI will be recorded at Screening only.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Vital sign measurements will be taken after the participant has been resting in the supine or semi-recumbent position for at least 5 minutes and will include temperature (tympanic or oral), respiratory rate, supine blood pressure, and pulse. Orthostatic (standing) blood pressure will only be measured at Screening.

The timing of vital sign measurements is described in the SoA (Section 1.3).

Out of range blood pressure or pulse measurements will be repeated at the Investigator's discretion. Confirmed, clinically significant vital sign measurements will be recorded as AEs.

8.2.3. Electrocardiograms

Triplicate 12-lead ECGs will be recorded at the time points described in the SoA (Section 1.3) to obtain heart rate, PR, QRS, and QT intervals. 12-lead ECG recordings will be made after the participants have been resting in a supine position for at least 10 minutes.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession but no more than 2 minutes apart.

8.2.3.1. Safety Review of 12-lead Electrocardiograms

All recorded ECGs will be reviewed by the Investigator or qualified designee. If a participant shows an abnormal ECG, additional safety recordings (including the use of 5- or 12-lead Holter equipment) may be made, and the abnormality will be followed to resolution.

8.2.3.2. 24-hour Holter Electrocardiograms/Real Time Display (Cardiac Telemetry)

Holter recording will be performed up to 3 months prior to Day 1, and telemetry will be used on dosing days as specified in Section 1.3. Electrocardiogram telemetry will be monitored by the Investigator or qualified member of clinical staff. This will allow the extraction of 10-second 12-lead ECG data files, which can be transferred onto the MUSE. All ECG files so acquired will then be analyzed and over-read using the same process as for any other 12-lead ECG. The ECG Holter/telemetry reports will be archived with study documents.

8.2.4. Clinical Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. Clinical and laboratory assessments will be performed by a local laboratory to assess safety.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

The maximum total blood volume collected from participants participating in this study will not exceed 500 mL every 16 weeks.

8.2.5. Clinical Safety Laboratory Assessments

8.2.5.1. Virus Serology

Blood samples collected at Screening will be analyzed for HIV-1, HIV-2, HbsAg, hepatitis B core antibody (anti-HBc IgG + IgM, if IgG positive), and hepatitis C virus antibody titers.

8.2.5.2. Vaccine Titer

A titer against meningococcal serogroups A, C, W135, and Y will be performed at Screening (Section 1.3). Titer measurements will be used to exclude participants without a confirmed immune response. For participants with a documented vaccine titer indicating sufficient protection within 6 months prior to Screening, the titer does not need to be repeated.

8.2.5.3. Tuberculosis Testing

Serum samples for a QuantiFERON®-TB test will be obtained at Screening as specified in the SoA (Section 1.3).

8.2.6. Pregnancy

No studies of ALXN1820 have been conducted in pregnant women. Pregnant or breastfeeding females are excluded from the clinical study. Participants enrolled in the study, and a spouse or partner, will use a highly effective or acceptable method of contraception. Refer to Section 10.4 for additional details.

Following the last study visit, female participants are required to perform a monthly pregnancy test until at least 5 months after the last dose. For the convenience of the participant, a serum sample will be collected when there is a clinic visit, otherwise, urine test need to be done at home (when there is no clinic visit) and the result is to be reported to the Sponsor within 3 days.

Pregnancy data from female participants and female spouses/partners of male participants will be collected from the signing of the ICF until the outcome of the pregnancy is known, which might occur after the last follow-up visit. Any female participant who becomes pregnant while participating in the study will be discontinued from the study intervention. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.4.

8.2.7. Injection or Infusion Site Evaluation

Injection/infusion of antibodies has been associated with injection/infusion reactions, with onset typically during or shortly after completion of the injection/infusion. For this reason, participants will be carefully observed during each injection/infusion.

Subcutaneous injection/infusion or IV infusion-site evaluations will be performed at the time points specified in the SoA (Section 1.3). Injection/infusion site reactions will not be recorded as AEs unless deemed clinically significant.

8.2.8. Injection/Infusion-associated Reactions

Injection/infusion-associated reactions are defined as systemic AEs (eg, fever, chills, flushing, alterations in heart rate and blood pressure, dyspnea, nausea, vomiting, diarrhea, and generalized skin rashes) occurring during or within 24 hours of the start of IV or SC injection/infusion that are assessed by the Investigator to be related to the study drug.

8.2.9. Vaccine and Antibiotic Prophylaxis

To mitigate the risk of *N. meningitidis* infection associated with complement inhibition, all participants in this study will be administered the following:

1. A MCV4 vaccination at least 56 days prior to dosing of ALXN1820 on Day 1 (if not vaccinated with MCV4 within the last 2 years and 6 months, or if participants 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 CAP assay). If penicillin is not tolerated, or the participant has a penicillin allergy, second-line antibiotics will be initiated at the discretion of the Investigator.

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, participants 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 participants' compliance with the antibiotic prophylaxis regimen.

Table 22: Predicted ALXN1820 CAP Activity Inhibition and Duration of Antibiotic Prophylaxis Estimates

Cohort	Planned Dose	Duration of Complete Inhibition of CAP Activity (Days After First Dose)	Time of CAP Activity Return to 80% Baseline (Days After First Dose)	Anticipated Antibiotic Prophylaxis Duration (Days)
1	12.5 mg SC	0	0	22
2	50 mg SC	4	9	29
3	150 mg SC	16	26	43
4	450 mg SC	39	54	57
5	450 mg IV	39	53	57
6	1200 mg SC	67	84	85
7	TBD (≤ 2250 mg SC)			
8 and 9	150 mg SC QW × 5 in healthy participants and participants of Japanese descent	66 (after the 1st dose)	83 (after the 1st dose)	113

Cohort	Planned Dose	Duration of Complete Inhibition of CAP Activity (Days After First Dose)	Time of CAP Activity Return to 80% Baseline (Days After First Dose)	Anticipated Antibiotic Prophylaxis Duration (Days)
10	TBD mg SC QW × 3			113

Abbreviations: CAP = complement alternate pathway; IV = intravenous; QC = once weekly; SC = subcutaneous; TBD = to be determined

Analysis of serum samples to establish actual complement activity will be performed using a CAP assay (Wieslab AP assay). The analysis will take place continuously and the results will be used in an interim PK/PD model to update the predicted duration of CAP inhibition. Results will be used to confirm that complement activity has returned to normal; once confirmed, prophylactic antibiotic treatment can be stopped. Antibiotics will be continued in all participants in a cohort, until complement activity for every participant in the cohort has normalized, in order to preserve blinding. All participants will be closely monitored for signs of infection throughout the study.

8.2.10. Participant Safety Card

Participants will always also be provided a safety card to carry with them. Risk of meningococcal infection will be explained and discussed with participants 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 participants during the course of the study, additional discussion and explanation of the potential risks, signs, and symptoms, as described in the ICF, will take place at specific time points throughout the study as noted in the SoA (Section 1.3).

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

All AEs will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3 (Appendix 3).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the last follow-up visit.

All SAEs will be recorded and reported to Alexion or the designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 (Appendix 3). The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE data after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow-up on each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/IECs, and Investigators.

Suspected unexpected serious adverse reactions (SUSARs) must be reported according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than that specified in the protocol will be considered an overdose. Any blinded dose greater than that specified in the protocol will be considered a suspected overdose. There is no specific treatment or antidote for overdose.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

In the event of an overdose or suspected overdose, the Investigator should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for any AE/SAE.
3. Obtain a plasma sample for PK/PD analysis if requested by the Medical Monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Whole blood samples will be collected for measurement of serum concentrations of ALXN1820 as specified in the SoA (Section 1.3). Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Alexion. The total blood volume will not exceed the volume limit for healthy participants (Section 8.2.4). The timing of sampling may be altered during the course of the study, based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of ALXN1820. Samples collected for analyses of ALXN1820 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to dysregulated complement activity.

Study intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Pharmacodynamics

Whole blood samples will be collected for measurement of serum total and free properdin concentrations, CAP activity, CCP activity, and potentially other measures of complement activation as specified in the SoA (Section 1.3). Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Alexion. The total blood volume will not exceed the blood volume limit for healthy participants (Section 8.2.4). The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PD of ALXN1820. Samples collected for analyses of ALXN1820 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Unused samples may be retained for a period of up to 5 years to perform additional assessments as necessary.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Collection of samples for biomarker research (eg, exploratory) is also part of this study. See Section 10.5, Appendix 5 for details.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3):

- Blood
- Urine

Samples will be collected for testing that may include, but are not limited to, markers of complement dysregulation (eg, Factor Ba), vascular inflammation (eg, soluble tumor necrosis factor receptors), and endothelial activation/damage (eg, soluble vascular cell adhesion molecule-1, thrombomodulin).

8.9. Immunogenicity

Antibodies to ALXN1820 (ADAs) will be evaluated in whole blood samples collected from all participants according to the SoA (Section 1.3)

Serum samples will be screened for ADAs that bind to ALXN1820. If the screen is positive, the sample will be analyzed using a confirmatory ADA assay and the titer of confirmed positive samples will be reported. The detection and characterization of antibodies to ALXN1820 will be performed using a validated assay method by or under the supervision of the Sponsor. Samples may be further characterized to determine the titer and the presence of neutralizing antibodies (as an exploratory analysis) if deemed necessary. Additional samples may be collected during the study if warranted and agreed upon between the Investigator and the Sponsor.

Subjects who remain ADA positive for ALXN1820 at the end of the study will be requested return to the clinic for blood collection to assess ADA for up to a year following the end of the study or until ADA returns to baseline levels (for a maximum of 3 follow-up visits).

The actual date and time (24-hour clock time) of each sample will be recorded. Samples may be banked for a period of up to 5 years in order to perform additional safety assessments, as necessary.

Detailed instructions on the procedure for collecting, processing, storing, and shipping serum samples for immunogenicity analysis will be provided in the laboratory manual.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data will not be evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Not applicable.

9.2. Sample Size Determination

The sample size is based on PK considerations. A sample size of up to 80 participants (8 participants per cohort) will be enrolled.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Safety	All participants who receive at least 1 dose of study drug
Pharmacokinetic	All participants who receive at least 1 dose of the study drug and have at least 1 post-dose PK sample.
Pharmacodynamic	All participants who receive at least 1 dose of study drug and who have evaluable properdin concentration, CAP or CCP activity data
Immunogenicity	All participants who have a predose and at least 1 postdose ADA sample collected

Abbreviations: ADA = antidrug antibody; CAP = complement alternative pathway; CCP = complement classical pathway; PK = pharmacokinetic(s).

9.4. Statistical Analyses

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.

A statistical analysis plan (SAP) will be developed and finalized before first data cutoff/database lock and will further describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data as appropriate. This section is a high-level summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

No efficacy analyses will be performed for this study.

9.4.2. Safety Analyses

The primary endpoint for the study is safety and tolerability.

All safety analyses will be performed on the Safety Population and will be reported by each cohort and treatment arm (ie, ALXN1820 or placebo). In addition, healthy participants on placebo treatment will be pooled together across cohorts.

Safety analyses will include an analysis of all treatment-emergent AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics. No inferential statistical analyses are planned on the safety parameters of this study. The prevalence of AEs and SAEs will be summarized, by SOC and Preferred Term for each cohort and treatment arm and overall, within each treatment arm, and by relationship to study drug. Adverse events will also be summarized by cohort and treatment arm, and overall, within each treatment arm, and by severity. Serious AEs and AEs resulting in withdrawal from the study will be listed. Participants having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity tables, a participant's most severe event within a category will be counted.

Changes from baseline in vital sign measurements and laboratory assessments (eg, chemistry, cell blood count with differential, and urinalysis) will be summarized by each cohort and treatment arm, and overall within placebo treated healthy participants. Laboratory parameter values will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE, v5.0, published 27 Nov 2017). Shift tables by cohort and treatment arm will be produced for these laboratory parameters. These tables will summarize the number of participants with each baseline grade relative to the reference ranges and changes to the worst highest grade assessed postdose during the study.

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

9.4.2.1. ECG Analysis

Intensive cardiac assessments will be performed in the Safety Population using food effects on ECG to establish assay sensitivity. Analysis of drug related QT/QTc interval changes relative to plasma PK concentrations will be conducted on all dose regimens. The principles of this analysis follow the statistical methods described by Garnett et al. (Garnett, 2018). The ECG utilized for this analysis requires adjudication by qualified cardiologists in accordance with principles set out in the International Conference on Harmonisation (ICH) E14 guideline and subsequent Q&A documents. All ECG recordings will be in triplicate and compliant with the correct recording and manual adjudication of ECG in thorough QT/QTc studies. The ECG analyses will be based on adjudicated selected triplicates from each time point.

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 and treatment arm.

An outlier analysis will be performed that will summarize the absolute count, frequency and percentage of participants who meet any of the following outlier criteria at each visit by cohort and treatment arm:

- 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

Detailed analysis will be specified in the SAP or a separate ECG analysis plan.

9.4.3. Other Analyses

9.4.3.1. Pharmacokinetic Analyses

All PK analyses will be performed on the PK Population and will be reported by cohort and study intervention within each cohort (ie, ALXN1820 or placebo).

The individual serum concentration data from participants who receive ALXN1820 SC or ALXN1820 IV with actual sampling dates and times will be used to derive the PK parameters by noncompartmental analyses methods.

The following PK parameters as appropriate and data permitting will be derived:

Parameters	Dosing Regimen	Definitions
C_{max}	SD, MD	Maximum observed serum concentration
t_{max}	SD, MD	Time to maximum observed serum concentration
AUC_t	SD, MD	Area under the serum concentration versus time curve from time 0 to the last quantifiable concentration
AUC_{tau}	MD	Area under the concentration-time curve during the dosing interval
$AUC_{0-\infty}$	SD	Area under the concentration-time curve from time 0 (dosing) to time infinity
$t_{½}$	SD, MD	Terminal elimination half-life
λ_z	SD, MD	Terminal-phase elimination rate constant
CL or CL/F	SD	Total body clearance or apparent clearance
V_d or V_d/F	SD	Volume of distribution or apparent volume of distribution
F	SD	Absolute bioavailability
R_{ac}	MD	Accumulation ratio

Abbreviations: SD = single-dose; MD = multiple-dose

The absolute bioavailability for the ALXN1820 SC cohorts will be defined by the ratio of the geometric means for the $AUC_{0-\infty}$ (area under the concentration-time curve from time 0 [dosing] to time infinity) parameter for the ALXN1820 SC cohort over the ALXN1820 IV cohort. For the absolute bioavailability estimates, a 95% CI for each of the ratio of the geometric means will be provided.

Additional details will be provided in the SAP.

9.4.3.2. Pharmacodynamic Analyses

All PD analyses will be performed on the PD Population and will be reported by cohort and study intervention within each cohort (ie, ALXN1820 or placebo).

The PD effects of all ALXN1820 SC and ALXN1820 IV doses administered will be evaluated by assessing changes in serum total and free properdin concentrations and CAP activity using the Weislab AP assay. In addition, an exploratory assessment of CCP activity and other measures of properdin activity over time may be considered as deemed appropriate.

Biomarker assays may be conducted as an exploratory analysis on collected samples.

9.4.3.3. Immunogenicity Analysis

For assessment of immunogenicity, the incidence of confirmed positive ADAs will be summarized. Additionally, following confirmation of positive ADAs, samples will be assessed for ADA titer and presence of neutralizing antibodies (if possible).

9.4.3.4. Interim Analyses

Interim assessments will be performed as follows:

1. An assessment of all available PK/PD and immunogenicity data will be performed when all participants in Cohorts 4 and 5 reach Day 29. These data will be used to project the exposure and duration of properdin and CAP activity inhibition (not to exceed 70 days) at the highest single dose planned in the study (Cohort 7) and the highest multiple dose in the study (Cohort 10).
2. CAP activity will be continuously analyzed and will be used to estimate the time of CAP activity returning to baseline for each individual participant based on PK/PD modeling.

Refer to a separate PK/PD analysis plan for further details on the interim assessments.

Further assessments of available data may be performed to inform Phase 2 study design in patients. Details of this analysis will be presented in the SAP.

No formal interim analysis for futility is planned.

9.5. Safety Review Committee (SRC)

An SRC, consisting of Investigators from participating sites, Safety physician, Medical Monitor, Study Statistician, and Clinical Pharmacologist, will evaluate the study data at prespecified time points for participant safety and make recommendations on dose escalation, dose modification, or termination of the study. In the event a significant safety issue is identified, an ad hoc SRC meeting will be convened within 24 hours following its identification (see SRC charter for description of membership, schedule of meetings, data required for each safety review, and requirements for documenting meeting discussions and outcome).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator to obtain signed (written or electronic signature) informed consent from all study participants prior to any study-related procedures including screening assessments.
- The Investigator or his/her representative will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent or a certified translation if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that signed (written or electronic) informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form(s).
- Participants must be reconsented to the most current version of the informed consent form(s) during their participation in the study.
- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Signed (written or electronic) consent [or assent] forms must remain in each participant's study file and must be available for verification at any time.
- Participants who are rescreened are required to sign a new ICF (see Section 5.4).

10.1.4. Data Protection

- Participants will be assigned a unique identifier by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the participants who will be required to give consent for their data to be used as described in the informed consent

- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the study intervention, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 participant.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Source documents are filed at the Investigator's site.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the first participant is consented.

Alexion reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the end of study or early discontinuation visit, all data have been collected and entered into electronic data capture (EDC) system, all required documents and study supplies have been collected, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12 to 18 months of the primary evaluation date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and to provide comments.

  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.

- In general, primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.
  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.
- Alexion will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 23 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: Women of childbearing potential should only be enrolled after a negative serum pregnancy test result at Screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB/IEC and should be performed per the time points specified in the SoA (Section 1.3).

Table 23: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Platelet count • Red blood cell (RBC) count • Hemoglobin • Hematocrit • RBC indices (MCV, MCH, %reticulocytes) • White blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Clinical chemistry[a]	• Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) • Alkaline phosphatase • Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) • Blood urea nitrogen (optional) • Calcium • Creatinine • Creatine kinase • Hemoglobin A1C • Potassium • Sodium • Serum albumin • Total and direct bilirubin • Total protein • Urea
Coagulation	• Prothrombin time, partial thromboplastin time, international normalized ratio
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if any leucocytes, more than a trace protein, nitrites, and blood [if not menstruating] are abnormal)
Complement activity	• Change in CAP activity using the Wieslab AP assay • Change in CCP and LP activities
Other screening tests	• Serum QuantiFERON®-TB test • Alcohol breath and urine drug screen (to include at minimum: amphetamines, barbiturates, benzodiazepines cocaine, opiates, phencyclidine, methamphetamine, 3,4

Table 23: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
	methylenedioxy-methamphetamine, methadone, and tetrahydrocannabinol [cannabinoids]) • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b] • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Human immunodeficiency virus (HIV)-1 and HIV-2 antibodies, hepatitis B surface antigen (HbsAg), anti-HBc IgG + IgM (if IgG positive) and hepatitis C virus antibodies (anti-HCV) • Vaccine titer (meningococcal serogroups A, C, W135, and Y)

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.2. All events of ALT ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (INR) > 1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[b] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Abbreviations: CAP = complement alternative pathway; CCP = complement classical pathway; HIV= human immunodeficiency virus; IEC = Independent Ethics Committee; IRB = Institutional Review Board; LP = lectin pathway; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; SAE = serious adverse event.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events Not Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening

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

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

4. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

Recording of AE and/or SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017:

- 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

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study intervention caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study intervention.
  - Related: There is a reasonable possibility the study intervention caused the AE.
    - The AE has a temporal relationship to the administration of the study intervention.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study intervention.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to Sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor or Delegate via Paper Safety Reporting Form

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours awareness.
- SAEs will be reported using the Safety Reporting Form and submitted to Alexion Global Drug Safety (GDS). The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the

SAE Reporting to Sponsor or Delegate via Paper Safety Reporting Form
information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below: – Email: [redacted] or Fax: [redacted] • Additional follow-up information, if required or available, should be entered into the eCRF and sent to Alexion GDS within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above. • For all SAEs, the Investigator must provide the following: – Appropriate and requested follow-up information in the time frame detailed above – Causality of the SAE(s) – Treatment of/intervention for the SAE(s) – Outcome of the SAE(s) – Medical records and laboratory/diagnostic information • All paper forms and follow-up information submitted to Alexion GDS **must** be accompanied by a cover page signed by the Investigator. • Paper source documents and/or reports should be kept in the appropriate section of the study file.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range, as per local laboratory reference ranges, may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Female participants on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

10.4.2.1. Female Participants

Female participants of non-childbearing potential are exempt from contraception requirements. Female participants of childbearing potential, if heterosexually active, must use highly effective contraception as defined below. Antibiotic prophylaxis may be administered during this study (see Section 8.2.9), which can compromise the efficacy of hormonal contraception. Therefore, participants using hormonal contraception must 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
- Vasectomized male partner (with documented evidence of azoospermia if possible)
- Sexual abstinence (in line with the preferred and usual lifestyle of the participant)

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal do NOT meet the definition of abstinence. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

Participants must use an appropriate form of highly effective contraception as stated for females of childbearing potential who are sexually active, from one complete menstrual cycle prior to the first intercourse with a male and continue until for at least 5 months after last dose.

10.4.2.2. Male Participants

To prevent transfer of study drug to a male or female partner or fetus/baby, all male participants including those who have had a vasectomy (even with documented evidence of azoospermia) must agree to use a barrier method (male condom) during intercourse with a male or female partner from the time of screening for at least 5 months after last dose.

Male participants, if sexually 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). Barrier contraception is required even with documented medical assessment of surgical success of a vasectomy. Female spouses or partners of male participants who are of childbearing potential must use highly effective contraception as defined above.

Contraception for all cohorts must start during Screening and continue for at least 5 months after last dose.

Male participants must not donate sperm and female participants must not donate ova for at least 5 months after last dose.

10.4.3. Collection of Pregnancy Information

- Pregnancy data will be collected during this study for all female participants and any female spouse/partner of a male participant, who become pregnant. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.
- If a female participant or a male participant's female sexual partner of childbearing potential becomes or is found to be pregnant while being treated or exposed to study drug, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion or designee via the same method as SAE reporting (Section 10.3). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion or designee. If additional follow-up is required, the Investigator will be requested to provide the information.
- Exposure of an infant to a Sponsor product during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding" form) and any AEs experienced by the infant must be reported to Alexion or designee via facsimile or email.
- A pregnancy in and of itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs (Section 8.2.6).
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5. Appendix 5: Biomarkers

- Whole blood samples will be collected for biomarker analyses and the data will be used for research (eg, exploratory) related to ALXN1820. The samples may also be used to develop tests/assays including diagnostic tests related to ALXN1820 and/or others of this study intervention class.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to ALXN1820 to understand study disease or related conditions. Analyses may be done to establish normal range of values for biomarkers which may include, but are not limited to, markers of complement dysregulation (eg, Factor Ba), vascular inflammation (eg, soluble tumor necrosis factor receptors), and endothelial activation/damage (eg, soluble vascular cell adhesion molecule-1, thrombomodulin).
- The results of biomarker analyses may be reported in the clinical study report or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on ALXN1820 continues but no longer than 5 years or other period as per local requirements.

10.6. Appendix 6: Management of Potential Adverse Events During Study Drug Administration

Infusion/injection-associated reactions are a potential risk with the use of therapeutic protein products; these reactions can be nonimmune or immune mediated (eg, hypersensitivity reactions). Signs and symptoms may include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Signs and symptoms of hypersensitivity or allergic reactions may include hives, swollen face, eyelids, lips, or tongue, or trouble with breathing. An acute infusion reaction algorithm will be used to manage infusion-associated reactions (See Study Operation Manual).

All infusion/injection-associated reactions will be reported to the Investigator and qualified designee. The Investigator and qualified designee are responsible for detecting, documenting, and recording events that meet the definition of AE or SAE and remain responsible for following up events that are serious, considered related to the study drug or study procedures, or that caused the participant to discontinue ALXN1820.

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

Before study drug administration, the treating physician and other appropriate personnel must make certain that medication (ie, adrenaline, inhaled beta agonists, antihistamines, corticosteroids) and other equipment to treat anaphylaxis are readily available. The infusion must be stopped immediately if Grade ≥ 3 allergic/hypersensitivity reactions (including drug fever) or Grade ≥ 3 cytokine release syndrome/acute infusion reaction occurs. Alexion must be notified within 24 hours of any infusion reaction requiring interruption or discontinuation of study drug. Participants who experience a reaction during the administration of study drug should be treated according to institutional guidelines.

For a Grade 2 infusion reaction, the infusion should be temporarily stopped and treatment with an antihistamine and acetaminophen/paracetamol/NSAIDs may be considered. If the participant's signs and symptoms have resolved (with or without administration of the above medication), the infusion may be restarted. However, the participant should be infused at a slower rate and be monitored closely for any signs and symptoms of infusion reactions during the remainder of the infusion. Participants experiencing an infusion reaction should be observed in the clinic until resolution of the reaction, or until the Investigator determines the participant is no longer at risk. Participants who experience a severe reaction during administration of study drug resulting in discontinuation of study drug should undergo all scheduled safety, PK, and PD evaluations required by the protocol, if possible.

If anaphylaxis occurs, please follow local guidance for the management. In the event that there is no local guidance, please see suggested management as follow:

Administration of epinephrine (1/1000, 0.3 mL to 0.5 mL, or equivalent) should be considered. In the case of bronchospasm, treatment with an inhaled beta agonist also should be considered. Participants administered an antihistamine for the treatment or prevention of an infusion reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

Table 24: Grading and Management of Allergic or Infusion-Related Reactions

Adverse Event	Grade				
	1	2	3	4	5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention required	Death
Allergic reaction	Transient flushing or rash, drug fever < 38.0°C. Intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention required	Death
Anaphylaxis	–	–	Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention required	Death
Cytokine release syndrome	Mild reaction: infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death

Abbreviations: IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs
Source: NCI CTCAE Version 5.0.

10.7. Appendix 7: COVID-19 Risk Assessment

ALXN1820 blocks properdin, which could result in immunosuppression; therefore, there is a theoretical concern that the risk for infection may be higher than in study participants who are not on immunosuppression. However, there is no specific data to inform this risk further. The Principal Investigator will balance the risk/benefit considerations in their participants, taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 25.

Table 25: Potential Risks and Mitigation Measures due to COVID-19

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

Abbreviations: COVID-19 = Coronavirus Disease 2019; eCRF = electronic case report form

10.8. Appendix 8: Abbreviations

Table 26: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
ADA	antidrug antibody
AE	adverse event
AP	alternative pathway
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 (dosing) to time infinity
AUC_{0-168}	area under the concentration-time curve from time 0 to 168 hours
BMI	body mass index
C5	complement component 5
CAP	complement alternative pathway
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed serum concentration
CONSORT	Consolidated Standards of Reporting Trials
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
% CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDS	Global Drug Safety
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
HBc	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
Ig	immunoglobulin
IRB	institutional review board
IV	intravenous(ly)
K_D	dissociation constant
mAb	monoclonal antibody
MABEL	minimally anticipated biologically effective dose
MAD	multiple ascending dose
MCV4	tetravalent meningococcal conjugate vaccine
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PI	prediction interval
PK	pharmacokinetic(s)

Table 26: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
QTcF	QT interval corrected using the Fridericia's formula
QW	once weekly
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TMDD	target-mediated drug disposition
ULN	upper limit of normal

10.9. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Original protocol	Not applicable	09 Oct 2020	Not applicable

11. REFERENCES

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