Statistical Analysis Plan for Interventional Studies
Sponsor: Alexion Pharmaceuticals, Inc.; Protocol No.: ALXN1820-HV-101

NCT #: NCT04631562

- Statistical Analysis Plan for Interventional Studies

Text only

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Sponsor Name: Alexion Pharmaceuticals, Inc.

Protocol Number: ALXN1820-HV-101
Protocol Title: Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study of Subcutaneous and Intravenous ALXN1820 in Healthy Participants

Protocol Version and Date: (DD-Mmm-YYYY): Version 1.0, 09-Oct-2020
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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	27-Aug-2021	███████████	Initial Release Version
2.0	28-Nov-2022	███████████	Added a sentence explaining that for Cohort 7, doses higher than 2250 mg will require SRC review and regulatory agency and EC approval prior to implementing a substantial amendment to the protocol, and for cohort 10, any increase in total number of doses or change in dosing interval will require SRC review and regulatory agency and EC approval prior to implementing a substantial amendment to the protocol. Added a sentence noting that Alexion will be performing a safety analysis of Cohort 6. Removed the subgroup analysis, as no subgroup analysis is being performed, instead all Japanese subjects were enrolled to one cohort (cohort 9).

I confirm that I have reviewed this document and agree with the content.

Approvals		
Syneos Health Approval		
██████████████████	████████████ Signature	Nov 30, 2022 Date (DD-Mmm-YYYY)
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████████████	████████████ Signature	Nov 30, 2022 Date (DD-Mmm-YYYY)
Alexion Pharmaceuticals, Inc. Approval		
█████████████ Name, Title Sponsor Contact	████████	29-Nov-2022 | 11:35 EST Date (DD-Mmm-YYYY)

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1.   Glossary of Abbreviations

Abbreviation	Description
%AUC$_{extrap}$	AUC extrapolated from time t to infinity as a percentage of total AUC$_\infty$
λ_z	Apparent terminal-phase elimination rate constant
ADA	Antidrug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AP	Alternative Pathway
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the serum concentration versus time curve
AUC$_t$	Area under the serum concentration versus time curve from time 0 to the last quantifiable concentration
AUC$_t$_n	Dose-normalized AUC$_t$
AUC$_\infty$ / AUC$_{inf}$	Area under the serum concentration versus time curve from zero to infinity
AUC$_\infty$_n / AUC$_{inf}$_n	Dose-normalized AUC$_\infty$ / AUC$_{nf}$
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CAP	Complement Alternative Pathway
CCP	Complement Classical Pathway
CFB	Change From Baseline
CI	Confidence Interval
CL/F	Apparent Oral Clearance
CLP	Complement Lectin Pathway
C$_{max}$	Maximum Observed Concentration
C$_{max}$_n	Dose-normalized C$_{max}$
COVID-19	Coronavirus Disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System

CV	Coefficient of Variation
ECG	Electrocardiogram
eDISH	Evaluation of drug-induced serious hepatotoxicity
EOS	End of Study
ET	Early Termination
F_{rel}	Relative bioavailability between test and reference treatments
FSH	Follicle-stimulating Hormone
GMR	Geometric Mean Ratio
HbA1c	Glycated Hemoglobin
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IGS	Immunogenicity Set
IQR	Interquartile Range
IP	Investigational Product
IV	Intravenous
MAD	Multiple Ascending Dose
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MCV4	Tetravalent Meningococcal Conjugate Vaccine
MD	Multiple-Dose
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable
NAb	Neutralizing Antibodies
NCI	National Cancer Institute
PD	Pharmacodynamic(s)
PDS	Pharmacodynamic Set
PK	Pharmacokinetic(s)

PKS	Pharmacokinetic Set
PT	Preferred Term
Q1	1st Quartile
Q3	3rd Quartile
QC	Quality Control
QTcF	QT interval corrected for heart rate using Fredericia's formula
QW	Once Weekly
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Single Dose
STD	Standard Deviation
SGPT	Serum Glutamic-pyruvic Transaminase
SGOT	Serum Glutamic-oxaloacetic Transaminase
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
SS	Safety Set
$t_{1/2}$	Terminal Elimination Half-life
TBD	To Be Determined
TEAE	Treatment-emergent Adverse Event
TERAE	Related Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
TFL	Table, Figure and Listing
t_{max}	Time to Maximum Concentration
ULN	Upper Limit of Normal

V_d/F	Apparent Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

2.   Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1.   Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2.   Timings of Analyses

The primary analysis of safety, tolerability, pharmacokinetics (PK)/pharmacodynamics (PD) and immunogenicity is planned after all participants complete the final study visit or terminate early from the study. The immunogenicity analysis will summarize the presence of confirmed positive antidrug antibodies (ADAs). Additionally, following confirmation of positive ADAs, samples will be assessed for ADA titer and presence of neutralizing antibodies (if possible).

An interim analysis of all available safety and toleratbility data will be performed by Alexion when all participants in Cohort 6 reach Day 15. This analysis will be used to support regulatory activity which is outside the scope of this SAP and will not be performed by Syneos Health.

An interim analysis, of all available PK/PD data, will be performed when all participants in Cohorts 4 and 5 reach Day 29. This data will be used to project the exposure and duration of properdin and Complement Alternative Pathway (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). Doses higher than 2250 mg (in Cohort 7) and an increase in total number of doses or change in dosing interval (in Cohort 10) will require SRC review and regulatory agency and EC approval prior to implementing a substantial amendment to the protocol. Further assessments of available data may be performed to inform Phase 2 study design in patients. The interim analysis is outside the scope of this SAP and will not be performed by Syneos Health.

A safety review committee (SRC), consisting of the Investigator, 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. A further description of the SRC analyses can be found in the SRC charter Version 1.0 dated 31-Mar-2021.

3.   Study Objectives

Objective	Endpoints
Primary	
To assess the safety and tolerability of ALXN1820 subcutaneous (SC) and ALXN1820 intravenous (IV)	Safety assessed by incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (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 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 Details/Design

4.1.   Brief Description

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 of 10 cohorts 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). The dosing cohorts are presented in Table 1.

Table 1: 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.

If it is seen during the interim PK/PD analysis that Cohort 6 (ALXN1820 1200 mg dose) suppresses properdin and CAP activity for approximately 68 days, it may be decided not to initiate Cohort 7.

The first two 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 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. 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 (*e.g.*, 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 of dosing cohorts is presented in Figure 1.

Figure 1: ALXN1820-HV-101 Schematic
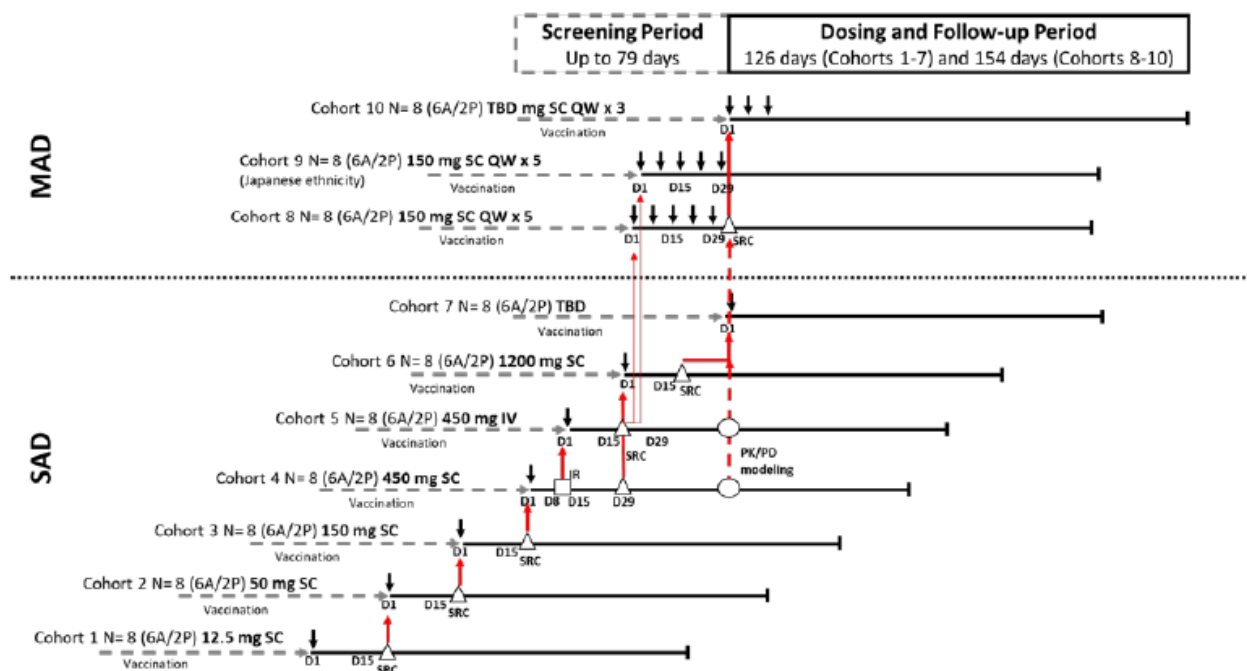
Note: black arrow(s) indicate dose(s) given; red arrow indicates decision for dose escalation.
Abbreviations: A = active (ALXN1820); D = day; IR = Investigator review; IV = intravenous; MAD = multiple ascending dose; N = number of participants; P = placebo; PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly; SAD = single ascending dose; SC = subcutaneous; SRC = Safety Review Committee; TBD = to be determined.

4.2. Participant Selection

Inclusion and exclusion criteria will be confirmed at Screening.

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

Refer to Section 5 of the Protocol for a complete list of requirements for inclusion and exclusion of participants.

4.3.   Determination of Sample Size

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

4.4.   Treatment Assignment and Blinding

- This is a double-blind study where, in order to minimize selection bias in treatment assignment, each participant will be randomly assigned in a 3:1 ratio to active treatment or placebo.

- Eligible participants who meet all inclusion and no exclusion criteria included in the study will be assigned unique study participant numbers for enrollment and randomization.

- The participants, on site medical/nursing staff at the study center, Syneos health biostatistics and the Sponsor will be blinded to study drug assignment throughout the study. The pharmacy staff preparing the SC/IV doses will not be blinded, nor will the study drug administrator(s).

- A masking technique will be used at the time of study drug administration due to the appearance of the placebo not matching that of the active study drug.

4.5.   Administration of Study Medication

The study drug composition and doses to be administered in this study are presented in Table 2. 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 2: Details of Study Medication Administration

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

4.6.   Study Procedures and Flowchart

Refer to Section 1.3 of the Protocol for the Schedule of Activities and refer to Section 4.1 for the timing and dependencies of the dosing cohorts.

5.   Endpoints

5.1.   Primary Endpoint

The primary endpoint for the study is to assess the safety and tolerability of ALXN1820 SC and ALXN1820 IV. Safety is assessed by incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), physical examination, vital sign measurements, clinical laboratory, and electrocardiogram results.

5.2.   Secondary Endpoints

- Serum ALXN1820 single- and multiple-dose PK profiles and PK parameters;

- Change in serum concentrations of total and free properdin over time;

- Change in CAP activity using the Wieslab AP assay;

- Incidence of ADAs to ALXN1820;

- ALXN1820 PK parameters (AUC) SC versus IV will be compared to estimate the absolute bioavailability of ALXN1820 SC;

- Quantitative assessment of safety, PK, PD parameters, and immunogenicity (ADA) between healthy non-Japanese participants and participants of Japanese descent.

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6. Analysis Sets

6.1. Enrolled Set

The Enrolled Set will include all participants who agree to participate in the study following completion of the informed consent process and who satisfy the inclusion/exclusion criteria and are randomized. Unless specified otherwise, this set will be used for participant listings and summaries of participant disposition.

6.2. Safety Set

The Safety Set (SS) will include all participants who receive at least 1 dose of study drug. Participants will be analyzed according to treatment received. The SS will be used for all analyses of safety endpoints.

6.3. Pharmacokinetic Set

The Pharmacokinetic Set (PKS) will include all participants who receive at least 1 dose of study drug and have at least 1 post-dose PK concentration measured. Serum concentrations will be summarized for all participants in the PKS. The exclusions from summary statistics for serum concentrations and/or PK parameters will be defined based on review of protocol deviations (if any) prior to database lock by PK scientist and study statistician at the discretion of the sponsor. Pharmacokinetic analyses will be performed using the PKS.

6.4. Pharmacodynamic Set

The Pharmacodynamic Set (PDS) will include all participants who receive at least 1 dose of study drug and have evaluable properdin concentration, CAP or Complement Classical Pathway (CCP) activity data. Pharmacodynamic analyses will be performed using the PDS.

6.5. Immunogenicity Set

The Immunogenicity Set (IGS) will include all participants who have a predose and at least 1 postdose ADA sample collected. Immunogenicity analyses will be performed using the IGS.

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7.   General Aspects for Statistical Analysis

7.1.   General Methods

- In general, descriptive statistics for continuous variables will include the number of non-missing values (n), arithmetic mean, 95% confidence interval (CI) of the mean, standard deviation (STD), 1st quartile (Q1), median, 3rd quartile (Q3), minimum, maximum, and interquartile range (IQR). Categorical variables will be summarized using percentages and frequency counts. Descriptive statistics and percentages and frequency counts will be summarized by cohort and study intervention within each cohort, where appropriate.

- For the summary statistics of continuous variables, unless specified otherwise, the minimum and maximum will be presented to the same number of decimal places as the raw data, mean, median, Q1 and Q3. The IQR will be presented to one more decimal place than the raw data and the STD will be presented to two more decimal places than the raw data.

- All statistical analyses will be conducted using SAS® for Windows® Version 9.4 or higher;

- All relevant participant data will be included in listings. All participants entered into the database will be included in participant data listings.

In general, the tables will include all cohorts and study intervention within each cohort and a total column as follows (see table shells for further details):

- Cohort 1: ALXN1820 12.5 mg SC
- Cohort 2: ALXN1820 50 mg SC
- Cohort 3: ALXN1820 150 mg SC
- Cohort 4: ALXN1820 450 mg SC
- Cohort 5: ALXN1820 450 mg IV
- Cohort 6: ALXN1820 1200 mg SC
- Cohort 7: ALXN1820 TBD (≤ 2250 mg SC)
- Cohort 8: ALXN1820 150 mg SC QW x 5
- Cohort 9: ALXN1820 150 mg SC QW x 5 Japanese Descent
- Cohort 10: ALXN1820 TBD SC QW x 3
- All Cohorts Placebo
- All Cohorts ALXN180 Total

7.2.   Key Definitions

End of Study (EOS)
The EOS for each participant is defined as the date the participant completes the last visit or date of discontinuation. EOS for each individual participant is anticipated to be Day 127 and Day 155 for single ascending dose (SAD) and multiple ascending dose (MAD) cohorts, respectively, or the time point at which complement activity has normalized, if later than Day 127 or Day 155.

Trial day
If the event date ≥ date of first dose of investigational product (IP), trial day = event date – date of first dose of IP + 1.
If the event date < date of first dose of IP, trial day = event date – date of first dose of IP.

Nominal Time
Nominal time is the scheduled measurement time relative to time 0. Time 0 is the time of study drug dosing on Day 1.

Baseline Value
Baseline is defined as the last non-missing assessment (including repeated and unscheduled assessments) prior to treatment on Day 1, unless otherwise specified.

Change from Baseline (CFB)
CFB = Post-baseline value – Value at baseline

7.3.   Missing Data

For participants who are withdrawn from the study prior to the end of the study, all data collected up to the point of discontinuation will be used for analysis. There will be no imputation for missing data, unless otherwise specified.

7.4.   Visit Windows

If there are multiple planned assessments for any study procedure at a given time point the latest non-missing value will be used for summarization, unless specified otherwise. Unscheduled assessments will be listed and will be used to flag baseline visit if this is the last non-missing assessment before the first dose of study drug, but unscheduled assessments will not be included in the summarization.

7.5.   Pooling of Centers

Not Applicable.

7.6.   Subgroups

Not Applicable.

8.   Participant Disposition, Demographic, Other Baseline Characteristics and Medication

8.1.   Participant Disposition and Withdrawals

Listings of treatment assignments, including the participant's identification and date of randomization will be presented.

The following frequencies (number and percent) will be displayed for all screened participants: participants randomized, screen failures with reasons and COVID-19 related reasons for screen failure.

The analysis sets will be summarized with counts and percentages by cohort and study intervention within each cohort and overall. This table will include the following: number of participants in the Enrolled Set, number of participants in the Safety Set, reasons for exclusion from the Safety Set, number of participants in the PK/PD sets, reasons for exclusion from the PK/PD sets, number of participants in the Immunogenicity Set and reasons for exclusion from the Immunogenicity Set.

The frequencies, number and percent, will be displayed for all participants in the Enrolled Set: participants who received treatment for each cohort, participants who completed the study, participants who discontinued early, participants who discontinued due to COVID-19 and study duration in days. The denominators will be the number of enrolled participants.

The number and percent of participants who discontinued early will also be presented by reason for early discontinuation, also for all participants combined. The denominators will be the number of participants who received the treatments.

Completion/discontinuation status, inclusion/exclusion criteria definitions and inclusion/exclusion criteria violations will be listed by participant.

A listing of participants excluded from the analysis sets will also be generated.

8.2.   Protocol Deviations

Protocol deviation management at Syneos Health is detailed in Protocol Deviation and Non-compliance Management (3101.W02). For details on the process for defining analysis datasets refer to (Blind) Data Review and Definition of Analysis Sets SOP (3911).

All protocol deviations recorded in Clinical Trial Management System (CTMS) will be listed. The Protocol deviation criteria are graded as not important or important. Important protocol deviations and important protocol deviations related to COVID-19 will be summarized by the number and percentage of participants for the Safety Set.

8.3.   Demographic and Baseline Characteristics

Demographic and baseline characteristics, including sex, female child-bearing potential, race, ethnicity, Japanese Descent, age, height, body weight, and body mass index (BMI) will be summarized on the Safety Set using standard descriptive statistics. No formal statistical comparisons between populations will be performed. Demographics and informed consent data will be listed for all participants in the Enrolled Set.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight(kg)/[Height(m)^2]

8.4.   Medical History and Concomitant Diseases

Medical history will be coded using MedDRA version 23.1 and summarized for the Safety Set, presenting the number and percentages of participants within each preferred term (PT) grouped by the system organ class (SOC). A participant with multiple occurrences of an event in a PT is counted only once. Medical history will be listed by participant.

8.5.   Medication

The WHO Drug Dictionary, WhoDrugGlobalB3 Sep 2020, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Prior medication is defined as any medication taken before the date of the first dose of study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of study treatment.

The use of prior and concomitant medications will be summarized by the number and percentage of participants for the Safety Set. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class.

Tetravalent Meningococcal Conjugate Vaccine (MCV4) and Meningococcal Serogroup B immunization results will be summarized for the Safety Set, presenting the number and percentages of participants who received the MCV4 and Meningococcal Serogroup B immunizations by timing (*i.e.* prior to consent or after consent). MCV4 and Meningococcal Serogroup B immunization results will be listed by participant.

8.6.   Extent of Exposure

Exposure data will be summarized by total dose administered (mg), total volume administered (mL) and the number of interruptions (SC Infusion/IV) by cohort. Exposure will be listed by participant.

8.7.   Treatment Compliance

Compliance of IP (%) intake will be calculated as follows:
*   (Total dose (mg) that the participant actually received and took / total expected dose (mg) that the participant was meant to receive) x 100

9.   Pharmacokinetics

Pharmacokinetic analyses will be performed using the PK Set and will be reported by cohort.

PK parameters will be calculated using noncompartmental methods with Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.0 or higher. Calculations of individual PK parameters will be based on individual serum concentration data from participants who receive ALXN1820 SC or ALXN1820 IV with actual sampling dates and times.

9.1.   PK/PD Sampling Schedule

Whole blood samples for PK analysis and pharmacodynamic (PD)/ biomarkers will be collected at various different timepoints for different cohorts. The timing of sampling may be altered during the course of the study based on newly available data to ensure appropriate monitoring.

9.2.   Serum PK Endpoint

The following PK parameters will be derived from the serum concentrations of ALXN1820:

For the single dose cohorts 1-7, PK parameters will be derived on Day 1.

For the multiple dose cohort 8, PK parameters will be derived on Day 1 and 29.

For the multiple dose cohorts 8 and 9, PK parameters will also be derived on Day 8, 15 and 22 (when possible using limited sampling schedule up to 24h*).

For the multiple dose cohort 10, PK parameters will be derived on Day 1, 8 (when possible using limited sampling schedule up to 24h*) and 15.

 * Only selected PK parameters might be derived due to limited sampling up to 24 h such as C_{max}, t_{max}, and AUC_{0-24} *etc*.

Refer to Section 1.3 of the Protocol for the full sample schedule.

Parameters	Dosing	Definition
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, MD	Area under the concentration-time curve from time 0 (dosing) to time infinity
$t_{\frac{1}{2}}$	SD, MD	Terminal elimination half-life
λ_z	SD, MD	Terminal-phase elimination rate constant
CL or CL/F	SD, MD	Total body clearance or apparent clearance
V_d or V_d/F	SD, MD	Volume of distribution or apparent volume of distribution
F	SD	Absolute bioavailability
R_{ac}	MD	Accumulation Ratio

Abbreviations: MD = Multiple-dose; SD = Single dose

Note: tau is the dosing interval for steady-state data, *i.e.*, the time between doses (tau = 1 week).

The absolute bioavailability for the ALXN1820 SC cohorts will be defined by the ratio of the geometric means for the $AUC_{0-\infty}$ 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.

The primary PK parameters will be summarized by overall treatment and the sub treatment category ADA status (at least one positive/negative). Boxplots will present PK levels by ADA status and by healthy non-Japanese participants and participants of Japanese descent. Some PK parameters may not be calculated for all or some subjects, at the discretion of the pharmacokineticist, if the concentration data are not deemed to be amenable to evaluation. Explanations for PK parameters that could not be estimated will be provided in the report.

9.3.   Presentation of Concentration Data

9.3.1.   Handling of Missing Data

Missing concentration data for all participants who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of AUC and for the individual serum concentration versus time curves, the following rules will apply:

- Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose Day 1 samples will be treated as zero;

- The sampling time of pre-dose samples relative to dosing will also be treated as zero;

- BLQ's between two quantifiable samples will be set to missing;

- The first BLQ after the last measurable sample will be set to missing; any subsequent BLQ's will be set to zero.

For serum concentration summary, the following rules will apply:

- All BLQ values will be set to zero;

- No further imputation will be applied to any missing values.

9.3.2.   Listing and Presentation of Individual PK Data

The actual and nominal sampling times of PK blood sample collection will be listed for each participant and will include the deviation in time from the protocol scheduled time (*i.e.*, nominal time), if applicable.

All measured concentrations will be presented in original precisions (*i.e.*, significant figures) and units as reported by Bioanalytical lab – *e.g.* ng/mL.

Serum concentrations and time deviation data will be presented in a data listing by participant.

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9.3.3.   Summary of PK Concentrations by Matrix

Serum concentration data will be summarized separately by time point for each cohort/actual treatment, using the following descriptive statistics: number of participants, arithmetic mean, STD, CV, geometric mean, geometric CV, median, minimum, and maximum.

Mean (STD) serum concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales. Individual serum concentration versus actual time profiles will be presented similarly.

9.4.   PK Parameters Derivation

- The apparent C_{max} and the corresponding t_{max} will be read directly from the concentration-time plot (observed data).

- AUC_t will be calculated using the log-linear trapezoidal interpolation rule for extravascular model.

- The terminal elimination rate constant (λ_z) will be determined by log linear regression obtained on at least the 3 last quantifiable concentrations and will not include C_{max}; $t_{1/2}$ is calculated by the program as $\ln2/\lambda_z$;

- The AUC_∞ will be calculated by the program as $AUC_\infty = AUC_t + AUC_{extrap}$ where last is the sampling time point of the last measurable concentration (t_{last}). AUC_{extrap} is calculated by the program as: C_{last}/λ_z, where C_{last} is the observed concentration at time t_{last} and λ_z is the elimination rate constant during the apparent terminal elimination phase; AUC_∞ will only be presented for participants with a reliable λz;

- CL will be calculated by program as $(dose/AUC_\infty)$;

- V_d will be calculated by the program as $(dose/AUC_\infty)/\lambda_z$.

The following PK acceptance criteria will be applied to assess the reliability of elimination parameters:

- Number of points to calculate λ_z is greater than or equal to 3 excluding C_{max} point;

- The adjusted square of the correlation coefficient or coefficient of determination (Rsquare adjusted) for the goodness of fit of the regression line through the data points must be ≥ 0.80;

- AUC_{extrap} ≤20%.

Unreliable PK parameters will be listed but flagged and excluded from summary.

9.4.1.   PK Parameters Summarization

Pharmacokinetic parameters derived from serum concentrations will be presented in data listings and summarized separately by cohort/actual treatment using the following descriptive statistics: number of participants, arithmetic mean, STD, arithmetic CV, geometric mean, geometric CV, median, minimum, and maximum.

9.5.   Planned Statistical Models for PK Parameters and Concentrations

The primary PK analysis will be based on the PK Set.

For the cohort 4 versus cohort 5 evaluation of the absolute bioavailability, the PK parameters (C_{max}, AUC_t, and AUC_∞) will be evaluated using an ANOVA statistical model with cohort, treatment, and sequence as the fixed effects, and participant-participant (sequence) as a random effect, using the natural logarithms of the data. Confidence intervals (CI, 90%) will be constructed for the least squares geometric mean ratio (GMR) for the cohort 4 versus cohort 5 for all 3 parameters using the natural log-transformed data. The GMRs and associated 90% confidence limits will be exponentiated back to the original scale.

The within-participant CV for the C_{max}, AUC_t, and AUC_∞ will be estimated using the mean squared error from the ANOVA.

In addition, the geometric means and the associated 95% CIs of C_{max}, AUC_t, and AUC_∞ will be reported for each treatment.

The evaluation of relative bioavailability, will be done for cohort 9 versus cohort 8 (for a comparison of non-Japanese versus Japanese descent).

All secondary analyses will be based on the PK Set.

Dose-proportionality will be assessed across all single dose (SD) cohorts (Cohort 1 (12.5 mg), Cohort 2 (50 mg), Cohort 3 (150 mg), Cohort 4 (450 mg), Cohort 6 (1200 mg) and Cohort 7 (≤ 2250 mg) ALXN1820) graphically and by using a power model (Smith, 2000; Newlands, 2006; EMA, 2010).

The following dose-normalized PK parameters will be assessed for dose proportionality: C_{max_n}, AUC_{t_n} and AUC_{∞_n}. The log (PK parameters) will be included as a response variable and log (dose) will be included as a fixed effect in the power model.

The form of the model is as follows:
PK Parameter = $e_\alpha \times Dose_\beta \times e_\epsilon$, where Dose ≥ 0, and e_ϵ represents the associated error. Thus, perfect dose proportionality is met when β=1 (ignoring error). This becomes a linear relationship following a natural-log transformation, to which a linear regression will be fit by ordinary least squares (OLS):
ln(PK Parameter) = α + β × ln(Dose) + ε, where Dose > 0, and ε represents the associated error.

The estimate of β together with a 90%CI will be provided (for each PK parameter model), and this will be used to quantify dose proportionality. According to Hummel et al. (2009), the following criterion may be used for exploratory dose proportionality evaluations: If the (two-sided) 90% CI for β is wholly contained within the interval, [1+ln(0.5)/ln(ρ), 1+ln(2)/ln(ρ)], then dose proportionality is suggested across the investigated dose range. Here, ρ is defined as the ratio of the highest to lowest dose. This interval criterion will be reported along with the corresponding 90% CI estimate for β (presented to three decimal places).

log(PK Parameter) = mu + beta*log(Dose)

*where beta = 1 indicates perfect dose proportionality. Estimation of beta, along with its 90% CI, will be provided.

9.6.　　　Deviation from Analyses Planned in Protocol

Not applicable.

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10.   Pharmacodynamics

Samples collected for the assessment of ALXN1820 concentration will be retained and may be analyzed in the future.

Samples for measurement of serum total and free properdin concentrations, CAP activity, CCP activity, CLP (complement lectin pathway) activity and potentially other measures of complement activation as specified in Section 1.3 of the Protocol will be used for the PD analysis described in this SAP/section.

Serum samples will be collected as defined in Section 1.3 of the Protocol.

10.1.1.   Endpoint(s)

•   Change in serum concentrations of total and free properdin over time;

•   Change in CAP activity using the Wieslab AP assay;

•   Subgroup analysis of the PD parameters between healthy non-Japanese participants and participants of Japanese descent.

10.1.2.   Analysis of the Endpoint

Pharmacodynamic analyses will be performed using the PD Set.

Missing concentration data for all participants who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the serum concentrations, actual values, changes from baseline and percentages change from baseline will be summarized by time point for each treatment using the following descriptive statistics: number of participants, arithmetic mean, STD, CV, geometric mean, geometric CV, median, minimum, and maximum.

Mean (STD) serum concentration (change from baseline and percentage change from baseline) versus scheduled time profiles will be presented in figures.

Individual serum concentration (change from baseline and percentage change from baseline) versus scheduled time profiles will be presented similarly.

Serum concentrations, change from baseline and percentage change from baseline will be presented in a data listing by participant.

11.   Safety

The population used for safety analyses will be the Safety Set (SS).

Safety analyses will include an analysis of all adverse events (AEs), Electrocardiograms (ECGs), clinical laboratory data, physical examinations, vital sign measurements and injection/infusion site evaluation measurements using descriptive statistics.

No inferential statistical analyses are planned on the safety parameters of this study.

11.1.   Adverse Events

AEs for all participants in the Safety Set will be included in the AE summaries.

Adverse events will be summarized by SOC and PT for each cohort, study intervention within each cohort and overall, based on the MedDRA dictionary version 23.1.

If the relationship to study drug is missing for TEAEs, then the relationship will be counted as related to study product for the summary tables. Missing severity for TEAEs will be counted as Grade 3.

Treatment-emergent AEs are defined as AEs which commence on or after first study drug administration, or those that first occur before first study drug administration but worsen in frequency or severity after first study drug administration.

If the start date of an AE is partially or completely missing, the date will be compared as far as possible with the date of the start of administration of study drug. The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or increase in severity during the treatment period (worst case approach). The following general rules will be used:

- If the start day is missing but the start month and year are complete, an AE will not be considered as being treatment-emergent only if the start month/year is before the month/year of the first study drug administration;

- If the start day and month are missing but the start year is complete, an AE will not be considered as being treatment-emergent only if the start year is before the year of the first Study Drug administration;

- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date is before the first study drug administration.

Time since first/last dose will be calculated as the difference between the event start date/time and the date/time of the first/last dose prior to start. Time since first/last dose will be expressed in days, hours and minutes. If time is missing, duration will be calculated as the difference between the start date and dosing date plus 1 and expressed in days. Time since first/last dose and duration will only be calculated when both dates are complete.

Duration will be calculated for AEs that resolve as the difference between the resolution date and onset date plus 1 and expressed in days. Should an AE have a short duration (*i.e.* < 24 hours), the duration will be calculated as the difference between the resolution time and the onset time.

The summary tables will include the number of participants and the number of events. Percentages will be based on the number of participants. Repeat AE summary tables will be created to display percentages based on the number of events. For summaries by SOC and PT, a participant will be counted once at the SOC level and once at each PT within the SOC level.

For summaries by SOC, PT and maximum Common Terminology Criteria for Adverse Events (CTCAE) grading, a participant will be counted once at the highest CTCAE grading for which the event occurred at the SOC level and the highest CTCAE grading for each unique PT within that SOC level. Therefore, participants may only contribute once to each PT and once to each SOC level.

The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following tables will be provided:

- An overall summary of the number and percentage of participants reporting TEAEs, serious TEAEs (TESAEs), TEAEs leading to death, TEAEs leading to withdrawal of study drug, TESAEs leading to withdrawal of study drug, TEAEs by relationship, TESAEs by relationship and TEAEs by CTCAE grade;

- TEAEs overall by system organ class and preferred term;

- TEAEs by maximum CTCAE grading, overall and by system organ class and preferred term;

- TEAEs by strongest relationship to study medication, overall and by system organ class and preferred term;

- TEAEs overall by system organ class;

- TEAEs overall by preferred term;

- Related TEAEs (TERAEs), overall by preferred term;

- TESAEs overall by system organ class and preferred term;

- TESAEs by maximum CTCAE grading, overall and by system organ class and preferred term;

- TESAEs by strongest relationship to study medication, overall and by system organ class and preferred term;

Only TEAEs (or TESAEs, as applicable) will be included in the summary tables, however we will generate separate listings for treatment-emergent and non-treatment-emergent AEs. Additional listings will be provided for deaths, serious adverse events, AEs resulting in withdrawal from the study and AEs resulting is study drug withdrawal.

11.2.   Laboratory Evaluations

Safety laboratory samples for hematology, chemistry, urinalysis and coagulation will be collected at various different timepoints for different cohorts.

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Samples for pregnancy test, alcohol breath test, urine drug screen, FSH, HIV (types 1 and 2) screen, hepatitis B and C screen will collected.

Refer to Section 1.3 of the Protocol for the schedule of activities indicating when the respective samples are taken for each cohort.

The following parameters will be included:

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: 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.

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).

Coagulation: Prothrombin time, partial thromboplastin time, international normalized ratio.

Serology: Human immune deficiency virus (HIV)-1 and HIV-2 antibodies, hepatitis B surface antigen (HbsAg), anti-HBc + IgM (if IgG positive) and anti-hepatitis C virus with confirmation by hepatitis C virus Ribonucleic acid (RNA).

Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential), Follicle-stimulating hormone estradiol (as needed in women of non-childbearing potential only).

Alcohol breath and urine drug screen: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, methamphetamine, 3,4-methylenedioxy-methamphetamine, methadone, and tetrahydrocannabinol [cannabinoids].

Other tests: Serum QuantiFERON®-TB test, Vaccine titer (meningococcal serogroups A, C, W135, and Y).

Laboratory parameter values will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

All summaries will be based on results in SI (standard international system of units) units and will be output in the order listed above.

Toxicity grading following the NCI CTCAE grades version 5.0 will also be derived for laboratory variables where applicable (see list below). Note, where gradings require investigator/clinical input, this will not be considered and only the numeric criteria will be used for the assignments. If this results in the criteria for more than one grade being met, the highest (worst) CTCAE grade will be assigned. For creatinine only, the criteria based on the upper limit of normal (ULN) will be used (changes compared to the baseline value will not be used), *e.g.*, CTCAE defines Grade 1 as > ULN - 1.5 x ULN or > 1 - 1.5 x baseline. Only the ULN – 1.5 x ULN criterion will be used (and not the baseline criterion).

The following parameters are CTCAE gradable:

• **Hematology**: Absolute neutrophil count (neutrophil), total leukocytes (Leukocytes), hemoglobin (only do the grading for Anemia, no grading for Hemoglobin increased), platelet count, Lymphocyte.

• **Coagulation:** International normalized ratio.

• **Chemistry:** Alanine aminotransferase albumin, alkaline phosphatase, aspartate aminotransferase, total bilirubin, creatinine, gamma-glutamyl transferase, glucose (only do the grading the Hypoglycemia, no grading for Hyperglycemia), creatine kinase.

Actual values and changes from baseline (screening) in hematology, coagulation, clinical chemistry, and urinalysis will be summarized by treatment.

Shift tables for hematology, clinical chemistry and coagulation from baseline CTCAE toxicity for each visit and to the maximum CTCAE grade on treatment for each parameter will be provided. Participants with both a non-missing baseline and at least one non-missing post-baseline grade will be included in the shift tables. Unscheduled data will be included in the worst case across all scheduled and unscheduled visits after the first dose of study treatment. This means that if there are CTCAE grades derived from both unscheduled and scheduled visits data per test per participant then the highest grade will be summarized.

For non-CTCAE gradable tests, a shift table will be provided showing shifts relative to the normal ranges. This summary of normal range category changes illustrates the number and percentage of participants who fall into specified categories (Decrease to Low, Change to Normal or No Change, Increase to High) by comparing the baseline normal range category to the planned time normal range category and the worst-case normal range category. The worst-case post-baseline row will be used to summarize the participants' overall worst-case normal range category change. The determination of the worst-case takes into account both planned and unscheduled assessments. Only laboratory tests which cannot be graded per CTCAE v. 5.0 specified criteria will be included.

Participants with missing baseline value are to be assumed to have normal baseline value. Worst-case can be either High or Low. If a participant has a Decrease to Low and an Increase to High during the same time interval, then the participant is counted in both the 'Decrease to Low' and 'Increase to High' categories. If a participant was high at baseline and decreases to Low during the time interval, then the participant is counted in the 'Decrease to Low' category. Likewise, if a participant was Low at baseline and increases to High during the time interval, then the participant is counted in the 'Increase to High' category. Participants are only counted in the 'Change to Normal or No Change' category if they are:

- Normal at baseline and have no normal range High and no normal range Low values during the time interval

- High at baseline and do not change to Low during the time interval

- Low at baseline and do not change to High during the time interval Shift tables by treatment 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 post-dose during the study.

All events of ALT ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 ×ULN (> 35% direct bilirubin) which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE. Optional outputs may be created if it is seen that ALXN1820 causes liver injury. For these optional outputs, liver function results will be presented in a summary table and eDISH (evaluation of drug-induced serious hepatotoxicity) plots.

All laboratory results, as well as CTCAE grades will be included in data listings. Abnormal results for hematology, clinical chemistry, urinalysis and coagulation will be listed separately. Laboratory results for serology, pregnancy and FSH, urine drug screen, alcohol breath test, QuantiFERON Tuberculosis test and MC4 Vaccine Titer will be listed only.

11.3.   Vital Signs

Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate (breaths per minute) and temperature (degree Celsius) will be measured at different timepoints as per the schedule of events (Section 1.3) in the Protocol.

Actual values and changes from baseline in vital sign measurements will be summarized by treatment.

Note temperature will be reported in centigrade. Any conversions required will be as follows:

Temperature (in °C) = 5/9 (Temperature [in °F]-32).

All vital signs will be provided in data listings.

11.4.   ECG

The ECG parameters include heart rate, PR, RR, QRS, QT, and corrected QTcF intervals.

Analysis of drug related QT/QTc interval changes relative to serum 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). 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 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. The average of the triplicate ECG readings will be used to derive QT/QTc at all visits (*i.e.* both pre- and post-baseline visits). 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:

-   QT, QTcF interval > 450 msec

-   QT, QTcF interval > 480 msec

-   QT, QTcF interval > 500 msec

-   QT, QTcF interval increases from baseline > 30 msec

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- QT, QTcF interval increases from baseline > 60 msec

Actual values and change from baseline of these average ECGs will be summarized by treatment.

All ECG parameters, including all single ECG measurements, but also the mean value and overall ECG evaluation will be provided in data listings.

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. The 24-hour Holter ECG recording results will be provided in data listings.

If deemed necessary, a separate concentration-QT analysis may be performed by Alexion. The concentration-QT analysis is not within the scope of this SAP.

11.5.   Physical Examination

A full physical examination will be performed at different timepoints as per the schedule of events (Section 1.3) in the Protocol.

A symptom-driven physical examination of relevant body systems may be performed at other times, at the Investigator's discretion.

Physical examination data will be listed.

11.6.   Injection or Infusion Site Evaluation

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

The severity (grade) of the injection/infusion site evaluation will be summarized by treatment and visit/timepoint.

Injection/infusion site evaluation data will be listed.

12.   Immunogenicity

The population used for immunogenicity analyses will be the Immunogenicity Set (IGS).

The immunogenicity analyses will include an analysis of ADAs using descriptive statistics. The results will summarize the difference between healthy non-Japanese participants and participants of Japanese descent.

Whole blood 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 actual date and time (24-hour clock time) of each sample will be recorded. Refer to Section 1.3 of the Protocol for the schedule of activities indicating when the ADA samples are taken for each cohort.

ADA and Neutralizing Antibodies (NAb) data reporting:

- Incidence, titer, duration, time to detection, pre-existing ADA;

- PK concentration or parameter by immunogenicity response;

- PD response by immunogenicity response;

- Individual data listing or spaghetti plots with ADA category overlaid.

For ADA categories and participants, summary of individual plots of PK, PD, ADA and NAb titer time course to better understand the clinical impact of immunogenicity at a subject level.

13.   Interim Analyses

Interim assessments will be performed as follows:

- 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).
- 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.

The interim analysis is outside the scope of this SAP.

14.   Changes from Analysis Planned in Protocol

Not Applicable.

15.   Reference List

Garnett C, Bonate PL, Dang Q, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018;45(3):383-397.

16.   Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907).

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

Syneos Health SOP Pharmacokinetic and Related Data Analysis (3913) describes the process for the interaction between the Biostatistics and Pharmacokinetics departments for the analysis of pharmacokinetic and pharmacodynamic data.

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Final Audit Report   2022-11-30

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